

# BMJ Open Risks for comorbidity in children with atopic disorders: 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 (the Netherlands Institute for Health Services Research-Primary Care Database) with routinely collected healthcare data in 2014 were selected. Children with atopic disorders were matched on age and gender with non-atopic controls within the same general practice. A total of 404 International Classification of Primary Care 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 ORs.

**Results** Having one of the atopic disorders 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=7887). Children with allergic rhinitis (n=6835) 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.

## 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 generalisability.
- A total of 404 International Classification of Primary Care codes were examined.
- A limitation regarding this type of explorative study is the unavoidable multiple testing.

study we refer to atopy as a (genetic) predisposition towards 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 general practitioner (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 (eg, birth cohorts, hospitals or paediatric clinics). Demonstrated interrelations exist with (among others) diabetes,<sup>3–5</sup> attention-deficit/hyperactivity disorder,<sup>6–8</sup> autism<sup>9–11</sup> and obesity.<sup>12–14</sup> 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.<sup>15 16</sup> Acute viral ‘non-respiratory syncytial virus’ bronchiolitis in infants aged <6 months is linked with an increased risk of developing asthma.<sup>17</sup> 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.<sup>18</sup> On the other hand, otitis media with effusion is associated with allergic rhinitis.<sup>19–21</sup> The quality of

## 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 paediatric diseases diagnosed in general practice<sup>1</sup>; allergic rhinitis is on the 12th place on this list. However, limited data are available on the comorbidities of children with atopic disorders in primary care.<sup>2</sup> In the present



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life of a child with atopic disorders can be significantly improved by providing sufficient treatment.

To our knowledge no study has investigated the complete range of potential comorbidities in children with atopic disorders in a general practice setting. A relevant question could be: Are children with atopic disorders 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-institutionalised 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](http://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.<sup>22</sup>

### 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.<sup>23</sup> 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.<sup>24</sup> Routinely collected general practice computer data, aggregated into large databases, are used for epidemiological research.<sup>25</sup> Hippisley-Cox *et al*<sup>26</sup> illustrate how routine clinical data, in selected high recording practices (this selection criterion was also applied in the present study), are now reaching reasonable levels of accuracy and completeness for a range of key variables. According to Britt *et al*<sup>27</sup>, morbidity data actively collected by GPs provide a reliable overview of morbidity managed in general practice.

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 labelled 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: (1) at least 500 listed patients (standard practice: 2350 patients), (2) complete morbidity registration (defined as  $\geq 46$  weeks/year) and (3) sufficient ICPC coding of diagnostic information (defined as  $\geq 70\%$  of the recorded disease episodes labelled with an ICPC code; the 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.

### Children with atopic disorders

For each child (0–18 years), a minimum follow-up of 3 years was required (eg, 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  $\geq 2$  years are presented here. In the Netherlands, GPs see about 72% of their patient population at least once a year.<sup>28</sup> 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 to 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 and 2014) the parent of 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<sup>29</sup> 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.<sup>30</sup> 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 of 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 (eg, presbycusis), pregnancy, childbearing, family planning, sexually 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 child with atopic disorders, 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 a child with atopic disorders was determined. ORs were calculated for children who solely had atopic eczema, asthma or allergic rhinitis and therefore no other atopic comorbidity. Online supplementary 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 generalisable 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

**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	7887	10.7 (4.5)	59.0
Only allergic rhinitis	6835	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: that is, they had the disorder mentioned, but none of the other disorders, whereas children in the atopic triad group had all three disorders.

analyses were conducted on Stata V.13 and Excel 2010. Prevalence rates are presented in percentages.

## RESULTS

### General characteristics

There were 409 312 children identified in the NIVEL-PCD in 2014, initially including 70 494 children with at least one atopic disorder. However, for a child with atopic disorder to be included in this study, one matched control patient had to be available (ie, a child without an atopic disorder). There were 21 285 children with atopic eczema identified, of whom 15 530 children had atopic eczema without another atopic disorder. For children with asthma, 13 196 children were identified, of whom 7887 had asthma only and no other atopic disorders. In children with allergic rhinitis, 11 483 were identified, of whom 6835 had allergic rhinitis 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 (table 1).

### Atopic eczema

A substantial part of the significantly related comorbidity for children with atopic eczema concerns skin diseases such as (among others) warts (OR: 1.2), localised rash (OR: 1.5), pruritus (OR: 1.7), impetigo (OR: 1.7), 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), which 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 localised rash (OR: 1.3 to 2.3) and impetigo (OR: 1.5 to 2.7). Compared with boys, girls had an increased risk to develop a localised

**Table 2** Significantly ( $p \leq 0.001$ ) associated comorbidity in children diagnosed with only atopic eczema (Ec) and at least 3-year follow-up versus controls (non-atopic children) ( $n=31\ 060$ )

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

Italics mean overall model not significant.

\*Significant ( $p \leq 0.01$ ) influence of gender.

†Significant ( $p \leq 0.01$ ) influence of age.

ICPC, International Classification of Primary Care.

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

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

Italics mean overall model not significant.

\*Significant ( $p \leq 0.01$ ) influence of gender.

†Significant ( $p \leq 0.01$ ) influence of age.

ICPC, International Classification of Primary Care.

**Table 4** Significantly ( $p \leq 0.001$ ) associated comorbidity in children diagnosed with only allergic rhinitis (AR) and at least 3-year follow-up versus controls (non-atopic children) ( $n=13670$ )

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

Italics mean overall model not significant.

\*Significant ( $p \leq 0.01$ ) influence of gender.

†Significant ( $p \leq 0.01$ ) influence of age.

ICPC, International Classification of Primary Care.

**Table 5** Significantly ( $p \leq 0.001$ ) associated comorbidity in children diagnosed with atopic triad and at least 3-year follow-up versus controls (non-atopic children) ( $n=1118$ )

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

ICPC, International Classification of Primary Care.

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) (table 2).

### Asthma

Noteworthy are asthma-related symptoms that were diagnosed separately, such as shortness of breath/dyspnoea (OR: 7.7) and wheezing (OR: 10.3). Furthermore, children with asthma were presented to their GPs 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, for example, general abdominal pain/cramps (OR: 1.4), localised abdominal pain (OR: 1.4), constipation (OR: 1.4) and vomiting (OR: 2.0). Acute bronchitis (OR: 3.7 to 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) (table 3).

### Allergic rhinitis

Children with allergic rhinitis were presented to 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/dyspnoea (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 localised abdominal pain (OR: 1.8)). Hypertrophy of the tonsils was diagnosed less frequently when children got older (OR: 3.2 to 1.0). On the other hand, children were more frequently diagnosed with a viral exanthem when they became older (OR: 0.3 to 4.5). A presumed gastrointestinal 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 (table 4).

### Atopic triad

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 (table 5).

## DISCUSSION

### Main findings

The present study used an extensive and representative general practice database.<sup>22</sup> The large number of children gives the study substantial power and generalisability. This could also allow evaluation of possible links between atopic disorders and rare childhood diseases. This study showed that children with atopic disorders 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. Second, a child with atopic eczema who is presented with ‘wheeze’ or ‘dyspnea’ is at a higher risk for the development of asthma compared with 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 (eg, wheeze as the provisional diagnosis of asthma). Regarding non-atopic comorbidity, 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, children with asthma are at risk of other airway diseases, and children with allergic rhinitis are at risk of ear-nose-throat-related symptoms and diseases.

Gastrointestinal and musculoskeletal diseases and symptoms were also seen more frequently in children with atopic disorders. 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 aetiology 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 interleukin-22 expression.<sup>31</sup> Although the clinical pictures of these two diseases can be very different, the observed association could also suggest 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 been presented to their GPs 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.<sup>2</sup> An explanation for this could be that airway infections increase asthma symptoms or vice versa, and that asthma resulted in increased susceptibility for infection, which increased their motivation to visit the GPs. 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 were presented to 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.<sup>32</sup> 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 children with atopic disorders. This is in accordance with a study in adults in a primary care setting.<sup>33</sup> These symptoms could be related to IgE-mediated food allergies or in rare cases even to eosinophilic oesophagitis, which is associated with atopic disorders<sup>34</sup>; 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, for example, serous otitis media in patients with allergic rhinitis,<sup>19 21</sup> and inflammatory bowel disease,<sup>35 36</sup> leukaemia<sup>37 38</sup> and diabetes<sup>39 40</sup> in patients with atopic disorders. 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 labelled as 'asthma' (R96) or labelled 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. Third, 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 neighbourhoods, and therefore the effect of most of the earlier mentioned risk factors is expected to be small. Fourth, children with atopic disorders might be presented to 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 children with atopic disorders 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, in the present study the diagnoses are based on a physician's assessment and not on confirmed sensitisation pattern for allergens. According to the Dutch medical guideline for eczema,<sup>41</sup> GPs are not advised to determine these sensitisation patterns, since these do not have any clinical consequences. Although atopy is clearly associated with atopic eczema, the role of IgE sensitisation in atopic eczema still needs further study.<sup>42</sup> Also in children with allergic rhinitis, sensitisation patterns do not have added value if the medical history clearly suggests, for example, a pollen allergy.<sup>43</sup> Only when the cause of the rhinitis is uncertain the determination of sensitisation patterns adds value. The medical guidelines for asthma in children advise to determine sensitisation patterns,<sup>44</sup> since it can help diagnose allergic asthma<sup>45</sup> and because it



could have clinical consequences. Finally, it is important to acknowledge the uncertainty of GPs to make a diagnosis of asthma or allergic rhinitis in young children (eg, under the age of 6).

### Implications for future research and practice

First of all, could comorbidity data be used to create proxies that could support GPs in identifying children with atopic disorders that are not labelled 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, how is the quality of life of these children with atopic disorders affected by the associated comorbidity? GPs should be aware of the described associations when treating a child with atopic disorder, since the quality of life of a child with atopic disorder 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 children with atopic disorders have an increased risk of clinically relevant comorbidity, both atopic and non-atopic. GPs 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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