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Risks for comorbidity in atopic children: an epidemiological study in general practice

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Abstract

Objective: This study aimed to investigate both atopic and non-atopic comorbid symptoms and diseases in children with physician-diagnosed atopic disorders (atopic eczema, asthma and allergic rhinitis).

Methods: All children aged 0-18 years listed in a nationwide primary care database (NIVEL-PCD) with routinely collected health care data in 2014 were selected. Atopic children were matched on age and gender with non-atopic controls within the same general practice. A total of 404 ICPC codes were examined. Logistic regression analyses were performed to examine the associations between the presence of atopic disorders and (non-) atopic symptoms and diseases by calculating odds ratios (OR).

Results: Having one of the atopic disorder significantly increased the risk of having other atopic-related symptoms, even if the child was not registered as having the related atopic disorder. Regarding non-atopic comorbidity, children with atopic eczema (n: 15,530) were at significantly increased risk for (infectious) skin diseases (OR: 1.2-3.4). Airway symptoms or (infectious) diseases (OR: 2.1-10.3) were observed significantly more frequently in children with asthma (n: 7,887). Children with allergic rhinitis (n: 6,835) had a significantly distinctive risk of ear-nose-throat related symptoms and diseases (OR: 1.5-3.9). Neither age nor gender explained these increased risks.

Conclusion: General practitioners are not always fully aware of relevant atopic and non-atopic comorbidity. In children known to have at least one atopic disorder, specific attention is required to avoid possible insufficient treatment and unnecessary loss of quality of life.

Keywords: Atopic dermatitis, Asthma, Allergic rhinitis, General practice, Comorbidity, Epidemiology

Strengths and limitations of this study

- The present study used an extensive and representative general practice database.
- The large number of children gives the study substantial power and generalizability.
- A total of 404 ICPC codes were examined.
- A limitation regarding this type of explorative study is the unavoidable multiple testing.

Introduction

Atopic disorders represent an important health problem in general practice. Acute upper airway infections, middle ear infections, warts, asthma, and atopic eczema represent the five most prevalent pediatric diseases diagnosed in general practice (1); allergic rhinitis is on the 12th place in this list. However, limited data are available on the co-morbidities of atopic children in primary care. In the present study we refer to atopy as one or more of the following established diagnosis: atopic eczema, asthma and/or allergic rhinitis.

Associations have been shown between atopic disorders and other diseases in children, but in different clinical settings (e.g. birth cohorts, hospitals, or pediatric clinics). Proven interrelations exist with (among others) diabetes (2-4), ADHD (5-7), autism (8-10), and obesity (11-13). According to other studies, the presence of some comorbidities may even influence the course of atopic disorders. For example, acute upper airway infections, especially in early childhood, are related to atopic disorders later in life (14, 15). Acute viral 'non-respiratory syncytial virus' bronchiolitis in infants aged <6 months is linked with an increased risk of developing asthma (16). The developing immune system of a child might be affected by frequent or severe infections of the middle ear, resulting in increased risk for asthma and atopic eczema (17). On the other hand, otitis media with effusion is associated with allergic rhinitis (18-20). The quality of life of an atopic child can be significantly improved by providing sufficient treatment.

To our knowledge no study has investigated the complete range of potential comorbidities in atopic children in a general practice setting. Relevant questions include: Are atopic children at increased risk for specific non-atopic symptoms or diseases, that general practitioners (GPs) should be aware in order to reduce the risk of underdiagnosing relevant comorbidity? Are children with one atopic disorder at risk to be underdiagnosed with another atopic disorder? To study possible associations between atopic disorders and 404 different symptoms

and diseases, an extensive and representative nationwide general practice database is explored using a cross-sectional design.

Methods

Study population

All non-institutionalized residents in the Netherlands are registered in a general practice, even if they do not visit the GP on a regular basis. The Netherlands Institute for Health Services Research-Primary Care Database (NIVEL-PCD) is based on routinely recorded data in electronic health records (EHRs) of all listed patients in the participating practices. In 2014, about 500 general practices participated, including data of about 1,700,000 patients (www.nivel.nl/en/dossier/nivel-primary-care-database), which is over 10% of the total Dutch population. EHR data include a variety of information regarding type of consultation, morbidity, and prescriptions. Data available for 2014 are representative for the Dutch population (21). Primary care physicians (gatekeepers for the Dutch healthcare system) recorded morbidity using the International Classification of Primary Care (ICPC), a classification method for primary care that is accepted by the WHO (22). Dutch GPs cluster relevant consultations, prescriptions and referrals, in ICPC classified episodes of care. Atopic disorders are labeled with ICPC codes: S87 (atopic eczema), R96 (asthma) and R97 (allergic rhinitis). ICPC-codes specific for food-allergies are not available.

For the present study, only morbidity data from EHRs of general practices with sufficient data quality were used that fulfilled the following criteria: i) at least 500 listed patients (standard practice: 2,350 patients), ii) complete morbidity registration (defined as ≥ 46 weeks/year), and iii) sufficient ICPC coding of diagnostic information (defined as ≥ 70% of the recorded disease episodes labeled with an ICPC code). The following descriptive data were routinely collected: period in which the individual child was registered in the general practice, the unique code of the GP practice, the child's gender, and year and quarter of birth.

Atopic children

For each child (0-18 years), a minimum follow-up of 3 years was required for the present study to reduce the risk of registration bias. In the Netherlands, GPs see about 67% of their patient population at least once a year (23). We considered a 3-year follow-up period to be sufficient time for a GP to diagnose a child with (atopic) disorders. Furthermore, in order not to miss any relevant atopic diagnosis, when available, the EHRs from 2002-2014 were examined. Since GPs inevitably work with probability diagnoses, there is a risk of misclassification. To select cases with a higher probability of a clinically relevant disorder, ICPC codes and their related episodes of care can be corrected. In practice, an atopic episode of care was maintained if (between 2002-2014) the child had at least two contact moments in that episode of care and had received at least two relevant prescriptions. If the child did not meet these criteria, the child was considered not to have that atopic disorder (24). If a child was diagnosed with an atopic disorder for the first time during 2014, the child was considered to have the atopic disorder that whole year. In the present study, the atopic diagnosis was based on the physician's assessment.

Atopic triad

A recent meta-analysis supported the hypothesis that there might be a fourth distinct group of children with all three atopic disorders, in contrast to the traditional classification of children with asthma *or* allergic rhinitis *or* atopic eczema (25). To learn more about this potentially unique group of children, 'atopic triad' episodes were developed for research purposes. These episodes were only created when a child was diagnosed with all three atopic disorders, based on available data from EHRs in the period 2002-2014.

Symptoms and diseases studied

After establishing which child had an atopic disorder (see above), a child was considered prevalent for a specific symptom or disease if the child had at least one active episode of care for that symptom or disorder in the year 2014. All ICPC codes that describe a symptom or a disease were examined, with the exception of trauma-related ICPC codes, ICPC codes not relevant for children (e.g. presbyacusis), pregnancy, childbearing, family

planning, sexual transmitted diseases and social problems, leaving 404 different ICPC codes. Furthermore, since different classifications are used for eczema, there is a risk of misclassification. The ICPC system distinguishes the codes S86 (seborrheic dermatitis), S87 (atopic eczema), S88 (contact dermatitis / eczema another) and S89 (diaper rash). Since clinical differentiation can be very difficult, especially between S87 and S88, S88 was excluded from our analyses, to get more reliable results for 'true' atopic eczema (S87).

Design

A nested case-control study design was used. For each atopic child, one matched control patient was selected (not diagnosed with an atopic disorder) within the same general practice, based on age and gender in 2014. Odds ratios (ORs) were calculated for children that solely had atopic eczema, asthma, or allergic rhinitis and therefore no other atopic comorbidity. Appendix 1 presents a list of all the ICPC codes that were examined. A 1:1 ratio was chosen to be able to include as many pairs of cases and controls as possible, allowing the results to carry more weight and making the conclusions more generalizable to future populations. In the present study, a 1:2 ratio would have resulted in dropping over 40% of the cases.

Statistical analyses

Logistic regression analysis was performed to study associations between the presence of atopic disorders and (non-) atopic comorbid symptoms and diseases in children. Similarly, associations between atopic triad and the above-mentioned comorbid symptoms and diseases were examined. Due to multiple testing, only associations with $p \leq 0.001$ were considered statistically significant. All associations were tested for the modifying effects of age and gender. In case of a significant effect ($p \leq 0.01$), associations were also presented for subgroups for age (0-6 vs. 7-12 vs. 13-18 years) and gender (boy vs. girl). Finally, due to the hierarchical structure of the data (patients registered in general practices), a multi-level logistic regression analysis was performed to test whether clustering effects influenced our findings. All analyses were conducted in Stata 13 and Excel 2010. Prevalence rates are presented in percentages.

Ethical approval

Dutch law allows the use of EHRs for research purposes under certain conditions. According to this legislation, it is not necessary to obtain informed consent from patients or approval from a medical ethics committee for this type of observational study that contains no directly identifiable data (Dutch Civil Law, Article 7: 458). Therefore, no waiver of ethical approval was obtained from an Institutional Review Board (IRB) or ethics committee. The authors had no access to any identifying information at any moment during the analysis of the data.

Results

General characteristics (Table 1)

409,312 children were identified in the NIVEL-PCD in 2014, initially including 70,494 atopic children with at least one atopic disorder. However, for an atopic child to be included in this study, one matched control patient had to be available (i.e. a child without an atopic disorder). After selecting children with an atopic disorder **and** with a higher probability of a clinically relevant disorder **and** with at least three years follow-up, 21,285 children with atopic eczema were identified, of which 15,530 children had atopic eczema without another atopic disorder. For asthmatic children, 13,196 children were identified, of which 7,887 had asthma only and no other atopic disorders. In children with AR, 11,483 were identified of which 6,835 had AR without another atopic disorder. Finally, 559 children had all three atopic disorders. All the children in these groups were selected from 316 different general practices participating in NIVEL-PCD. Clustering effects did not influence our findings.

Atopic eczema (Table 2)

A substantial part of the significantly related comorbidity for children with atopic eczema concerns skin diseases such as (among others): warts (OR 1.2), localized rash (OR 1.5), pruritus (OR 1.7), impetigo (OR1.7), dermatophytosis (OR 1.8), urticaria (OR 1.8), molluscum contagiosum (OR 1.9) and psoriasis (OR 3.4). Otitis externa (OR 1.6) and blepharitis (OR 1.5) were also significantly associated with atopic eczema. The symptom diagnosis of wheezing (OR 2.0), that could be attributed to asthma, is noteworthy since these children were not diagnosed or coded in the EHRs with asthma. The same applies to symptoms associated with allergic rhinoconjunctivitis, such as sneezing/nasal congestion (OR 2.0) and allergic conjunctivitis (OR 2.0). Older children with atopic eczema were at increased risk to develop a localized rash (OR 1.3 - > 2.3) and impetigo (OR

1.5 - >2.7). Compared to boys, girls had an increased risk, to develop a localized rash (OR 2.0 vs. 1.1), breathing problems (OR 3.6 vs. 0.9) and stomach function disorder (OR 3.3 vs. 0.7).

Asthma (Table 3)

Noteworthy are asthma-related symptoms that were diagnosed separately, such as shortness of breath/dyspnea (OR 7.7) and wheezing (OR 10.3). Furthermore, asthmatic children consulted their GP more frequently for airway-related infections such as: acute laryngitis/tracheitis (OR 2.3), acute upper respiratory infection (OR 2.4), pneumonia (OR 4.0) and acute bronchitis (OR 4.8). In children with asthma, there seems to be a higher risk for the development of gastrointestinal symptoms, e.g.: general abdominal pain/cramps (OR 1.4), localized abdominal pain (OR 1.4), constipation (OR 1.4) and vomiting (OR 2.0). Acute bronchitis (OR 3.7 - >8.1) was diagnosed more often in older children. Inguinal hernias were seen more frequently in girls than in boys (OR 4.5 vs. 0.3).

Allergic rhinitis (Table 4)

Children with allergic rhinitis visit their GPs more frequently for ear-nose-throat related symptoms and diseases. Among others, the following were diagnosed more often: throat symptom/complaint (OR 1.5), ear pain/earache (OR 1.9), hypertrophy tonsils/adenoids (OR 1.9), acute/chronic sinusitis (OR 2.0), nose symptom (OR 2.6) and sneezing/nasal congestion (OR 3.9). Furthermore, symptoms associated with atopic eczema (pruritus; OR 2.2) and asthma [shortness of breath/dyspnea (OR 2.7) and wheezing (OR 4.3)] were seen more frequently. Also, when a child was diagnosed with allergic rhinitis, there was a substantial risk for the development of gastrointestinal symptoms [constipation (OR 1.5) and localized abdominal pain (OR 1.8)]. Hypertrophy of the tonsils was diagnosed less frequently when children got older (OR 3.2 - >1.0). On the other hand, children were more frequently diagnosed with a viral exanthema when they became older (OR 0.3 - >4.5). A presumed gastro-intestinal infection (OR 3.4 vs. 1.3), speech disorder (OR 2.4 vs. 0.9) and blepharitis/style/chalazion (OR 3.3 vs. 1.2) were diagnosed more frequently in girls with allergic rhinitis.

Atopic triad (Table 5)

Having all three atopic disorders is relatively rare, with only a few symptoms and diseases being significantly related. The risk for developing an 'allergy', that the GP considers relevant to register in the EHR can be considered high (OR 17.8). Allergic conjunctivitis (OR 6.8) is also frequently seen in children with all three atopic disorders.

Discussion

Main findings

The present study used an extensive and representative general practice database (21). The large number of children gives the study substantial power and generalizability. This could also allow evaluation of possible links between atopic disorders and rare childhood diseases. This study showed that atopic children have an increased risk for the development of both atopic and non-atopic diseases and symptoms. Children diagnosed with one atopic disorder were frequently diagnosed by their GP with symptoms associated with one of the other atopic disorders. This suggests that GPs are not always fully aware of relevant atopic comorbidity, or at least do not label it correctly. For example, a child with atopic eczema that presents with 'wheeze' or 'dyspnea' is at a higher risk for the development of asthma compared to a child without atopic eczema. A GP should be aware of this increased risk, since it could result in insufficient treatment of a child. Regarding non-atopic co-morbidity, strong associations were found between the atopic disorder and diseases and symptoms related to the same organ system. For example, children with atopic eczema are at increased risk for the development of other skin diseases, asthmatic children are at risk of other airway diseases, and children with allergic rhinitis are at risk of ear-nose-throat-related symptoms and diseases. Gastro-intestinal and musculoskeletal diseases and symptoms were also seen more frequently in atopic children. When exploring possible interactions of age and gender in children with one atopic disorders, no clear patterns arose.

Interpretation of findings in relation to previously published work

Children with atopic eczema had an increased risk of developing infectious skin diseases such as warts, impetigo, dermatophytosis and molluscum contagiosum. The common etiology could be the barrier dysfunction of the skin in children with atopic eczema. This barrier dysfunction is also seen in psoriasis, a disease that, according to the present study, is associated with atopic eczema (OR 3.4). Although the clinical

pictures of these two diseases are different, they share some common pathological backgrounds such as barrier dysfunction and enhanced IL-22 expression (26). Otitis externa and blepharitis both had significant ORs. These disorders could in fact be an expression of atopic eczema.

Children with asthma seem to have consulted their GP more frequently for airway-related infections such as acute laryngitis/tracheitis, acute upper respiratory infection, pneumonia and bronchitis. An explanation for this could be that airway infections increase asthma symptoms or vice versa, that asthma resulted in increased susceptibility for infection, which increased their motivation to visit the GP. Furthermore, the awareness of parents is likely to be increased when a child suffers from asthma, since such an infection could predispose for an asthma exacerbation.

Children with allergic rhinitis consulted their GPs more frequently for ear-nose-throat-related symptoms and diseases. However, even more striking are the asthma-related symptoms. Both shortness of breath (OR 2.7) and wheeze (OR 4.3) were frequently seen in children with allergic rhinitis. There is strong evidence that allergic rhinitis has an adverse impact on asthma severity (27). Because allergic rhinitis can provoke asthma symptoms, allergic rhinitis symptoms should be taken more seriously by GPs to reduce insufficient treatment.

Gastrointestinal-related symptoms are also frequently diagnosed by GPs in atopic children. This is in accordance with a study in adults in a primary care setting (28). These symptoms could be related to IgE-mediated food allergies or in rare cases even to eosinophilic esophagitis that are associated with atopic disorders (29); however, in children, abdominal pains can also be a general expression of not feeling well. Unfortunately, the ICPC classification system does not cover the above-mentioned gastrointestinal diseases with unique code and, therefore, gastrointestinal-related symptoms might have been used by the GP to label these diseases.

Some associations described in the literature were not confirmed in the present study, e.g. serous otitis media in patients with allergic rhinitis (18, 20), and inflammatory bowel disease (30, 31), leukemia (32, 33) and

diabetes (34, 35) in atopic patients. The prevalence rates of some of these disorders are low and a cross-sectional design (as used in the present study), might not be sufficient to prove this relationship.

Strengths and limitations of this study

Using general practice databases (by means of a cross-sectional design) also has its limitations. First of all, a limitation for the present study is the GP's choice for ICPC coding of an episode of care. For example, a child with a wheeze could either be labeled as 'asthma' (R96) or labeled as 'wheeze' (R03). This could result in both overestimation or underestimation of asthma. To decrease this risk of overestimation regarding atopic disorders, some episodes were corrected in order to increase the clinical relevance of the atopic disorder of interest. However, the risk of underestimation was not tackled, since too many assumptions need to be made. The second limitation regarding this type of explorative study is the unavoidable multiple testing. Although conservative p-values were used, type 1 errors cannot be avoided. In this study, some suggested associations might in fact reflect these type 1 errors. Thirdly, because data on socioeconomic status, tobacco smoke exposure and other lifestyle-related risk factors are not recorded in NIVEL-PCD, we cannot rule out the effect of these risk factors on the observed relations. However, since the children with atopic disorders were matched with controls within the same general practice, all children are most likely living in the same neighborhoods and therefore the effect of most of the earlier mentioned risk factors is expected to be small. Fourthly, atopic children might visit the GP more frequently than non-atopic children. And although this may be more representative of parental fears, rather than an indication of morbidity, it can result in more ICPC codes in atopic children and could partly explain some of the associations found. In future research, the number of consultations might need to be taken into account in the analyses. Fifth of all, in the present study the diagnosis are based on a physician's assessment and not on confirmed sensitization pattern for allergens. According to the Dutch medical guideline for eczema (36), GPs are not advised to determine these sensitization patterns, since this doesn't have any clinical consequences. Although atopy is clearly associated

with atopic eczema, the role of IgE sensitization in atopic eczema still needs further study (37). Also in children with AR, sensitization patterns don't have added value if the medical history clearly suggests e.g. a pollen allergy (38). Only when the cause of the rhinitis is uncertain, the determination of sensitization patterns adds value. The medical guidelines for asthma in children advises to determine sensitization patterns (39), since it can help diagnose allergic asthma (40) and because it could have clinical consequences. Finally, it is important to acknowledge the uncertainty of general practitioners to make a diagnosis of asthma or AR in young children (e.g. under the age of six).

Implications for future research and practice

First of all, could comorbidity data be used to create proxies that could support GPs in identifying atopic children that are not labeled as such? For example, could comorbidity data be incorporated in 'clinical decision support systems' to improve early diagnosis of both atopic and non-atopic disorders. Second of all, how is the quality of life of these atopic children affected by the associated comorbidity? GPs should be aware of the described associations when treating an atopic child, since the quality of life of an atopic child could be improved by paying more attention to diagnosis and treatment of these related disorders. Furthermore, one must be aware that atopic disorders and associated symptoms and diseases may well persist into adulthood.

Conclusions

The present study shows that atopic children have an increased risk of clinically relevant comorbidity, both atopic and non-atopic. General practitioners may not always be fully aware of relevant atopic and non-atopic comorbidity. In children known to have at least one atopic disorder, specific attention is required to avoid possible insufficient treatment and unnecessary loss of quality of life.

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Competing Interests

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Contributions

Study conception and design: DP, MN, JK, PB, AB

Acquisition of data: DP, MN

Analysis and interpretation of data: DP, MN

Drafting of manuscript: DP

Critical revision: MN, JK, PB, AB

Guarantor: MN, AB

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Data sharing statement

Data will be available from the repository of Data Archiving and Networked Services (DANS; www.dans.knaw.nl).

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Figure legends

Table 1. General characteristics of the total study population

Table 2. Significantly (p ≤0.001) associated comorbidity in children diagnosed with only atopic eczema (Ec) and at least three year follow-up versus controls (non-atopic children) (n=31,060)

Table 3. Significantly (p ≤0.001) associated comorbidity in children diagnosed with only asthma (As) and at least three year follow-up versus controls (non-atopic children) (n=15,774)

Table 4. Significantly (p ≤0.001) associated comorbidity in children diagnosed with only allergic rhinitis (AR) and at least three year follow-up versus controls (non-atopic children) (n=13,670)

Table 5. Significantly (p≤0.001) associated comorbidity in children diagnosed with Atopic Triad (AT) and at least three year follow-up versus controls (non-atopic children) (n= 1,118)

Table 1. General characteristics of the total study population

	n	Age in years (SD)	Male
Only atopic eczema	15,530	8.7 (4.5)	48.2%
Only asthma	7,887	10.7 (4.5)	59.0%
Only allergic rhinitis	6,835	13.5 (3.5)	57.8%
Atopic triad	559	11.6 (4.0)	61.4%

NB. Children in the first three groups had **only one** of the three atopic disorders: i.e. they had the disorder mentioned, but none of the **other** disorders, whereas children in the Atopic triad group had **all three** disorders.

Table 2. Significantly (p ≤0.001) associated comorbidity in children diagnosed with only atopic eczema (Ec) and at least three year follow-up versus controls (non-atopic children) (n=31,060).

ICPC	OR	95% CI	Prevalence		OR sex		OR age			Description ICPC codes
			Ec	No Ec	boy	girl	0-6	7-12	13-18	
Skin-related diseases and symptoms										
S03	1.15	1.06 – 1.26	7.85	6.88						Warts
S06	1.51	1.25 – 1.82	1.76	1.18	1.11	2.02	1.29	1.54	2.30	Rash localized [1, 2]
S99	1.57	1.24 – 2.00	1.12	0.71						Skin disease, other
S02	1.71	1.31 – 2.23	0.97	0.57						Pruritus
S84	1.71	1.54 – 1.90	6.23	3.75			1.54	1.78	2.72	Impetigo [2]
S04	1.76	1.30 – 2.39	0.73	0.42						Lump/swelling localized
S74	1.76	1.54 – 2.00	4.20	2.44						Dermatophytosis
S98	1.77	1.50 – 2.09	2.49	1.42						Urticaria
S21	1.89	1.49 – 2.40	1.26	0.67						Skin texture symptom/complaint
S95	1.92	1.69 – 2.19	4.44	2.38						Molluscum contagiosum
S86	2.31	1.87 – 2.84	1.89	0.83						Dermatitis seborrhoeic
S91	3.36	2.23 – 5.06	0.64	0.19						Psoriasis
Airway-related diseases and symptoms										
R05	1.29	1.17 – 1.43	5.94	4.67						Cough
R74	1.33	1.23 – 1.43	10.42	8.13						Upper respiratory infection acute
R78	1.49	1.22 – 1.80	1.66	1.13						Acute bronchitis/bronchiolitis
R04	***1.55***	***0.97 – 2.48***	***0.29***	***0.19***	0.91	3.58				Breathing problem, other [1]
R03	1.95	1.30 – 2.92	0.45	0.23						Wheezing
Ear-nose-throat-related diseases and symptoms										
H71	1.20	1.09 – 1.31	7.46	6.35						Acute otitis media/myringitis
H72	1.40	1.21 – 1.62	2.92	2.11						Serous otitis media
H01	1.43	1.24 – 1.65	3.01	2.13						Ear pain/earache
H04	1.47	1.17 – 1.86	1.13	0.77						Ear discharge
R21	1.50	1.27 – 1.78	2.13	1.43						Throat symptom/complaint
H70	1.56	1.27 – 1.90	1.58	1.02						Otitis externa
R07	1.95	1.32 – 2.89	0.48	0.24						Sneezing/nasal congestion
Gastro-intestinal-related diseases and symptoms										
D01	1.27	1.12 – 1.45	3.61	2.85						Abdominal pain/cramps general
D12	1.32	1.19 – 1.47	5.29	4.07						Constipation
D87	***1.48***	***0.87 – 2.51***	***0.22***	***0.15***	0.69	3.29				Stomach function disorder [1]
D99	2.28	1.51 – 3.44	0.48	0.21						Disease digestive system. other
Musculoskeletal										
L17	1.30	1.15 – 1.48	3.50	2.71						Foot/toe symptom/complaint
L98	1.39	1.20 – 1.60	2.90	2.11						Acquired deformity of limb
Miscellaneous										
A04	1.25	1.09 – 1.44	3.07	2.47						Weakness/tiredness general
S12	1.41	1.19 – 1.66	2.24	1.60						Insect bite / sting
F72	1.53	1.22 – 1.93	1.20	0.79			0.96	2.79	1.76	Blepharitis/stye/chalazion [2]
F70	1.53	1.29 – 1.81	2.18	1.44						Conjunctivitis infectious
Y81	1.83	1.47 – 2.72	1.49	0.83						Phimosis/redundant prepuce
F71	1.99	1.59 – 2.49	1.45	0.73						Conjunctivitis allergic
A12	3.11	2.62 – 3.69	3.42	1.13						Allergy

1. significant (p ≤0.01) influence of gender; 2. significant (p ≤0.01) influence of age; # OR could not be calculated; ***Italics**: Overall model not significant*

Table 3. Significantly (p ≤0.001) associated comorbidity in children diagnosed with only asthma (As) and at least three year follow-up versus controls (non-atopic children) (n=15,774)

ICPC	OR	95% CI	Prevalence		OR sex		OR age			Description ICPC codes
			As	No As	boy	girl	0-6	7-12	13-18	
Skin-related diseases and symptoms										
S98	2.10	1.61 – 2.73	2.21	1.07						Urtiacaria
Airway-related diseases and symptoms										
R05	2.14	1.86 – 2.46	7.99	3.93						Cough
R77	2.34	1.54 – 3.56	0.94	0.41						Laryngitis/tracheitis acute
R74	2.35	2.09 – 2.64	12.34	5.78						Upper respiratory infection
R81	4.04	3.03 – 5.37	2.97	0.76						Pneumonia
R78	4.80	3.78 – 6.11	4.79	1.05			3.74	5.63	8.09	Acute bronchitis/bronchiolitis [2]
R91	5.66	3.14–10.23	0.93	0.16						Chronic bronchitis
R02	7.74	5.05–11.87	2.31	0.30						Shortness of breath/dyspnoea
R03	10.30	4.73–22.42	0.90	0.09						Wheezing
Ear-nose-throat-related diseases and symptoms										
H76	***0.86***	***0.40 – 1.85***	***0.15***	***0.18***	2.51	0.20				Foreign body in ear [1]
H01	1.45	1.16 – 1.81	2.46	1.71						Ear pain/earache
H71	1.52	1.32 – 1.76	6.44	4.4						Acute otitis media/myringitis
H70	1.60	1.22 – 2.08	1.79	1.13						Otitis externa
R75	1.90	1.32 – 2.75	1.05	0.56						Sinusitis acute/chronic
Gastro-intestinal-related diseases and symptoms										
D89	***0.76***	***0.37 – 1.57***	***0.16***	***0.22***	0.27	4.52				Inguinal hernia [1]
D01	1.40	1.16 – 1.69	3.32	2.40						Abdominal pain/cramps general
D06	1.43	1.15 – 1.77	2.59	1.83						Abdominal pain localized other
D12	1.44	1.22 – 1.70	4.43	3.12						Constipation
D73	1.60	1.25 – 2.05	2.10	1.33						Gastroenteritis, infection
D10	2.02	1.37 – 2.97	0.99	0.49						Vomiting
D99	2.70	1.52 – 4.79	0.55	0.20						Disease digestive system, other
Musculoskeletal										
L15	***1.11***	***0.90 – 1.37***	***2.42***	***2.18***			1.34	1.49	0.97	Knee symptom/complaint [1]
L12	***1.37***	***1.09 – 1.71***	***2.27***	***1.67***	1.00	2.13				Hand symptom/complaint [1]
L98	1.40	1.16 – 1.68	3.54	2.56						Acquired deformity of limb
L99	1.52	1.22 – 1.89	2.66	1.78						Musculoskeletal disease, other
L11	1.98	1.48 – 2.65	1.71	0.87						Wrist symptom/complaint
Miscellaneous										
P21	1.34	1.13 – 1.58	4.18	3.17						ADHD
A04	1.39	1.17 – 1.65	4.04	2.97						Weakness/tiredness general
N01	1.51	1.21 – 1.89	2.49	1.66						Headache
F70	1.72	1.31 – 2.27	1.78	1.04						Conjunctivitis infectious
T10	1.82	1.35 – 2.44	1.60	0.89						Growth delay
T83	2.09	1.41 – 3.10	0.98	0.47						Overweight
T82	2.47	1.50 – 4.05	0.68	0.28						Obesity
F71	2.55	1.85 – 3.49	1.72	0.68						Conjunctivitis allergic
A12	3.40	2.74 – 4.23	4.55	1.38						Allergy

1. significant (p ≤0.01) influence of gender; 2. significant (p ≤0.01) influence of age; # OR could not be calculated; ***Italics****: Overall model not significant*

Table 4. Significantly (p ≤0.001) associated comorbidity in children diagnosed with only allergic rhinitis (AR) and at least three year follow-up versus controls (non-atopic children) (n=13,670)

ICPC	OR	95% CI	Prevalence		OR sex		OR age			Description ICPC codes
			AR	No AR	boy	girl	0-6	7-12	13-18	
Skin-related diseases and symptoms										
A76	***0.86***	***0.47 – 1.60***	***0.28***	***0.32***			0.32	0.64	4.51	Viral exanthem other
S03	1.26	1.10 – 1.43	7.65	6.20						Warts
S74	1.39	1.15 – 1.68	3.85	2.79						Dermatophytosis
S82	1.39	1.15 – 1.67	3.99	2.91						Naevus/mole
S84	1.71	1.35 – 2.15	2.87	1.71						Impetigo
S98	1.71	1.31 – 2.23	2.15	1.27						Urticaria
S86	1.86	1.38 – 2.53	1.76	0.95						Dermatitis seborrheic
S02	2.21	1.44 – 3.38	0.99	0.45						Pruritus
Airway-related diseases and symptoms										
R05	1.89	1.58 – 2.25	5.24	2.85						Cough
R74	1.92	1.66 – 2.23	8.00	4.35						Upper respiratory infection acute
R78	2.32	1.60 – 3.37	1.35	0.59						Acute bronchitis/bronchiolitis
R02	2.67	1.74 – 4.11	1.13	0.42						Shortness of breath/dyspnoe
R80	3.89	1.79 – 8.47	0.45	0.12						Influenza
R03	4.30	1.89 – 9.80	0.44	0.10						Wheezing
Ear-nose-throat-related diseases and symptoms										
R21	1.48	1.20 – 1.84	3.13	2.14						Throat symptom/complaint
H01	1.87	1.36 – 2.56	1.62	0.88						Ear pain/earache
R90	1.92	1.34 – 2.74	1.30	0.69			3.22	2.80	1.04	Hypertrophy tonsils/adenoids [2]
R75	1.95	1.45 – 2.63	1.89	0.98						Sinusitis acute/chronic
R08	2.62	1.72 – 4.00	1.14	0.44						Nose symptom/complaint other
R07	3.93	2.57 – 6.01	1.54	0.40						Sneezing/nasal congestion
Gastro-intestinal-related diseases and symptoms										
D12	1.50	1.23 – 1.82	3.79	2.57						Constipation
D06	1.76	1.39 – 2.22	2.90	1.67						Abdominal pain localized other
D73	1.96	1.42 – 2.71	1.59	0.82	1.29	3.39				Gastroenteritis presumed infection [1]
Musculoskeletal										
L98	1.36	1.15 – 1.62	4.54	3.37						Acquired deformity of limb
L17	1.42	1.19 – 1.70	4.40	3.15						Foot/toe symptom/complaint
L13	2.80	1.66 – 4.74	0.78	0.28						Hip symptom/complaint
Miscellaneous										
N19	***1.18***	***0.85 – 1.65***	***1.17***	***0.99***	0.89	2.43				Speech disorder
N01	1.45	1.18 – 1.78	3.29	2.30						Headache
P24	1.45	1.18 – 1.78	3.37	2.37						Specific learning problem
A04	1.58	1.35 – 1.85	6.10	3.96						Weakness/tiredness general
F70	1.73	1.28 – 2.32	1.76	1.02						Conjunctivitis infectious
S12	1.92	1.40 – 2.63	1.67	0.88						Insect bite/sting
F72	1.95	1.36 – 2.79	1.27	0.66	1.21	3.29				Blepharitis/stye/chalazion [1]
A12	4.02	3.15 – 5.13	4.70	1.21						Allergy
F71	5.44	4.08 – 7.25	4.29	0.82						Conjunctivitis allergic

1. significant (p ≤0.01) influence of gender; 2. significant (p ≤0.01) influence of age; # OR could not be calculated; ***Italics****: Overall model not significant*

Table 5. Significantly (p≤0.001) associated comorbidity in children diagnosed with Atopic Triad (AT) and at least three year follow-up versus controls (non-atopic children) (n= 1,118)

ICPC	OR	95% CI			Prevalence		Description ICPC codes
					A. triad	No A. triad	
R05	2.42	1.43	-	4.10	8.59	3.76	Cough
L17	3.25	1.63	-	6.50	6.08	1.97	Foot/toe symptom/complaint
R74	3.75	2.33	-	6.04	14.13	4.29	Upper respiratory infection acute
F71	6.79	2.35	-	19.60	4.65	0.72	Conjunctivitis allergic
A12	17.83	7.15	-	44.43	13.77	0.89	Allergy

Appendix 1

ICPC codes	Description
A03	Fever
A04	Weakness/tiredness general
A12	Allergic reaction
A15	Excessive crying infant
A16	Irritable infant
A70	Tuberculosis
A71	Measles
A72	Chickenpox
A73	Malaria
A74	Rubella
A75	Infectious mononucleosis
A76	Viral exanthem other
A77	Viral disease other/NOS
A78	Infectious disease other/NOS
A79	Malignancy NOS
A84	Poisoning by medical agent
A85	Adverse effect medical agent
A86	Toxic effect non-medicinal substance
A87	Complication of medical treatment
A88	Adverse effect physical factor
A90	Congenital anomaly OS/multiple
A92	Allergy/allergic reaction NOS
A93	Premature newborn
A94	Perinatal morbidity other
A95	Perinatal mortality
A96	Death
B02	Lymph gland(s) enlarged/painful
B70	Lymphadenitis acute
B71	Lymphadenitis non-specific
B72	Hodgkin's disease/lymphoma
B73	Leukaemia
B74	Malignant neoplasm blood other
B75	Benign/unspecified neoplasm blood
B78	Hereditary haemolytic anaemia
B79	Congen.anom. blood/lymph other
B80	Iron deficiency anaemia
B81	Anaemia, Vitamin B12/folate def.
B82	Anaemia other/unspecified
B83	Purpura/coagulation defect

B84	Unexplained abnormal white cells
B87	Splenomegaly
B90	HIV-infection/aids
D01	Abdominal pain/cramps general
D02	Abdominal pain epigastric
D03	Heartburn
D04	Rectal/anal pain
D05	Perianal itching
D06	Abdominal pain localized other
D07	Dyspepsia/indigestion
D08	Flatulence/gas/belching
D09	Nausea
D10	Vomiting
D11	Diarrhoea
D12	Constipation
D13	Jaundice
D22	Parasites
D70	Gastrointestinal infection
D71	Mumps
D72	Viral hepatitis
D73	Gastroenteritis presumed infection
D74	Malignant neoplasm stomach
D75	Malignant neoplasm colon/rectum
D76	Malignant neoplasm pancreas
D77	Malig. neoplasm digest other/NOS
D78	Neoplasm digest benign/uncertain
D79	Foreign body digestive system
D81	Congen. anomaly digestive system
D83	Mouth/tongue/lip disease
D84	Oesophagus disease
D85	Duodenal ulcer
D86	Peptic ulcer other
D87	Stomach function disorder
D88	Appendicitis
D89	Inguinal hernia
D90	Hiatus hernia
D91	Abdominal hernia other
D92	Diverticular disease
D93	Irritable bowel syndrome
D94	Chronic enteritis/ulcerative colitis
D95	Anal fissure/perianal abscess
D96	Worms/other parasites
D97	Liver disease NOS

D98	Cholecystitis/cholelithiasis
D99	Disease digestive system, other
F01	Eye pain
F02	Red eye
F03	Eye discharge
F04	Visual floaters/spots
F05	Visual disturbance other
F70	Conjunctivitis infectious
F71	Conjunctivitis allergic
F72	Blepharitis/stye/chalazion
F73	Eye infection/inflammation other
F74	Neoplasm of eye/adnexa
F75	Contusion/haemorrhage eye
F76	Foreign body in eye
F80	Blocked lacrimal duct of infant
F81	Congenital anomaly eye other
F82	Detached retina
F83	Retinopathy
F84	Macular degeneration
F85	Corneal ulcer
F86	Trachoma
F91	Refractive error
F92	Cataract
F93	Glaucoma
F94	Blindness
F95	Strabismus
F99	Eye/adnexa disease, other
H01	Ear pain/earache
H02	Hearing complaint
H03	Tinnitus, ringing/buzzing ear
H04	Ear discharge
H05	Bleeding ear
H70	Otitis externa
H71	Acute otitis media/myringitis
H72	Serous otitis media
H73	Eustachian salpingitis
H74	Chronic otitis media
H75	Neoplasm of ear
H76	Foreign body in ear
H77	Perforation ear drum
H80	Congenital anomaly of ear
H81	Excessive ear wax
H82	Vertiginous syndrome

H83	Otosclerosis
H86	Deafness
K01	Heart pain
K02	Pressure/tightness of heart
K04	Palpitations/awareness of heart
K05	Irregular heartbeat other
K07	Swollen ankles/oedema
K29	Cardiovascular sympt./complt. other
K70	Infection of circulatory system
K71	Rheumatic fever/heart disease
K72	Neoplasm cardiovascular
K73	Congenital anomaly cardiovascular
K74	Ischaemic heart disease w. angina
K75	Acute myocardial infarction
K76	Ischaemic heart disease w/o angina
K77	Heart failure
K78	Atrial fibrillation/flutter
K79	Paroxysmal tachycardia
K80	Cardiac arrhythmia NOS
K81	Heart/arterial murmur NOS
K82	Pulmonary heart disease
K83	Heart valve disease NOS
K84	Heart disease other
K85	Elevated blood pressure
K86	Hypertension uncomplicated
K87	Hypertension complicated
K88	Postural hypotension
K89	Transient cerebral ischaemia
K90	Stroke/cerebrovascular accident
K91	Cerebrovascular disease
K92	Atherosclerosis/PVD
K93	Pulmonary embolism
K94	Phlebitis/thrombophlebitis
K95	Varicose veins of leg
K96	Haemorrhoids
K99	Cardiovascular disease other
L01	Neck symptom/complain
L02	Back symptom/complaint
L03	Low back symptom/complaint
L04	Chest symptom/complaint
L05	Flank symptom/complaint
L06	Axilla symptom/complaint
L07	Jaw symptom/complaint

L08	Shoulder symptom/complaint
L09	Arm symptom/complaint
L10	Elbow symptom/complaint
L11	Wrist symptom/complaint
L12	Hand/finger symptom/complaint
L13	Hip symptom/complaint
L14	Leg/thigh symptom/complaint
L15	Knee symptom/complaint
L16	Ankle symptom/complaint
L17	Foot/toe symptom/complaint
L18	Muscle pain
L19	Muscle symptom/complaint NOS
L20	Joint symptom/complaint NOS
L70	Infections musculoskeletal system
L71	Malignant neoplasm musculoskeletal
L82	Congenital anomaly musculoskeletal
L83	Neck syndrome
L84	Back syndrome w/o radiating pain
L85	Acquired deformity of spine
L86	Back syndrome with radiating pain
L87	Bursitis/tendinitis/synovitis NOS
L88	Rheumatoid/seropositive arthritis
L92	Shoulder syndrome
L93	Tennis elbow
L94	Osteochondrosis
L95	Osteoporosis
L97	Neoplasm benign/unspec musculo.
L98	Acquired deformity of limb
L99	Musculoskeletal disease, other
N01	Headache
N02	Tension headache
N03	Pain face
N04	Restless legs
N05	Tingling fingers/feet/toes
N06	Sensation disturbance other
N07	Convulsion/seizure
N16	Disturbance of smell/taste
N17	Vertigo/dizziness
N18	Paralysis/weakness
N19	Speech disorder
N70	Poliomyelitis
N71	Meningitis/encephalitis
N72	Tetanus

N73	Neurological infection other
N74	Malignant neoplasm nervous system
N75	Benign neoplasm nervous system
N76	Neoplasm nervous system unspec.
N85	Congenital anomaly neurological
N86	Multiple sclerosis
N87	Parkinsonism
N88	Epilepsy
N89	Migraine
N90	Cluster headache
N91	Facial paralysis/bell's palsy
N92	Trigeminal neuralgia
N93	Carpal tunnel syndrome
N94	Peripheral neuritis/neuropathy
N99	Neurological disease, other
P01	Feeling anxious/nervous/tense
P02	Acute stress reaction
P03	Feeling depressed
P04	Feeling/behaving irritable/angry
P06	Sleep disturbance
P10	Stammering/stuttering/tic
P11	Eating problem in child
P12	Bedwetting/enuresis
P13	Encopresis/bowel training problem
P20	Memory disturbance
P21	ADHD
P22	Child behaviour symptom/complaint
P23	Adolescent behav. Symptom/complt.
P24	Specific learning problem
P71	Organic psychosis other
P72	Schizophrenia
P73	Affective psychosis
P74	Anxiety disorder/anxiety state
P75	Somatization disorder
P76	Depressive disorder
P78	Neuraesthenia/surmenage
P79	Phobia/compulsive disorder
P85	Mental retardation
P98	Psychosis NOS/other
P99	Psychological disorders, other
R01	Pain respiratory system
R02	Shortness of breath/dyspnoea
R03	Wheezing

R04	Breathing problem, other
R05	Cough
R06	Nose bleed/epistaxis
R07	Sneezing/nasal congestion
R08	Nose symptom/complaint other
R09	Sinus symptom/complaint
R21	Throat symptom/complaint
R22	Tonsils symptom/complaint
R23	Voice symptom/complaint
R24	Haemoptysis
R25	Sputum/phlegm abnormal
R29	Respiratory symptom/complaint oth.
R70	Tuberculosis airways
R71	Whooping cough
R72	Strep throat
R73	Boil/abscess nose
R74	Upper respiratory infection acute
R75	Sinusitis acute/chronic
R76	Tonsillitis acute
R77	Laryngitis/tracheitis acute
R78	Acute bronchitis/bronchiolitis
R80	Influenza
R81	Pneumonia
R82	Pleurisy/pleural effusion
R83	Respiratory infection other
R84	Malignant neoplasm bronchus/lung
R85	Malinant neoplasm respiratory, other
R86	Benign neoplasm respiratory
R87	Foreign body nose/larynx/bronch
R89	Congenital anomaly respiratory
R90	Hypertrophy tonsils/adenoids
R91	Chronic bronchitis
R93	Pleural effusion
R95	Chronic obstructive pulmonary dis
R96	Asthma
R97	Allergic rhinitis
R98	Hyperventilation syndrome
R99	Respiratory disease other
S01	Pain/tenderness of skin
S02	Pruritus
S03	Warts
S04	Lump/swelling localized
S05	Lumps/swellings generalized

S06	Rash localized
S07	Rash generalized
S08	Skin colour change
S09	Infected finger/toe
S10	Boil/carbuncle
S11	Skin infection post-traumatic
S12	Insect bite/sting
S13	Animal/human bite
S14	Burn/scald
S15	Foreign body in skin
S20	Corn/callosity
S21	Skin texture symptom/complaint
S22	Nail symptom/complaint
S23	Hair loss/baldness
S24	Hair/scalp symptom/complaint
S70	Herpes zoster
S71	Herpes simplex
S72	Scabies/other acariasis
S73	Pediculosis/skin infestation other
S74	Dermatophytosis
S75	Moniliasis/candidiasis skin
S76	Skin infection other
S77	Malignant neoplasm of skin
S78	Lipoma
S79	Neoplasm skin benign/unspecified
S80	Solar keratosis/sunburn
S81	Haemangioma/lymphangioma
S82	Naevus/mole
S83	Congenital skin anomaly other
S84	Impetigo
S85	Pilonidal cyst/fistula
S86	Dermatitis seborrhoeic
S87	Dermatitis/atopic eczema
S89	Diaper rash
S90	Pityriasis rosea
S91	Psoriasis
S92	Sweat gland disease
S93	Sebaceous cyst
S94	Ingrowing nail
S95	Molluscum contagiosum
S96	Acne
S97	Chronic ulcer skin
S98	Urticaria

S99	Skin disease, other
T01	Excessive thirst
T02	Excessive appetite
T03	Loss of appetite
T04	Feeding problem of infant/child
T05	Feeding problem of adult
T06	Anorexia nervosa
T07	Weight gain
T08	Weight loss
T10	Growth delay
T11	Dehydration
T15	Tumor thyroid
T70	Endocrine infection
T71	Malignant neoplasm thyroid
T72	Benign neoplasm thyroid
T73	Neoplasm endocrine oth/unspecified
T78	Thyroglossal duct/cys
T80	Congenital anom endocrine/metab
T81	Goitre
T82	Obesity
T83	Overweight
T85	Hyperthyroidism/thyrotoxicosis
T86	Hypothyroidism/myxoedema
T87	Hypoglycaemia
T88	Renal glycosuria
T89	Diabetes insulin dependent
T90	Diabetes non-insulin dependent
T91	Vitamin/nutritional deficiency
T92	Gout
T93	Lipid disorder
T99	Endocrine/metab/nutrit. dis. other
U01	Dysuria/painful urination
U02	Urinary frequency/urgency
U04	Incontinence urine
U05	Urination problems other
U06	Haematuria
U07	Urine symptom/complaint other
U13	Bladder symptom/complaint other
U14	Kidney symptom/complaint
U70	Pyelonephritis/pyelitis
U71	Cystitis/urinary infection other
U72	Urethritis
U75	Malignant neoplasm of kidney

U76	Malignant neoplasm of bladder
U77	Malignant neoplasm urinary other
U78	Benign neoplasm urinary tract
U79	Neoplasm urinary tract NOS
U85	Congenital anomaly urinary tract
U88	Glomerulonephritis/nephrosis
U90	Orthostatic albumin/proteinuria
U95	Urinary calculus
U98	Abnormal urine test NOS
U99	Urinary disease, other
X83	Congenital anomaly genital female
X84	Vaginitis/vulvitis NOS
X85	Cervical disease NOS
X99	Genital disease female, other
Y74	Orchitis/epididymitis
Y75	Balanitis
Y81	Phimosis/redundant prepuce
Y82	Hypospadias
Y83	Undescended testicle
Y84	Congenital genl anomaly (m) other
Y99	Genital disease male, other

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Risks for comorbidity in atopic children: an observational study in Dutch general practices

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Abstract

Objective: This study aimed to investigate both atopic and non-atopic comorbid symptoms and diseases in children with physician-diagnosed atopic disorders (atopic eczema, asthma and allergic rhinitis).

Methods: All children aged 0-18 years listed in a nationwide primary care database (NIVEL-PCD) with routinely collected health care data in 2014 were selected. Atopic children were matched on age and gender with non-atopic controls within the same general practice. A total of 404 ICPC codes were examined. Logistic regression analyses were performed to examine the associations between the presence of atopic disorders and (non-) atopic symptoms and diseases by calculating odds ratios (OR).

Results: Having one of the atopic disorder significantly increased the risk of having other atopic-related symptoms, even if the child was not registered as having the related atopic disorder. Regarding non-atopic comorbidity, children with atopic eczema (n: 15,530) were at significantly increased risk for (infectious) skin diseases (OR: 1.2-3.4). Airway symptoms or (infectious) diseases (OR: 2.1-10.3) were observed significantly more frequently in children with asthma (n: 7,887). Children with allergic rhinitis (n: 6,835) had a significantly distinctive risk of ear-nose-throat related symptoms and diseases (OR: 1.5-3.9). Neither age nor gender explained these increased risks.

Conclusion: General practitioners are not always fully aware of relevant atopic and non-atopic comorbidity. In children known to have at least one atopic disorder, specific attention is required to avoid possible insufficient treatment and unnecessary loss of quality of life.

Keywords: Atopic dermatitis, Asthma, Allergic rhinitis, General practice, Comorbidity, Epidemiology

Strengths and limitations of this study

- The present study used an extensive and representative general practice database.
- The large number of children gives the study substantial power and generalizability.
- A total of 404 ICPC codes were examined.
- A limitation regarding this type of explorative study is the unavoidable multiple testing.

Introduction

Atopic disorders represent an important health problem in general practice. Acute upper airway infections, middle ear infections, warts, asthma, and atopic eczema represent the five most prevalent pediatric diseases diagnosed in general practice (1); allergic rhinitis is on the 12th place in this list. However, limited data are available on the co-morbidities of atopic children in primary care (2). In the present study we refer to atopy as a (genetic) predisposition toward developing certain allergic hypersensitivity. Therefore the clinical manifestation of atopy is allergy. However, not all allergies are based on atopy. In this study the word 'atopic' refers to this genetically mediated predisposition, which did result in the clinical diagnosis by a GP of atopic eczema, asthma and allergic rhinitis.

Associations have been shown between atopic disorders and other diseases in children, but in different clinical settings (e.g. birth cohorts, hospitals, or pediatric clinics). Demonstrated interrelations exist with (among others) diabetes (3-5), ADHD (6-8), autism (9-11), and obesity (12-14). According to other studies, the presence of some comorbidities may even influence the course of atopic disorders. For example, acute upper airway infections, especially in early childhood, are related to atopic disorders later in life (15, 16). Acute viral 'non-respiratory syncytial virus' bronchiolitis in infants aged <6 months is linked with an increased risk of developing asthma (17). The developing immune system of a child might be affected by frequent or severe infections of the middle ear, resulting in increased risk for asthma and atopic eczema (18). On the other hand, otitis media with effusion is associated with allergic rhinitis (19-21). The quality of life of an atopic child can be significantly improved by providing sufficient treatment.

To our knowledge no study has investigated the complete range of potential comorbidities in atopic children in a general practice setting. A relevant question could be: Are atopic children at increased risk for non-atopic symptoms or diseases? Awareness by GPs of these risks may reduce the probability that relevant comorbidity is

not diagnosed. To study possible associations between atopic disorders and 404 different symptoms and diseases, an extensive and representative nationwide general practice database is explored using a cross-sectional design. The design of this study allows new hypotheses to be generated, providing valuable input for future research.

Methods

Study population

All non-institutionalized residents in the Netherlands are registered in a general practice, even if they do not visit the GP on a regular basis. The Netherlands Institute for Health Services Research-Primary Care Database (NIVEL-PCD) is based on routinely recorded data in electronic health records (EHRs) of all listed patients in the participating practices. In 2014, about 500 general practices participated, including data of about 1,700,000 patients (www.nivel.nl/en/dossier/nivel-primary-care-database), which is over 10% of the total Dutch population. EHR data include a variety of information regarding type of consultation, morbidity, and prescriptions. Data available for 2014 are representative for the Dutch population (22).

ICPC and episodes of care

Primary care physicians (gatekeepers for the Dutch healthcare system) recorded morbidity using the International Classification of Primary Care (ICPC), a classification method for primary care that is accepted by the WHO (23). It has been translated in 22 languages and is now widely used for the routine collection of data on episodes of care, but also in encounter studies (24). Routinely collected general practice computer data, aggregated into large databases, is used for epidemiological research(25). Hippisley-Cox et al. illustrates how routine clinical data, in selected high recording practices (this selection criteria was also applied in the present study), are now reaching reasonable levels of accuracy and completeness for a range of key variables (26). According to Britt et al., morbidity data actively collected by GPs provide a reliable overview of morbidity managed in general practice (27).

Dutch GPs cluster relevant consultations, prescriptions and referrals, in ICPC classified “episodes of care”. An episode of care is a health problem or disease from its first presentation to the GP to the last presentation for

the same problem. Atopic disorders are labeled with ICPC codes: S87 (atopic eczema), R96 (asthma) and R97 (allergic rhinitis). ICPC-codes specific for food-allergies are not available.

For the present study, only morbidity data from EHRs of general practices with sufficient data quality were used that fulfilled the following criteria: i) at least 500 listed patients (standard practice: 2,350 patients), ii) complete morbidity registration (defined as ≥ 46 weeks/year), and iii) sufficient ICPC coding of diagnostic information (defined as ≥ 70% of the recorded disease episodes labeled with an ICPC code; average ICPC coding in a Dutch general practice is >95%). The following descriptive data were routinely collected: period in which the individual child was registered in the general practice, the unique code of the GP practice, the child's gender, and year and quarter of birth.

Atopic children

For each child (0-18 years), a minimum follow-up of 3 years was required (e.g. data had to be available for 2012-2014) for the present study to reduce the risk of registration bias. For this reason, only data for children aged ≥ 2 years are presented here. In the Netherlands, GPs see about 72% of their patient population at least once a year (28). We considered a 3-year follow-up period to be sufficient time for a GP to diagnose a child with (atopic) disorders. Furthermore, in order not to miss any relevant atopic diagnosis, when available, the EHRs from 2002-2014 were examined. Since GPs inevitably work with probability diagnoses, there is a risk of misclassification. To select cases with a higher probability of a clinically relevant disorder, ICPC codes and their related episodes of care can be corrected. In practice, an atopic episode of care was maintained if (between 2002-2014) the child had at least contacted the GP twice in that episode of care and had received at least two relevant prescriptions. If the child did not meet these criteria, the child was considered not to have that atopic disorder (29) and was excluded from the study (this child could not be used as a control patient, to make sure that controls did not have any atopic disorder). If a child was diagnosed with an atopic disorder for the first

time during 2014, the child was considered to have the atopic disorder that whole year. In the present study, the atopic diagnosis was based on the physician's assessment and was considered to be a chronic problem.

Atopic triad

A recent meta-analysis supported the hypothesis that there might be a fourth distinct group of children with all three atopic disorders, in contrast to the traditional classification of children with asthma *or* allergic rhinitis *or* atopic eczema (30). To learn more about this potentially unique group of children, 'atopic triad' episodes were developed for research purposes. These episodes were only created when a child was diagnosed with all three atopic disorders, based on available data from EHRs in the period 2002-2014.

Symptoms and diseases studied

After establishing which child had an atopic disorder (see above), a child was considered prevalent for a specific symptom or disease if the child had at least one active episode of care for that symptom or disorder between January and December of 2014. All ICPC codes that describe a symptom or a disease were examined, with the exception of trauma-related ICPC codes, ICPC codes not relevant for children (e.g. presbyacusis), pregnancy, childbearing, family planning, sexual transmitted diseases and social problems, leaving 404 different ICPC codes. Furthermore, since different classifications are used for eczema, there is a risk of misclassification. The ICPC system distinguishes the codes S86 (seborrheic dermatitis), S87 (atopic eczema), S88 (contact dermatitis / eczema another) and S89 (diaper rash). Since clinical differentiation can be very difficult, especially between S87 and S88, S88 was excluded from our analyses, to get more reliable results for 'true' atopic eczema (S87).

Design

An observational study design was used in which cases with one atopic disorder were matched with controls without any atopic disorder. For each atopic child, one matched control patient was selected (not diagnosed with an atopic disorder) within the same general practice, based on age and gender in 2014. Controls were only

matched if a 100%- match on age, gender and general practice with an atopic child was determined. Odds ratios (ORs) were calculated for children that solely had atopic eczema, asthma, or allergic rhinitis and therefore no other atopic comorbidity. Appendix 1 presents a list of all the ICPC codes that were examined. A 1:1 ratio was chosen to be able to include as many pairs of cases and controls as possible, allowing the results to carry more weight and making the conclusions more generalizable to future populations. In the present study, a 1:2 ratio would have resulted in dropping over 40% of the cases.

Statistical analyses

Logistic regression analysis was performed to study associations between the presence of atopic disorders and (non-) atopic comorbid symptoms and diseases in children. Similarly, associations between atopic triad and the above-mentioned comorbid symptoms and diseases were examined. Due to multiple testing, only associations with $p \leq 0.001$ were considered statistically significant. All associations were tested for the modifying effects of age and gender. In case of a significant effect ($p \leq 0.01$), associations were also presented for subgroups for age (2-6 vs. 7-12 vs. 13-18 years) and gender (boy vs. girl). Finally, due to the hierarchical structure of the data (patients registered in general practices), a multi-level logistic regression analysis was performed to test whether clustering effects influenced our findings. All analyses were conducted in Stata 13 and Excel 2010. Prevalence rates are presented in percentages.

Ethical approval

Dutch law allows the use of EHRs for research purposes under certain conditions. According to this legislation, it is not necessary to obtain informed consent from patients or approval from a medical ethics committee for this type of observational study that contains no directly identifiable data (Dutch Civil Law, Article 7: 458). Therefore, no waiver of ethical approval was obtained from an Institutional Review Board (IRB) or ethics committee. The authors had no access to any identifying information at any moment during the analysis of the data.

Results

General characteristics (Table 1)

409,312 children were identified in the NIVEL-PCD in 2014, initially including 70,494 atopic children with at least one atopic disorder. However, for an atopic child to be included in this study, one matched control patient had to be available (i.e. a child without an atopic disorder). There were 21,285 children with atopic eczema identified, of which 15,530 children had atopic eczema without another atopic disorder. For asthmatic children, 13,196 children were identified, of which 7,887 had asthma only and no other atopic disorders. In children with AR, 11,483 were identified of which 6,835 had AR without another atopic disorder. Finally, 559 children had all three atopic disorders. All the children in these groups were selected from 316 different general practices participating in NIVEL-PCD. Clustering effects did not influence our findings.

Atopic eczema (Table 2)

A substantial part of the significantly related comorbidity for children with atopic eczema concerns skin diseases such as (among others): warts (OR 1.2), localized rash (OR 1.5), pruritus (OR 1.7), impetigo (OR1.7), dermatophytosis (OR 1.8), urticaria (OR 1.8), molluscum contagiosum (OR 1.9) and psoriasis (OR 3.4). Otitis externa (OR 1.6) and blepharitis (OR 1.5) were also significantly associated with atopic eczema. The symptom diagnosis of wheezing (OR 2.0), that could be attributed to asthma, is noteworthy since these children were not diagnosed or coded in the EHRs with asthma. The same applies to symptoms associated with allergic rhinoconjunctivitis, such as sneezing/nasal congestion (OR 2.0) and allergic conjunctivitis (OR 2.0). Older children with atopic eczema were at increased risk to develop a localized rash (OR 1.3 - > 2.3) and impetigo (OR 1.5 - >2.7). Compared to boys, girls had an increased risk, to develop a localized rash (OR 2.0 vs. 1.1), breathing problems (OR 3.6 vs. 0.9) and stomach function disorder (OR 3.3 vs. 0.7).

Asthma (Table 3)

Noteworthy are asthma-related symptoms that were diagnosed separately, such as shortness of breath/dyspnea (OR 7.7) and wheezing (OR 10.3). Furthermore, asthmatic children consulted their GP more frequently for airway-related infections such as: acute laryngitis/tracheitis (OR 2.3), acute upper respiratory infection (OR 2.4), pneumonia (OR 4.0) and acute bronchitis (OR 4.8). In children with asthma, there seems to be a higher risk for the development of gastrointestinal symptoms, e.g.: general abdominal pain/cramps (OR 1.4), localized abdominal pain (OR 1.4), constipation (OR 1.4) and vomiting (OR 2.0). Acute bronchitis (OR 3.7 - >8.1) was diagnosed more often in older children. Inguinal hernias were seen more frequently in girls than in boys (OR 4.5 vs. 0.3).

Allergic rhinitis (Table 4)

Children with allergic rhinitis visit their GPs more frequently for ear-nose-throat related symptoms and diseases. Among others, the following were diagnosed more often: throat symptom/complaint (OR 1.5), ear pain/earache (OR 1.9), hypertrophy tonsils/adenoids (OR 1.9), acute/chronic sinusitis (OR 2.0), nose symptom (OR 2.6) and sneezing/nasal congestion (OR 3.9). Furthermore, symptoms associated with atopic eczema (pruritus; OR 2.2) and asthma [shortness of breath/dyspnea (OR 2.7) and wheezing (OR 4.3)] were seen more frequently. Also, when a child was diagnosed with allergic rhinitis, there was a substantial risk for the development of gastrointestinal symptoms [constipation (OR 1.5) and localized abdominal pain (OR 1.8)]. Hypertrophy of the tonsils was diagnosed less frequently when children got older (OR 3.2 - >1.0). On the other hand, children were more frequently diagnosed with a viral exanthema when they became older (OR 0.3 - >4.5). A presumed gastro-intestinal infection (OR 3.4 vs. 1.3), speech disorder (OR 2.4 vs. 0.9) and blepharitis/style/chalazion (OR 3.3 vs. 1.2) were diagnosed more frequently in girls with allergic rhinitis.

Atopic triad (Table 5)

Having all three atopic disorders is relatively rare, with only a few symptoms and diseases being significantly related. The risk for developing an 'allergy', that the GP considers relevant to register in the EHR can be

considered high (OR 17.8). Allergic conjunctivitis (OR 6.8) is also frequently seen in children with all three atopic disorders.

Discussion

Main findings

The present study used an extensive and representative general practice database (22). The large number of children gives the study substantial power and generalizability. This could also allow evaluation of possible links between atopic disorders and rare childhood diseases. This study showed that atopic children have an increased risk for the development of both atopic and non-atopic diseases and symptoms. Children diagnosed with one atopic disorder were frequently diagnosed by their GP with symptoms associated with one of the (other) atopic disorder(s). This suggests that GPs are not always fully aware of relevant atopic comorbidity, or at least do not label it correctly. Two examples support this hypothesis. First of all, a child diagnosed with atopic eczema is also diagnosed with pruritus, suggesting possible misclassification. Secondly, a child with atopic eczema that presents with 'wheeze' or 'dyspnea' is at a higher risk for the development of asthma compared to a child without atopic eczema. A GP should be aware of this increased risk, since it could result in insufficient treatment of a child. However, a GP could also use symptom-related ICPC-codes deliberately when the purpose is to record a provisional diagnosis (e.g. wheeze as the provisional diagnosis of asthma). Regarding non-atopic co-morbidity, strong associations were found between the atopic disorder and diseases and symptoms related to the same organ system. For example, children with atopic eczema are at increased risk for the development of other skin diseases, asthmatic children are at risk of other airway diseases, and children with allergic rhinitis are at risk of ear-nose-throat-related symptoms and diseases. Gastro-intestinal and musculoskeletal diseases and symptoms were also seen more frequently in atopic children. When exploring possible interactions of age and gender in children with one atopic disorders, no clear patterns arose.

Interpretation of findings in relation to previously published work

Children with atopic eczema had an increased risk of developing infectious skin diseases such as warts, impetigo, dermatophytosis and molluscum contagiosum. The common etiology could be the barrier dysfunction of the skin in children with atopic eczema. This barrier dysfunction is also seen in psoriasis, a disease that, according to the present study, is associated with atopic eczema (OR 3.4). They share some common pathological backgrounds such as barrier dysfunction and enhanced IL-22 expression (31). Although the clinical pictures of these two diseases can be very different, the observed association could also suggests misclassification among these two chronic skin diseases that are often confused for one another. Otitis externa and blepharitis both had significant ORs. These disorders could in fact be an expression of atopic eczema.

Children with asthma seem to have consulted their GP more frequently for airway-related infections such as acute laryngitis/tracheitis, acute upper respiratory infection, pneumonia and bronchitis. This is in agreement with another primary healthcare study (2). An explanation for this could be that airway infections increase asthma symptoms or vice versa, that asthma resulted in increased susceptibility for infection, which increased their motivation to visit the GP. Furthermore, the awareness of parents is likely to be increased when a child suffers from asthma, since such an infection could predispose for an asthma exacerbation.

Children with allergic rhinitis consulted their GPs more frequently for ear-nose-throat-related symptoms and diseases. However, even more striking are the asthma-related symptoms. Both shortness of breath (OR 2.7) and wheeze (OR 4.3) were frequently seen in children with allergic rhinitis. There is strong evidence that allergic rhinitis has an adverse impact on asthma severity (32). Because allergic rhinitis can provoke asthma symptoms, allergic rhinitis symptoms should be taken more seriously by GPs to reduce insufficient treatment.

Gastrointestinal-related symptoms are also frequently diagnosed by GPs in atopic children. This is in accordance with a study in adults in a primary care setting (33). These symptoms could be related to IgE-mediated food allergies or in rare cases even to eosinophilic esophagitis that are associated with atopic disorders (34); however, in children, abdominal pains can also be a general expression of not feeling well.

Unfortunately, the ICPC classification system does not cover the above-mentioned gastrointestinal diseases with unique code and, therefore, gastrointestinal-related symptoms might have been used by the GP to label these diseases.

Some associations described in the literature were not confirmed in the present study, e.g. serous otitis media in patients with allergic rhinitis (19, 21), and inflammatory bowel disease (35, 36), leukemia (37, 38) and diabetes (39, 40) in atopic patients. The prevalences of some of these disorders are low and a cross-sectional design (as used in the present study), might not have enough power to prove these relationships.

Strengths and limitations of this study

Using general practice databases (by means of a cross-sectional design) also has its limitations. First of all, a limitation for the present study is the GP's choice for ICPC coding of an episode of care. For example, a child with a wheeze could either be labeled as 'asthma' (R96) or labeled as 'wheeze' (R03). This could result in both overestimation or underestimation of asthma. To decrease this risk of overestimation regarding atopic disorders, some episodes were corrected in order to increase the clinical relevance of the atopic disorder of interest. However, the risk of underestimation was not tackled, since too many assumptions need to be made. The second limitation regarding this type of explorative study is the unavoidable multiple testing. Although conservative p-values were used, type 1 errors cannot be avoided. In this study, some suggested associations might in fact reflect these type 1 errors. Thirdly, because data on socioeconomic status, tobacco smoke exposure and other lifestyle-related risk factors are not recorded in NIVEL-PCD, we cannot rule out the effect of these risk factors on the observed relations. However, since the children with atopic disorders were matched with controls within the same general practice, all children are most likely living in the same neighborhoods and therefore the effect of most of the earlier mentioned risk factors is expected to be small. Fourthly, atopic children might visit the GP more frequently than non-atopic children. And although this may be more representative of parental fears, rather than an indication of morbidity, it can result in more detected

morbidity in atopic children and could partly explain some of the associations found. In future research, the number of consultations might need to be taken into account in the analyses. Fifth of all, in the present study the diagnosis are based on a physician's assessment and not on confirmed sensitization pattern for allergens. According to the Dutch medical guideline for eczema (41), GPs are not advised to determine these sensitization patterns, since this doesn't have any clinical consequences. Although atopy is clearly associated with atopic eczema, the role of IgE sensitization in atopic eczema still needs further study (42). Also in children with AR, sensitization patterns don't have added value if the medical history clearly suggests e.g. a pollen allergy (43). Only when the cause of the rhinitis is uncertain, the determination of sensitization patterns adds value. The medical guidelines for asthma in children advises to determine sensitization patterns (44), since it can help diagnose allergic asthma (45) and because it could have clinical consequences. Finally, it is important to acknowledge the uncertainty of general practitioners to make a diagnosis of asthma or AR in young children (e.g. under the age of six).

Implications for future research and practice

First of all, could comorbidity data be used to create proxies that could support GPs in identifying atopic children that are not labeled as such? For example, could comorbidity data be incorporated in 'clinical decision support systems' to improve early diagnosis of both atopic and non-atopic disorders. Second of all, how is the quality of life of these atopic children affected by the associated comorbidity? GPs should be aware of the described associations when treating an atopic child, since the quality of life of an atopic child could be improved by paying more attention to diagnosis and treatment of these related disorders. Furthermore, one must be aware that atopic disorders and associated symptoms and diseases may well persist into adulthood.

Conclusions

The present study shows that atopic children have an increased risk of clinically relevant comorbidity, both atopic and non-atopic. General practitioners may not always be fully aware of relevant atopic and non-atopic

comorbidity. In children known to have at least one atopic disorder, specific attention is required to avoid possible insufficient treatment and unnecessary loss of quality of life.

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Competing Interests

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Contributions

Study conception and design: DP, MN, JK, PB, AB

Acquisition of data: DP, MN

Analysis and interpretation of data: DP, MN

Drafting of manuscript: DP

Critical revision: MN, JK, PB, AB

Guarantor: MN, AB

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Data sharing statement

Data will be available from the repository of Data Archiving and Networked Services (DANS; www.dans.knaw.nl).

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Figure legends

Table 1. General characteristics of the total study population

Table 2. Significantly (p ≤0.001) associated comorbidity in children diagnosed with only atopic eczema (Ec) and at least three year follow-up versus controls (non-atopic children) (n=31,060)

Table 3. Significantly (p ≤0.001) associated comorbidity in children diagnosed with only asthma (As) and at least three year follow-up versus controls (non-atopic children) (n=15,774)

Table 4. Significantly (p ≤0.001) associated comorbidity in children diagnosed with only allergic rhinitis (AR) and at least three year follow-up versus controls (non-atopic children) (n=13,670)

Table 5. Significantly (p≤0.001) associated comorbidity in children diagnosed with Atopic Triad (AT) and at least three year follow-up versus controls (non-atopic children) (n= 1,118)

Table 1. General characteristics of the total study population

	n	Age in years (SD)	Male
Only atopic eczema	15,530	8.7 (4.5)	48.2%
Only asthma	7,887	10.7 (4.5)	59.0%
Only allergic rhinitis	6,835	13.5 (3.5)	57.8%
Atopic triad	559	11.6 (4.0)	61.4%

NB. Children in the first three groups had **only one** of the three atopic disorders: i.e. they had the disorder mentioned, but none of the **other** disorders, whereas children in the Atopic triad group had **all three** disorders.

Table 2. Significantly (p ≤0.001) associated comorbidity in children diagnosed with only atopic eczema (Ec) and at least three year follow-up versus controls (non-atopic children) (n=31,060).

ICPC	Description ICPC codes	OR	95% CI	Prevalence		OR sex		OR age		
				Ec	No Ec	boy	girl	2-6	7-12	13-18
Skin-related diseases and symptoms										
S03	Warts	1.15	1.06 – 1.26	7.85	6.88					
S06	Rash localized [1, 2]	1.51	1.25 – 1.82	1.76	1.18	1.11	2.02	1.29	1.54	2.30
S99	Skin disease, other	1.57	1.24 – 2.00	1.12	0.71					
S02	Pruritus	1.71	1.31 – 2.23	0.97	0.57					
S84	Impetigo [2]	1.71	1.54 – 1.90	6.23	3.75			1.54	1.78	2.72
S04	Lump/swelling localized	1.76	1.30 – 2.39	0.73	0.42					
S74	Dermatophytosis	1.76	1.54 – 2.00	4.20	2.44					
S98	Urticaria	1.77	1.50 – 2.09	2.49	1.42					
S21	Skin texture symptom/complaint	1.89	1.49 – 2.40	1.26	0.67					
S95	Molluscum contagiosum	1.92	1.69 – 2.19	4.44	2.38					
S86	Dermatitis seborrhoeic	2.31	1.87 – 2.84	1.89	0.83					
S91	Psoriasis	3.36	2.23 – 5.06	0.64	0.19					
Airway-related diseases and symptoms										
R05	Cough	1.29	1.17 – 1.43	5.94	4.67					
R74	Upper respiratory infection acute	1.33	1.23 – 1.43	10.42	8.13					
R78	Acute bronchitis/bronchiolitis	1.49	1.22 – 1.80	1.66	1.13					
R04	Breathing problem, other [1]	***1.55***	***0.97 – 2.48***	***0.29***	***0.19***	0.91	3.58			
R03	Wheezing	1.95	1.30 – 2.92	0.45	0.23					
Ear-nose-throat-related diseases and symptoms										
H71	Acute otitis media/myringitis	1.20	1.09 – 1.31	7.46	6.35					
H72	Serous otitis media	1.40	1.21 – 1.62	2.92	2.11					
H01	Ear pain/earache	1.43	1.24 – 1.65	3.01	2.13					
H04	Ear discharge	1.47	1.17 – 1.86	1.13	0.77					
R21	Throat symptom/complaint	1.50	1.27 – 1.78	2.13	1.43					
H70	Otitis externa	1.56	1.27 – 1.90	1.58	1.02					
R07	Sneezing/nasal congestion	1.95	1.32 – 2.89	0.48	0.24					
Gastro-intestinal-related diseases and symptoms										
D01	Abdominal pain/cramps general	1.27	1.12 – 1.45	3.61	2.85					
D12	Constipation	1.32	1.19 – 1.47	5.29	4.07					
D87	Stomach function disorder [1]	***1.48***	***0.87 – 2.51***	***0.22***	***0.15***	0.69	3.29			
D99	Disease digestive system. other	2.28	1.51 – 3.44	0.48	0.21					
Musculoskeletal										
L17	Foot/toe symptom/complaint	1.30	1.15 – 1.48	3.50	2.71					
L98	Acquired deformity of limb	1.39	1.20 – 1.60	2.90	2.11					
Miscellaneous										
A04	Weakness/tiredness general	1.25	1.09 – 1.44	3.07	2.47					
S12	Insect bite / sting	1.41	1.19 – 1.66	2.24	1.60					
F72	Blepharitis/stye/chalazion [2]	1.53	1.22 – 1.93	1.20	0.79			0.96	2.79	1.76
F70	Conjunctivitis infectious	1.53	1.29 – 1.81	2.18	1.44					
Y81	Phimosis/redundant prepuce	1.83	1.47 – 2.72	1.49	0.83					
F71	Conjunctivitis allergic	1.99	1.59 – 2.49	1.45	0.73					
A12	Allergy	3.11	2.62 – 3.69	3.42	1.13					

1. significant (p ≤0.01) influence of gender; 2. significant (p ≤0.01) influence of age

***Italics**: Overall model not significant*

Table 3. Significantly (p ≤0.001) associated comorbidity in children diagnosed with only asthma (As) and at least three year follow-up versus controls (non-atopic children) (n=15,774)

ICPC	Description ICPC codes	OR	95% CI	Prevalence		OR sex		OR age		
				As	No As	boy	girl	2-6	7-12	13-18
Skin-related diseases and symptoms										
S98	Urtiacaria	2.10	1.61 – 2.73	2.21	1.07					
Airway-related diseases and symptoms										
R05	Cough	2.14	1.86 – 2.46	7.99	3.93					
R77	Laryngitis/tracheitis acute	2.34	1.54 – 3.56	0.94	0.41					
R74	Upper respiratory infection	2.35	2.09 – 2.64	12.34	5.78					
R81	Pneumonia	4.04	3.03 – 5.37	2.97	0.76					
R78	Acute bronchitis/bronchiolitis [2]	4.80	3.78 – 6.11	4.79	1.05			3.74	5.63	8.09
R91	Chronic bronchitis	5.66	3.14–10.23	0.93	0.16					
R02	Shortness of breath/dyspnoea	7.74	5.05–11.87	2.31	0.30					
R03	Wheezing	10.30	4.73–22.42	0.90	0.09					
Ear-nose-throat-related diseases and symptoms										
H76	Foreign body in ear [1]	***0.86***	***0.40 – 1.85***	***0.15***	***0.18***	2.51	0.20			
H01	Ear pain/earache	1.45	1.16 – 1.81	2.46	1.71					
H71	Acute otitis media/myringitis	1.52	1.32 – 1.76	6.44	4.4					
H70	Otitis externa	1.60	1.22 – 2.08	1.79	1.13					
R75	Sinusitis acute/chronic	1.90	1.32 – 2.75	1.05	0.56					
Gastro-intestinal-related diseases and symptoms										
D89	Inguinal hernia [1]	***0.76***	***0.37 – 1.57***	***0.16***	***0.22***	0.27	4.52			
D01	Abdominal pain/cramps general	1.40	1.16 – 1.69	3.32	2.40					
D06	Abdominal pain localized other	1.43	1.15 – 1.77	2.59	1.83					
D12	Constipation	1.44	1.22 – 1.70	4.43	3.12					
D73	Gastroenteritis, infection	1.60	1.25 – 2.05	2.10	1.33					
D10	Vomiting	2.02	1.37 – 2.97	0.99	0.49					
D99	Disease digestive system, other	2.70	1.52 – 4.79	0.55	0.20					
Musculoskeletal										
L15	Knee symptom/complaint [2]	***1.11***	***0.90 – 1.37***	***2.42***	***2.18***			1.34	1.49	0.97
L12	Hand symptom/complaint [1]	***1.37***	***1.09 – 1.71***	***2.27***	***1.67***	1.00	2.13			
L98	Acquired deformity of limb	1.40	1.16 – 1.68	3.54	2.56					
L99	Musculoskeletal disease, other	1.52	1.22 – 1.89	2.66	1.78					
L11	Wrist symptom/complaint	1.98	1.48 – 2.65	1.71	0.87					
Miscellaneous										
P21	ADHD	1.34	1.13 – 1.58	4.18	3.17					
A04	Weakness/tiredness general	1.39	1.17 – 1.65	4.04	2.97					
N01	Headache	1.51	1.21 – 1.89	2.49	1.66					
F70	Conjunctivitis infectious	1.72	1.31 – 2.27	1.78	1.04					
T10	Growth delay	1.82	1.35 – 2.44	1.60	0.89					
T83	Overweight	2.09	1.41 – 3.10	0.98	0.47					
T82	Obesity	2.47	1.50 – 4.05	0.68	0.28					
F71	Conjunctivitis allergic	2.55	1.85 – 3.49	1.72	0.68					
A12	Allergy	3.40	2.74 – 4.23	4.55	1.38					

1. significant (p ≤0.01) influence of gender; 2. significant (p ≤0.01) influence of age

***Italics**: Overall model not significant*

Table 4. Significantly (p ≤0.001) associated comorbidity in children diagnosed with only allergic rhinitis (AR) and at least three year follow-up versus controls (non-atopic children) (n=13,670)

ICPC	Description ICPC codes	OR	95% CI	Prevalence		OR sex		OR age		
				AR	No AR	boy	girl	2-6	7-12	13-18
Skin-related diseases and symptoms										
A76	Viral exanthem other [2]	***0.86***	***0.47 – 1.60***	***0.28***	***0.32***			0.32	0.64	4.51
S03	Warts	1.26	1.10 – 1.43	7.65	6.20					
S74	Dermatophytosis	1.39	1.15 – 1.68	3.85	2.79					
S82	Naevus/mole	1.39	1.15 – 1.67	3.99	2.91					
S84	Impetigo	1.71	1.35 – 2.15	2.87	1.71					
S98	Urticaria	1.71	1.31 – 2.23	2.15	1.27					
S86	Dermatitis seborrheic	1.86	1.38 – 2.53	1.76	0.95					
S02	Pruritus	2.21	1.44 – 3.38	0.99	0.45					
Airway-related diseases and symptoms										
R05	Cough	1.89	1.58 – 2.25	5.24	2.85					
R74	Upper respiratory infection acute	1.92	1.66 – 2.23	8.00	4.35					
R78	Acute bronchitis/bronchiolitis	2.32	1.60 – 3.37	1.35	0.59					
R02	Shortness of breath/dyspnoe	2.67	1.74 – 4.11	1.13	0.42					
R80	Influenza	3.89	1.79 – 8.47	0.45	0.12					
R03	Wheezing	4.30	1.89 – 9.80	0.44	0.10					
Ear-nose-throat-related diseases and symptoms										
R21	Throat symptom/complaint	1.48	1.20 – 1.84	3.13	2.14					
H01	Ear pain/earache	1.87	1.36 – 2.56	1.62	0.88					
R90	Hypertrophy tonsils/adenoids [2]	1.92	1.34 – 2.74	1.30	0.69			3.22	2.80	1.04
R75	Sinusitis acute/chronic	1.95	1.45 – 2.63	1.89	0.98					
R08	Nose symptom/complaint other	2.62	1.72 – 4.00	1.14	0.44					
R07	Sneezing/nasal congestion	3.93	2.57 – 6.01	1.54	0.40					
Gastro-intestinal-related diseases and symptoms										
D12	Constipation	1.50	1.23 – 1.82	3.79	2.57					
D06	Abdominal pain localized other	1.76	1.39 – 2.22	2.90	1.67					
D73	Gastroenteritis presumed infection [1]	1.96	1.42 – 2.71	1.59	0.82	1.29	3.39			
Musculoskeletal										
L98	Acquired deformity of limb	1.36	1.15 – 1.62	4.54	3.37					
L17	Foot/toe symptom/complaint	1.42	1.19 – 1.70	4.40	3.15					
L13	Hip symptom/complaint	2.80	1.66 – 4.74	0.78	0.28					
Miscellaneous										
N19	Speech disorder [1]	***1.18***	***0.85 – 1.65***	***1.17***	***0.99***	0.89	2.43			
N01	Headache	1.45	1.18 – 1.78	3.29	2.30					
P24	Specific learning problem	1.45	1.18 – 1.78	3.37	2.37					
A04	Weakness/tiredness general	1.58	1.35 – 1.85	6.10	3.96					
F70	Conjunctivitis infectious	1.73	1.28 – 2.32	1.76	1.02					
S12	Insect bite/sting	1.92	1.40 – 2.63	1.67	0.88					
F72	Blepharitis/stye/chalazion [1]	1.95	1.36 – 2.79	1.27	0.66	1.21	3.29			
A12	Allergy	4.02	3.15 – 5.13	4.70	1.21					
F71	Conjunctivitis allergic	5.44	4.08 – 7.25	4.29	0.82					

1. significant (p ≤0.01) influence of gender; 2. significant (p ≤0.01) influence of age

***Italics**: Overall model not significant*

Table 5. Significantly (p≤0.001) associated comorbidity in children diagnosed with Atopic Triad (AT) and at least three year follow-up versus controls (non-atopic children) (n= 1,118)

ICPC	Description ICPC codes	OR	95% CI			Prevalence	
						A. triad	No A. triad
R05	Cough	2.42	1.43	-	4.10	8.59	3.76
L17	Foot/toe symptom/complaint	3.25	1.63	-	6.50	6.08	1.97
R74	Upper respiratory infection acute	3.75	2.33	-	6.04	14.13	4.29
F71	Conjunctivitis allergic	6.79	2.35	-	19.60	4.65	0.72
A12	Allergy	17.83	7.15	-	44.43	13.77	0.89

Appendix 1

ICPC codes	Description
A03	Fever
A04	Weakness/tiredness general
A12	Allergic reaction
A15	Excessive crying infant
A16	Irritable infant
A70	Tuberculosis
A71	Measles
A72	Chickenpox
A73	Malaria
A74	Rubella
A75	Infectious mononucleosis
A76	Viral exanthem other
A77	Viral disease other/NOS
A78	Infectious disease other/NOS
A79	Malignancy NOS
A84	Poisoning by medical agent
A85	Adverse effect medical agent
A86	Toxic effect non-medicinal substance
A87	Complication of medical treatment
A88	Adverse effect physical factor
A90	Congenital anomaly OS/multiple
A92	Allergy/allergic reaction NOS
A93	Premature newborn
A94	Perinatal morbidity other
A95	Perinatal mortality
A96	Death
B02	Lymph gland(s) enlarged/painful
B70	Lymphadenitis acute
B71	Lymphadenitis non-specific
B72	Hodgkin's disease/lymphoma
B73	Leukaemia
B74	Malignant neoplasm blood other
B75	Benign/unspecified neoplasm blood
B78	Hereditary haemolytic anaemia
B79	Congen.anom. blood/lymph other
B80	Iron deficiency anaemia
B81	Anaemia, Vitamin B12/folate def.
B82	Anaemia other/unspecified
B83	Purpura/coagulation defect

B84	Unexplained abnormal white cells
B87	Splenomegaly
B90	HIV-infection/aids
D01	Abdominal pain/cramps general
D02	Abdominal pain epigastric
D03	Heartburn
D04	Rectal/anal pain
D05	Perianal itching
D06	Abdominal pain localized other
D07	Dyspepsia/indigestion
D08	Flatulence/gas/belching
D09	Nausea
D10	Vomiting
D11	Diarrhoea
D12	Constipation
D13	Jaundice
D22	Parasites
D70	Gastrointestinal infection
D71	Mumps
D72	Viral hepatitis
D73	Gastroenteritis presumed infection
D74	Malignant neoplasm stomach
D75	Malignant neoplasm colon/rectum
D76	Malignant neoplasm pancreas
D77	Malig. neoplasm digest other/NOS
D78	Neoplasm digest benign/uncertain
D79	Foreign body digestive system
D81	Congen. anomaly digestive system
D83	Mouth/tongue/lip disease
D84	Oesophagus disease
D85	Duodenal ulcer
D86	Peptic ulcer other
D87	Stomach function disorder
D88	Appendicitis
D89	Inguinal hernia
D90	Hiatus hernia
D91	Abdominal hernia other
D92	Diverticular disease
D93	Irritable bowel syndrome
D94	Chronic enteritis/ulcerative colitis
D95	Anal fissure/perianal abscess
D96	Worms/other parasites
D97	Liver disease NOS

D98	Cholecystitis/cholelithiasis
D99	Disease digestive system, other
F01	Eye pain
F02	Red eye
F03	Eye discharge
F04	Visual floaters/spots
F05	Visual disturbance other
F70	Conjunctivitis infectious
F71	Conjunctivitis allergic
F72	Blepharitis/stye/chalazion
F73	Eye infection/inflammation other
F74	Neoplasm of eye/adnexa
F75	Contusion/haemorrhage eye
F76	Foreign body in eye
F80	Blocked lacrimal duct of infant
F81	Congenital anomaly eye other
F82	Detached retina
F83	Retinopathy
F84	Macular degeneration
F85	Corneal ulcer
F86	Trachoma
F91	Refractive error
F92	Cataract
F93	Glaucoma
F94	Blindness
F95	Strabismus
F99	Eye/adnexa disease, other
H01	Ear pain/earache
H02	Hearing complaint
H03	Tinnitus, ringing/buzzing ear
H04	Ear discharge
H05	Bleeding ear
H70	Otitis externa
H71	Acute otitis media/myringitis
H72	Serous otitis media
H73	Eustachian salpingitis
H74	Chronic otitis media
H75	Neoplasm of ear
H76	Foreign body in ear
H77	Perforation ear drum
H80	Congenital anomaly of ear
H81	Excessive ear wax
H82	Vertiginous syndrome

H83	Otosclerosis
H86	Deafness
K01	Heart pain
K02	Pressure/tightness of heart
K04	Palpitations/awareness of heart
K05	Irregular heartbeat other
K07	Swollen ankles/oedema
K29	Cardiovascular sympt./complt. other
K70	Infection of circulatory system
K71	Rheumatic fever/heart disease
K72	Neoplasm cardiovascular
K73	Congenital anomaly cardiovascular
K74	Ischaemic heart disease w. angina
K75	Acute myocardial infarction
K76	Ischaemic heart disease w/o angina
K77	Heart failure
K78	Atrial fibrillation/flutter
K79	Paroxysmal tachycardia
K80	Cardiac arrhythmia NOS
K81	Heart/arterial murmur NOS
K82	Pulmonary heart disease
K83	Heart valve disease NOS
K84	Heart disease other
K85	Elevated blood pressure
K86	Hypertension uncomplicated
K87	Hypertension complicated
K88	Postural hypotension
K89	Transient cerebral ischaemia
K90	Stroke/cerebrovascular accident
K91	Cerebrovascular disease
K92	Atherosclerosis/PVD
K93	Pulmonary embolism
K94	Phlebitis/thrombophlebitis
K95	Varicose veins of leg
K96	Haemorrhoids
K99	Cardiovascular disease other
L01	Neck symptom/complain
L02	Back symptom/complaint
L03	Low back symptom/complaint
L04	Chest symptom/complaint
L05	Flank symptom/complaint
L06	Axilla symptom/complaint
L07	Jaw symptom/complaint

L08	Shoulder symptom/complaint
L09	Arm symptom/complaint
L10	Elbow symptom/complaint
L11	Wrist symptom/complaint
L12	Hand/finger symptom/complaint
L13	Hip symptom/complaint
L14	Leg/thigh symptom/complaint
L15	Knee symptom/complaint
L16	Ankle symptom/complaint
L17	Foot/toe symptom/complaint
L18	Muscle pain
L19	Muscle symptom/complaint NOS
L20	Joint symptom/complaint NOS
L70	Infections musculoskeletal system
L71	Malignant neoplasm musculoskeletal
L82	Congenital anomaly musculoskeletal
L83	Neck syndrome
L84	Back syndrome w/o radiating pain
L85	Acquired deformity of spine
L86	Back syndrome with radiating pain
L87	Bursitis/tendinitis/synovitis NOS
L88	Rheumatoid/seropositive arthritis
L92	Shoulder syndrome
L93	Tennis elbow
L94	Osteochondrosis
L95	Osteoporosis
L97	Neoplasm benign/unspec musculo.
L98	Acquired deformity of limb
L99	Musculoskeletal disease, other
N01	Headache
N02	Tension headache
N03	Pain face
N04	Restless legs
N05	Tingling fingers/feet/toes
N06	Sensation disturbance other
N07	Convulsion/seizure
N16	Disturbance of smell/taste
N17	Vertigo/dizziness
N18	Paralysis/weakness
N19	Speech disorder
N70	Poliomyelitis
N71	Meningitis/encephalitis
N72	Tetanus

N73	Neurological infection other
N74	Malignant neoplasm nervous system
N75	Benign neoplasm nervous system
N76	Neoplasm nervous system unspec.
N85	Congenital anomaly neurological
N86	Multiple sclerosis
N87	Parkinsonism
N88	Epilepsy
N89	Migraine
N90	Cluster headache
N91	Facial paralysis/bell's palsy
N92	Trigeminal neuralgia
N93	Carpal tunnel syndrome
N94	Peripheral neuritis/neuropathy
N99	Neurological disease, other
P01	Feeling anxious/nervous/tense
P02	Acute stress reaction
P03	Feeling depressed
P04	Feeling/behaving irritable/angry
P06	Sleep disturbance
P10	Stammering/stuttering/tic
P11	Eating problem in child
P12	Bedwetting/enuresis
P13	Encopresis/bowel training problem
P20	Memory disturbance
P21	ADHD
P22	Child behaviour symptom/complaint
P23	Adolescent behav. Symptom/complt.
P24	Specific learning problem
P71	Organic psychosis other
P72	Schizophrenia
P73	Affective psychosis
P74	Anxiety disorder/anxiety state
P75	Somatization disorder
P76	Depressive disorder
P78	Neuraesthenia/surmenage
P79	Phobia/compulsive disorder
P85	Mental retardation
P98	Psychosis NOS/other
P99	Psychological disorders, other
R01	Pain respiratory system
R02	Shortness of breath/dyspnoea
R03	Wheezing

R04	Breathing problem, other
R05	Cough
R06	Nose bleed/epistaxis
R07	Sneezing/nasal congestion
R08	Nose symptom/complaint other
R09	Sinus symptom/complaint
R21	Throat symptom/complaint
R22	Tonsils symptom/complaint
R23	Voice symptom/complaint
R24	Haemoptysis
R25	Sputum/phlegm abnormal
R29	Respiratory symptom/complaint oth.
R70	Tuberculosis airways
R71	Whooping cough
R72	Strep throat
R73	Boil/abscess nose
R74	Upper respiratory infection acute
R75	Sinusitis acute/chronic
R76	Tonsillitis acute
R77	Laryngitis/tracheitis acute
R78	Acute bronchitis/bronchiolitis
R80	Influenza
R81	Pneumonia
R82	Pleurisy/pleural effusion
R83	Respiratory infection other
R84	Malignant neoplasm bronchus/lung
R85	Malinant neoplasm respiratory, other
R86	Benign neoplasm respiratory
R87	Foreign body nose/larynx/bronch
R89	Congenital anomaly respiratory
R90	Hypertrophy tonsils/adenoids
R91	Chronic bronchitis
R93	Pleural effusion
R95	Chronic obstructive pulmonary dis
R96	Asthma
R97	Allergic rhinitis
R98	Hyperventilation syndrome
R99	Respiratory disease other
S01	Pain/tenderness of skin
S02	Pruritus
S03	Warts
S04	Lump/swelling localized
S05	Lumps/swellings generalized

S06	Rash localized
S07	Rash generalized
S08	Skin colour change
S09	Infected finger/toe
S10	Boil/carbuncle
S11	Skin infection post-traumatic
S12	Insect bite/sting
S13	Animal/human bite
S14	Burn/scald
S15	Foreign body in skin
S20	Corn/callosity
S21	Skin texture symptom/complaint
S22	Nail symptom/complaint
S23	Hair loss/baldness
S24	Hair/scalp symptom/complaint
S70	Herpes zoster
S71	Herpes simplex
S72	Scabies/other acariasis
S73	Pediculosis/skin infestation other
S74	Dermatophytosis
S75	Moniliasis/candidiasis skin
S76	Skin infection other
S77	Malignant neoplasm of skin
S78	Lipoma
S79	Neoplasm skin benign/unspecified
S80	Solar keratosis/sunburn
S81	Haemangioma/lymphangioma
S82	Naevus/mole
S83	Congenital skin anomaly other
S84	Impetigo
S85	Pilonidal cyst/fistula
S86	Dermatitis seborrhoeic
S87	Dermatitis/atopic eczema
S89	Diaper rash
S90	Pityriasis rosea
S91	Psoriasis
S92	Sweat gland disease
S93	Sebaceous cyst
S94	Ingrowing nail
S95	Molluscum contagiosum
S96	Acne
S97	Chronic ulcer skin
S98	Urticaria

S99	Skin disease, other
T01	Excessive thirst
T02	Excessive appetite
T03	Loss of appetite
T04	Feeding problem of infant/child
T05	Feeding problem of adult
T06	Anorexia nervosa
T07	Weight gain
T08	Weight loss
T10	Growth delay
T11	Dehydration
T15	Tumor thyroid
T70	Endocrine infection
T71	Malignant neoplasm thyroid
T72	Benign neoplasm thyroid
T73	Neoplasm endocrine oth/unspecified
T78	Thyroglossal duct/cys
T80	Congenital anom endocrine/metab
T81	Goitre
T82	Obesity
T83	Overweight
T85	Hyperthyroidism/thyrotoxicosis
T86	Hypothyroidism/myxoedema
T87	Hypoglycaemia
T88	Renal glycosuria
T89	Diabetes insulin dependent
T90	Diabetes non-insulin dependent
T91	Vitamin/nutritional deficiency
T92	Gout
T93	Lipid disorder
T99	Endocrine/metab/nutrit. dis. other
U01	Dysuria/painful urination
U02	Urinary frequency/urgency
U04	Incontinence urine
U05	Urination problems other
U06	Haematuria
U07	Urine symptom/complaint other
U13	Bladder symptom/complaint other
U14	Kidney symptom/complaint
U70	Pyelonephritis/pyelitis
U71	Cystitis/urinary infection other
U72	Urethritis
U75	Malignant neoplasm of kidney

U76	Malignant neoplasm of bladder
U77	Malignant neoplasm urinary other
U78	Benign neoplasm urinary tract
U79	Neoplasm urinary tract NOS
U85	Congenital anomaly urinary tract
U88	Glomerulonephritis/nephrosis
U90	Orthostatic albumin/proteinuria
U95	Urinary calculus
U98	Abnormal urine test NOS
U99	Urinary disease, other
X83	Congenital anomaly genital female
X84	Vaginitis/vulvitis NOS
X85	Cervical disease NOS
X99	Genital disease female, other
Y74	Orchitis/epididymitis
Y75	Balanitis
Y81	Phimosis/redundant prepuce
Y82	Hypospadias
Y83	Undescended testicle
Y84	Congenital genl anomaly (m) other
Y99	Genital disease male, other

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any pre-specified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	6-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8-9*
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	6-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	8-9

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10 + Table 1
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	10-12
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-147
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.