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

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| 3 4 5 6 | 1 | Risks for comorbidity in atopic children: an epidemiological |
| 7 8 9 10 | 2 | study in general practice |
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| 60 | | Comorbidity in atopic children in general practice For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml |

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 nonatopic 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.

<text>

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 nonatopic 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

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| ∠ 3 | 62 | and diseases, an extensive and representative nationwide general practice database is explored using a cross- |
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| 5456789101123415678902122342567890312334567890112344567890555555555555555555555555555555555555 | 62 | and diseases, an extensive and representative nationwide general practice database is explored using a cross- sectional design. |
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| | | Comorbidity in atopic children in general practice |

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

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 \geq 46 weeks/year), and iii) sufficient ICPC coding of diagnostic information (defined as \geq 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 guarter of birth.

Atopic children

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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.

97 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.

03 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 traumarelated ICPC codes, ICPC codes not relevant for children (e.g. presbyacusis), pregnancy, childbearing, family

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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.

121 Statistical analyses

39 122 Logistic regression analysis was performed to study associations between the presence of atopic disorders and 123 (non-) atopic comorbid symptoms and diseases in children. Similarly, associations between atopic triad and the 44 124 above-mentioned comorbid symptoms and diseases were examined. Due to multiple testing, only associations 46 125 with p ≤ 0.001 were considered statistically significant. All associations were tested for the modifying effects of ⁴⁸ 126 age and gender. In case of a significant effect ($p \le 0.01$), associations were also presented for subgroups for age 127 (0-6 vs. 7-12 vs. 13-18 years) and gender (boy vs. girl). Finally, due to the hierarchical structure of the data 53 128 (patients registered in general practices), a multi-level logistic regression analysis was performed to test 55 <u>12</u>9 whether clustering effects influenced our findings. All analyses were conducted in Stata 13 and Excel 2010. 130 Prevalence rates are presented in percentages. 58

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| 3 | 131 | Ethical approval |
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| 5 6 7 | 132 | Dutch law allows the use of EHRs for research purposes under certain conditions. According to this legislation, |
| 8 9 10 | 133 | it is not necessary to obtain informed consent from patients or approval from a medical ethics committee for |
| 10 11 12 | 134 | this type of observational study that contains no directly identifiable data (Dutch Civil Law, Article 7: 458). |
| 13 14 | 135 | Therefore, no waiver of ethical approval was obtained from an Institutional Review Board (IRB) or ethics |
| 15 16 17 | 136 | committee. The authors had no access to any identifying information at any moment during the analysis of the |
| 18 19 | 137 | data. |
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Results

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General characteristics (Table 1)

11 140 409,312 children were identified in the NIVEL-PCD in 2014, initially including 70,494 atopic children with at 141 least one atopic disorder. However, for an atopic child to be included in this study, one matched control patient 16 142 had to be available (i.e. a child without an atopic disorder). After selecting children with an atopic disorder and 18 143 with a higher probability of a clinically relevant disorder and with at least three years follow-up, 21,285 144 children with atopic eczema were identified, of which 15,530 children had atopic eczema without another 23 ¹⁴⁵ atopic disorder. For asthmatic children, 13,196 children were identified, of which 7,887 had asthma only and 25 146 no other atopic disorders. In children with AR, 11,483 were identified of which 6,835 had AR without another 27 ₁₄₇ atopic disorder. Finally, 559 children had all three atopic disorders. All the children in these groups were 148 selected from 316 different general practices participating in NIVEL-PCD. Clustering effects did not influence our findings. 32 149

35 150 Atopic eczema (Table 2)

38 151 A substantial part of the significantly related comorbidity for children with atopic eczema concerns skin 40 152 diseases such as (among others): warts (OR 1.2), localized rash (OR 1.5), pruritus (OR 1.7), impetigo (OR1.7), 42 43 153 dermatophytosis (OR 1.8), urticaria (OR 1.8), molluscum contagiosum (OR 1.9) and psoriasis (OR 3.4). Otitis 44 45 154 externa (OR 1.6) and blepharitis (OR 1.5) were also significantly associated with atopic eczema. The symptom 46 47 155 diagnosis of wheezing (OR 2.0), that could be attributed to asthma, is noteworthy since these children were not 50 156 diagnosed or coded in the EHRs with asthma. The same applies to symptoms associated with allergic 52 157 rhinoconjunctivitis, such as sneezing/nasal congestion (OR 2.0) and allergic conjunctivitis (OR 2.0). Older 53 ⁵⁴ 158 children with atopic eczema were at increased risk to develop a localized rash (OR 1.3 - > 2.3) and impetigo (OR

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| $\frac{3}{4}$ 15 | 9 | 1.5 - >2.7). Compared to boys, girls had an increased risk, to develop a localized rash (OR 2.0 vs. 1.1), breathing |
| 5 6 16 7 | 0 | problems (OR 3.6 vs. 0.9) and stomach function disorder (OR 3.3 vs. 0.7). |
| 8 9 16 10 | 1 | Asthma (Table 3) |
| 12 16 13 | 2 | Noteworthy are asthma-related symptoms that were diagnosed separately, such as shortness of |
| 14 16 15 | 3 | breath/dyspnea (OR 7.7) and wheezing (OR 10.3). Furthermore, asthmatic children consulted their GP more |
| 16 17 16 19 | 4 | frequently for airway-related infections such as: acute laryngitis/tracheitis (OR 2.3), acute upper respiratory |
| 19 16 20 | 5 | infection (OR 2.4), pneumonia (OR 4.0) and acute bronchitis (OR 4.8). In children with asthma, there seems to |
| 21 16 22 | 6 | be a higher risk for the development of gastrointestinal symptoms, e.g.: general abdominal pain/cramps (OR |
| 23 24 16 | 7 | 1.4), localized abdominal pain (OR 1.4), constipation (OR 1.4) and vomiting (OR 2.0). Acute bronchitis (OR 3.7 - |
| 25 26 16 27 | 8 | >8.1) was diagnosed more often in older children. Inguinal hernias were seen more frequently in girls than in |
| 28 16 29 | 9 | boys (OR 4.5 vs. 0.3). |
| 30 31 17 32 33 | 0 | Allergic rhinitis (Table 4) |
| 34 35 17 | 1 | Children with allergic rhinitis visit their GPs more frequently for ear-nose-throat related symptoms and |
| 36 37 17 | 2 | diseases. Among others, the following were diagnosed more often: throat symptom/complaint (OR 1.5), ear |
| 39 17 40 | 3 | pain/earache (OR 1.9), hypertrophy tonsils/adenoids (OR 1.9), acute/chronic sinusitis (OR 2.0), nose symptom |
| 41 17 42 | 4 | (OR 2.6) and sneezing/nasal congestion (OR 3.9). Furthermore, symptoms associated with atopic eczema |
| 43 44 17 45 | 5 | (pruritus; OR 2.2) and asthma [shortness of breath/dyspnea (OR 2.7) and wheezing (OR 4.3)] were seen more |
| 45 46 17 47 | 6 | frequently. Also, when a child was diagnosed with allergic rhinitis, there was a substantial risk for the |
| 48 17 49 | 7 | development of gastrointestinal symptoms [constipation (OR 1.5) and localized abdominal pain (OR 1.8)]. |
| 50 51 17 | 8 | Hypertrophy of the tonsils was diagnosed less frequently when children got older (OR 3.2 - >1.0). On the other |
| 52 53 17 54 | 9 | hand, children were more frequently diagnosed with a viral exanthema when they became older (OR 0.3 - |
| 55 <u>18</u> 56 | 0 | >4.5). A presumed gastro-intestinal infection (OR 3.4 vs. 1.3), speech disorder (OR 2.4 vs. 0.9) and |
| 57 58 59 | 1 | blepharitis/style/chalazion (OR 3.3 vs. 1.2) were diagnosed more frequently in girls with allergic rhinitis. |

182 Atopic triad (Table 5)

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| 3 | 182 | Atopic triad (Table 5) |
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| 6 7 | 183 | Having all three atopic disorders is relatively rare, with only a few symptoms and diseases being significantly |
| 8 9 10 | 184 | related. The risk for developing an 'allergy', that the GP considers relevant to register in the EHR can be |
| 11 12 | 185 | considered high (OR 17.8). Allergic conjunctivitis (OR 6.8) is also frequently seen in children with all three atopic |
| 14 15 16 17 18 19 20 21 22 | 186 | disorders. |
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188 Main findings

11 189 The present study used an extensive and representative general practice database (21). The large number of 12 13 190 children gives the study substantial power and generalizability. This could also allow evaluation of possible links 14 15 16 191 between atopic disorders and rare childhood diseases. This study showed that atopic children have an 17 18 192 increased risk for the development of both atopic and non-atopic diseases and symptoms. Children diagnosed 19 20 193 with one atopic disorder were frequently diagnosed by their GP with symptoms associated with one of the 21 22 23 ¹⁹⁴ other atopic disorders. This suggests that GPs are not always fully aware of relevant atopic comorbidity, or at 24 25 195 least do not label it correctly. For example, a child with atopic eczema that presents with 'wheeze' or 'dyspnea' 26 27 ₁₉₆ is at a higher risk for the development of asthma compared to a child without atopic eczema. A GP should be 28 29 197 aware of this increased risk, since it could result in insufficient treatment of a child. Regarding non-atopic co-30 31 morbidity, strong associations were found between the atopic disorder and diseases and symptoms related to 32 198 33 34 199 the same organ system. For example, children with atopic eczema are at increased risk for the development of 35 36 200 other skin diseases, asthmatic children are at risk of other airway diseases, and children with allergic rhinitis are 37 38 39 201 at risk of ear-nose-throat-related symptoms and diseases. Gastro-intestinal and musculoskeletal diseases and 40 41 202 symptoms were also seen more frequently in atopic children. When exploring possible interactions of age and 42 43 44 203 gender in children with one atopic disorders, no clear patterns arose.

46 204 Interpretation of findings in relation to previously published work 47

₅₀ 205 Children with atopic eczema had an increased risk of developing infectious skin diseases such as warts, 52 206 impetigo, dermatophytosis and molluscum contagiosum. The common etiology could be the barrier ⁵⁴ 207 dysfunction of the skin in children with atopic eczema. This barrier dysfunction is also seen in psoriasis, a 57 208 disease that, according to the present study, is associated with atopic eczema (OR 3.4). Although the clinical

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1 2 3 209 pictures of these two diseases are different, they share some common pathological backgrounds such as 4 5 6 210 barrier dysfunction and enhanced IL-22 expression (26). Otitis externa and blepharitis both had significant ORs. 7 8 211 These disorders could in fact be an expression of atopic eczema. 9 10 11 212 Children with asthma seem to have consulted their GP more frequently for airway-related infections such as 12 13 213 acute laryngitis/tracheitis, acute upper respiratory infection, pneumonia and bronchitis. An explanation for this 14 15 16 214 could be that airway infections increase asthma symptoms or vice versa, that asthma resulted in increased 17 18 215 susceptibility for infection, which increased their motivation to visit the GP. Furthermore, the awareness of 19 ²⁰ 216 parents is likely to be increased when a child suffers from asthma, since such an infection could predispose for 21 22 23 217 an asthma exacerbation. 24 25 26 218 Children with allergic rhinitis consulted their GPs more frequently for ear-nose-throat-related symptoms and 27 28 219 diseases. However, even more striking are the asthma-related symptoms. Both shortness of breath (OR 2.7) 29 30 220 and wheeze (OR 4.3) were frequently seen in children with allergic rhinitis. There is strong evidence that 31 32 ₃₃ 221 allergic rhinitis has an adverse impact on asthma severity (27). Because allergic rhinitis can provoke asthma 34 35 222 symptoms, allergic rhinitis symptoms should be taken more seriously by GPs to reduce insufficient treatment. 36 37 38 223 Gastrointestinal-related symptoms are also frequently diagnosed by GPs in atopic children. This is in 39 40 224 accordance with a study in adults in a primary care setting (28). These symptoms could be related to IgE-41 42 43 225 mediated food allergies or in rare cases even to eosinophilic esophagitis that are associated with atopic 44 45 226 disorders (29); however, in children, abdominal pains can also be a general expression of not feeling well. 46 47 227 Unfortunately, the ICPC classification system does not cover the above-mentioned gastrointestinal diseases 48 49 ₅₀ 228 with unique code and, therefore, gastrointestinal-related symptoms might have been used by the GP to label 51 52 229 these diseases. 53 54 55 230 Some associations described in the literature were not confirmed in the present study, e.g. serous otitis media 56 57 58 231 in patients with allergic rhinitis (18, 20), and inflammatory bowel disease (30, 31), leukemia (32, 33) and 59 60 Comorbidity in atopic children in general practice. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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| 3 232 4 | diabetes (34, 35) in atopic patients. The prevalence rates of some of these disorders are low and a cross- |
| 5 6 233 7 | sectional design (as used in the present study), might not be sufficient to prove this relationship. |
| 8 9 234 10 | Strengths and limitations of this study |
| 12 235 13 | Using general practice databases (by means of a cross-sectional design) also has its limitations. First of all, a |
| ¹⁴ 236 15 | limitation for the present study is the GP's choice for ICPC coding of an episode of care. For example, a child |
| 16 17 237 18 | with a wheeze could either be labeled as 'asthma' (R96) or labeled as 'wheeze' (R03). This could result in both |
| 19 238 20 | overestimation or underestimation of asthma. To decrease this risk of overestimation regarding atopic |
| 21 239 22 | disorders, some episodes were corrected in order to increase the clinical relevance of the atopic disorder of |
| 23 24 25 | interest. However, the risk of underestimation was not tackled, since too many assumptions need to be made. |
| 25 26 241 27 | The second limitation regarding this type of explorative study is the unavoidable multiple testing. Although |
| 28 242 29 | conservative p-values were used, type 1 errors cannot be avoided. In this study, some suggested associations |
| ³⁰ 243 31 | might in fact reflect these type 1 errors. Thirdly, because data on socioeconomic status, tobacco smoke |
| 32 33 244 34 | exposure and other lifestyle-related risk factors are not recorded in NIVEL-PCD, we cannot rule out the effect of |
| 35 245 36 | these risk factors on the observed relations. However, since the children with atopic disorders were matched |
| 37 246 38 | with controls within the same general practice, all children are most likely living in the same neighborhoods |
| 39 40 247 41 | and therefore the effect of most of the earlier mentioned risk factors is expected to be small. Fourthly, atopic |
| 42 248 43 | children might visit the GP more frequently than non-atopic children. And although this may be more |
| 44 249 45 | representative of parental fears, rather than an indication of morbidity, it can result in more ICPC codes in |
| 46 47 250 48 | atopic children and could partly explain some of the associations found. In future research, the number of |
| 49 251 50 | consultations might need to be taken into account in the analyses. Fifth of all, in the present study the |
| 51 252 52 | diagnosis are based on a physician's assessment and not on confirmed sensitization pattern for allergens. |
| 53 54 55 | According to the Dutch medical guideline for eczema (36), GPs are not advised to determine these |
| 56 254 57 58 59 60 | 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).

2 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.

70 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

| 2 3 4 291 5 6 | Data sharing statement |
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| 7 8 292 | Data will be available from the repository of Data Archiving and Networked Services (DANS; |
| 0 292 9 10 11 12 13 14 15 16 17 18 18 19 201 22 223 22 232 24 232 24 233 33 333 34 35 36 37 38 38 30 44 44 44 44 44 45 55 55 56 57 | www.dans.knaw.nl). |

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392 Figure legends

Table 1. General characteristics of the total study population 10 394 **Table 2.** Significantly ($p \le 0.001$) associated comorbidity in children diagnosed with only atopic eczema (Ec) and 13 at least three year follow-up versus controls (non-atopic children) (n=31,060) 16 ³⁹⁶ **Table 3.** Significantly ($p \le 0.001$) associated comorbidity in children diagnosed with only asthma (As) and at least 18 397 three year follow-up versus controls (non-atopic children) (n=15,774) 21 398 **Table 4.** Significantly ($p \le 0.001$) associated comorbidity in children diagnosed with only allergic rhinitis (AR) and 23 ₃₉₉ 24 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 29 401 three year follow-up versus controls (non-atopic children) (n= 1,118) 33⁴⁰²

| | n | Age in years (SD) | Male | | |
|------------------------|---------------------|----------------------|-------------------------------|--|------------|
| Only atopic eczema | 15,530 | 8.7 (4.5) | 48.2% | | |
| Only asthma | 7 <i>,</i> 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) | <u>61.4%</u> | | ام مالد ام |
| mentioned but none (| of the oth e | ar disorders wh | ne of the th pereas childr | ree alopic disorders. i.e. they have en in the Atonic triad group had | all thre |
| nemioned, but none (| | | | | |
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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 | Preva | lence | OR se | x | OR ag | ge | | Description ICPC codes |
|--------|---------|-----------------|----------|---------|-------|------|-------|------|-------|---------------------------------------|
| | | | Ec | No Ec | boy | girl | 0-6 | 7-12 | 13-18 | |
| Skin-r | elated | diseases and | symptor | ns | | | | | | |
| 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/con |
| 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 |
| Airwa | y-relat | ed diseases a | nd symp | toms | | | | | | |
| 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 infectior |
| R78 | 1.49 | 1.22 – 1.80 | 1.66 | 1.13 | | | | | | Acute bronchitis/bronchiol |
| 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-no | ose-thr | oat-related di | seases a | nd symp | otoms | | | | | |
| H71 | 1.20 | 1.09 - 1.31 | 7.46 | 6.35 | | | | | | Acute otitis media/myringi |
| 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/complain |
| 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 | o-intes | tinal-related o | liseases | and sym | ptoms | | | | | |
| D01 | 1.27 | 1.12 – 1.45 | 3.61 | 2.85 | | | | | | Abdominal pain/cramps ge |
| 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 |
| D99 | 2.28 | 1.51 – 3.44 | 0.48 | 0.21 | | | | | | Disease digestive system. o |
| Musc | uloskel | etal | | | | | | | | |
| L17 | 1.30 | 1.15 – 1.48 | 3.50 | 2.71 | | | | | | Foot/toe symptom/compla |
| L98 | 1.39 | 1.20 - 1.60 | 2.90 | 2.11 | | | | | | Acquired deformity of limb |
| Misce | llaneou | us | | | | | | | | |
| A04 | 1.25 | 1.09 - 1.44 | 3.07 | 2.47 | | | | | | Weakness/tiredness gener |
| 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 |
| 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 prepu |
| F71 | 1.99 | 1.59 – 2.49 | 1.45 | 0.73 | | | | | | Conjunctivitis allergic |
| | | | 2 4 2 | 4 4 2 | | | | | | , |

1. significant (p \leq 0.01) influence of gender; 2. significant (p \leq 0.01) influence of age; # OR could not be 57 409 calculated; Italics: Overall model not significant

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2 3 4 5 6 410 Table 3. Significantly (p ≤0.001) associated comorbidity in children diagnosed with only asthma (As) and at least 411 three year follow-up versus controls (non-atopic children) (n=15,774)

| ICPC | OR | 95% CI | Preva | alence | OR se | ex | OR ag | ge | | Description ICPC codes |
|--------|----------|------------------|----------|----------|-------|------|-------|------|-------|---|
| | | | As | No As | boy | girl | 0-6 | 7-12 | 13-18 | |
| Skin-r | elated o | diseases and sy | mptom | s | | | | | | |
| S98 | 2.10 | 1.61 – 2.73 | 2.21 | 1.07 | | | | | | Urtiacaria |
| Airwa | y-relate | d diseases and | l sympto | oms | | | | | | |
| 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-n | ose-thro | oat-related dise | eases an | d sympto | oms | | | | | |
| 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 |
| Gastr | o-intest | inal-related dis | seases a | nd symp | toms | | | | | |
| 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 |
| Musc | uloskele | etal | | | | | | | | |
| 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 |
| Misce | llaneou | s | | | | | | | | |
| 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 |

53 54 412 1. significant ($p \le 0.01$) influence of gender; 2. significant ($p \le 0.01$) influence of age; # OR could not be 55 413 calculated; Italics: Overall model not significant

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415 Table 4. Significantly (p ≤0.001) associated comorbidity in children diagnosed with only allergic rhinitis (AR) and 416 at least three year follow-up versus controls (non-atopic children) (n=13,670)

| ICPC | OR | 95% CI | Prev | alence | OR se | ex | OR ag | ge | | Description ICPC codes |
|--------|---------|-----------------|---------|-----------|-------|------|-------|------|-------|---|
| | | | AR | No AR | boy | girl | 0-6 | 7-12 | 13-18 | |
| Skin-r | elated | diseases and | sympt | oms | | | | | | |
| 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 |
| Airwa | y-relat | ed diseases ar | nd sym | ptoms | | | | | | |
| 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-n | ose-thr | oat-related di | seases | and syr | nptom | s | | | | |
| 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 |
| Gastr | o-intes | tinal-related d | lisease | es and sy | mpton | ns | | | | |
| 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 |
| Musc | uloskel | etal | | | | | | | | |
| 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 |
| Misce | llaneo | JS | | | | | | | | |
| 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 |
| | 1 02 | 3.15 - 5.13 | 4.70 | 1.21 | | _ | | | | Allergy |
| A12 | 4.072 | | | | | | | | | |

53 417 1. significant ($p \le 0.01$) influence of gender; 2. significant ($p \le 0.01$) influence of age; # OR could not be 54 418 calculated; Italics: Overall model not significant

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

| | • | 95 | % C | I | Prevalen | се | Description ICPC codes |
|-----|-------|------|-----|-------|----------|-------------|-----------------------------------|
| рог | | | | | A. triad | No A. triad | |
| RUS | 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 |
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| Comorbidity in atopic children in general practice. For peer review only - http://bmiopen.bmi.com/site/about/guidelines.xhtml |
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Appendix 1

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|----------|------------|--------------------------------------|
| 6 7 | ICPC codes | Description |
| 8 | A03 | Fever |
| 9 | A04 | Weakness/tiredness general |
| 10 | A12 | Allergic reaction |
| 11 | A15 | Excessive crying infant |
| 12 | A16 | |
| 13 | A10 A70 | |
| 15 | A70 | |
| 16 | A/1 | Measles |
| 17 | A72 | Chickenpox |
| 18 | A73 | Malaria |
| 20 | A74 | Rubella |
| 21 | A75 | Infectious mononucleosis |
| 22 | A76 | Viral exanthem other |
| 23 | A77 | Viral disease other/NOS |
| 24 | A78 | Infectious disease other/NOS |
| 25 | Δ79 | Malignancy NOS |
| 20 27 | A84 | Deiconing by modical agent |
| 28 | A04 | |
| 29 | A85 | Adverse effect medical agent |
| 30 | A86 | Toxic effect non-medicinal substance |
| 31 | A87 | Complication of medical treatment |
| 32 33 | A88 | Adverse effect physical factor |
| 34 | A90 | Congenital anomaly OS/multiple |
| 35 | A92 | Allergy/allergic reaction NOS |
| 36 | A93 | Premature newborn |
| 37 | A94 | Perinatal morbidity other |
| 38 | A95 | Perinatal mortality |
| 40 | A96 | Death |
| 41 | B02 | Lymph gland(s) enlarged/painful |
| 42 | B70 | Lymphadenitic acute |
| 43 | D70 D71 | |
| 44 45 | D/1 | |
| 46 | B/2 | Hodgkin's disease/lymphoma |
| 47 | B73 | Leukaemia |
| 48 | B74 | Malignant neoplasm blood other |
| 49 | B75 | Benign/unspecified neoplasm blood |
| 50 | B78 | Hereditary haemolytic anaemia |
| 51 52 | B79 | Congen.anom. blood/lymph other |
| 53 | B80 | Iron deficiency anaemia |
| 54 | B81 | Anaemia. Vitamin B12/folate def. |
| 55 | B82 | Anaemia other/unspecified |
| 56 | B83 | Purpura/coogulation defect |
| 5/ | 005 | r ui pui a/ cuaguiatiui uerect |
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| 3 | DQ1 | Unavalained abnormal white calls | |
| 4 | D04 | | |
| 5 | B07 | Spienomegaly | |
| 7 | B90 | HIV-Infection/aids | |
| 8 | DUI | Abdominal pain/cramps general | |
| 9 | D02 | Abdominal pain epigastric | |
| 10 | D03 | Heartburn | |
| 11 | D04 | Rectal/anal pain | |
| 13 | D05 | Perianal itching | |
| 14 | D06 | Abdominal pain localized other | |
| 15 | D07 | Dyspepsia/indigestion | |
| 16 17 | D08 | Flatulence/gas/belching | |
| 18 | D09 | Nausea | |
| 19 | D10 | Vomiting | |
| 20 | D11 | Diarrhoea | |
| 21 | D12 | Constipation | |
| 22 | D13 | Jaundice | |
| 24 | D22 | Parasites | |
| 25 | D70 | Gastrointestinal infection | |
| 26 27 | D71 | Mumps | |
| 28 | D72 | Viral hepatitis | |
| 29 | D73 | Gastroenteritis presumed infection | |
| 30 | D74 | Malignant neonlasm stomach | |
| 31 | D75 | Malignant neoplasm colon/rectum | |
| 32 33 | D76 | Malignant neoplasm paperoas | |
| 34 | D70 | Malignant neoplasm digast other/NOS | |
| 35 | 077 | Nooplasm digest banign (uncertain | |
| 36 | D78 | Foreign hody digestive system | |
| 38 38 | D73 | Conser one well directive system | |
| 39 | D01 | Congen. anomaly digestive system | |
| 40 | D83 | Mouth/tongue/lip disease | |
| 41 | D84 | Oesophagus disease | |
| 42 43 | D85 | Duodenal ulcer | |
| 44 | D86 | Peptic ulcer other | |
| 45 | D87 | Stomach function disorder | |
| 46 | D88 | Appendicitis | |
| 47 19 | D89 | Inguinal hernia | |
| 40 49 | D90 | Hiatus hernia | |
| 50 | D91 | Abdominal hernia other | |
| 51 | D92 | Diverticular disease | |
| 52 52 | D93 | Irritable bowel syndrome | |
| 53 54 | D94 | Chronic enteritis/ulcerative colitis | |
| 55 | D95 | Anal fissure/perianal abscess | |
| 56 | D96 | Worms/other parasites | |
| 57 59 | D97 | Liver disease NOS | |
| 50 59 | | | |

| 3 | D98 | Cholecystitis/cholelithiasis |
|----------|-----|----------------------------------|
| 4 5 | D99 | Disease digestive system other |
| 5 6 | E01 | Eve pain |
| 7 | F02 | Pod ovo |
| 8 | F02 | Fue discharge |
| 9 | F03 | Eye discharge |
| 10 11 | F04 | Visual floaters/spots |
| 12 | F05 | Visual disturbance other |
| 13 | F70 | Conjunctivitis infectious |
| 14 | F71 | Conjunctivitis allergic |
| 15 16 | F72 | Blepharitis/stye/chalazion |
| 17 | F73 | Eye infection/inflammation other |
| 18 | F74 | Neoplasm of eye/adnexa |
| 19 | F75 | Contusion/haemorrhage eye |
| 20 | F76 | Foreign body in eye |
| 21 22 | F80 | Blocked lacrimal duct of infant |
| 23 | F81 | Congenital anomaly eye other |
| 24 | F82 | Detached retina |
| 25 | F83 | Retinopathy |
| 26 27 | F84 | Macular degeneration |
| 28 | F85 | Corneal ulcer |
| 29 | F86 | Trachoma |
| 30 | F91 | Refractive error |
| 31 32 | F92 | Cataract |
| 33 | F93 | Glaucoma |
| 34 | F94 | Blindness |
| 35 | F95 | Strahismus |
| 30 37 | F99 | Eve/adneva dicease other |
| 38 | H01 | Eye/autiexa disease, ottien |
| 39 | | |
| 40 | | |
| 41 42 | | For discharge |
| 42 | | Ear discharge |
| 44 | | Bleeding ear |
| 45 | H70 | Otitis externa |
| 46 47 | H/1 | Acute otitis media/myringitis |
| 47 48 | H72 | Serous otitis media |
| 49 | H73 | Eustachian salpingitis |
| 50 | H74 | Chronic otitis media |
| 51 52 | H75 | Neoplasm of ear |
| 5∠ 53 | H76 | Foreign body in ear |
| 54 | H77 | Perforation ear drum |
| 55 | H80 | Congenital anomaly of ear |
| 56 | H81 | Excessive ear wax |
| 57 58 | H82 | Vertiginous syndrome |
| 50 | | |

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|------------------|------------|------------------------------------|--|
| 3 | H83 | Otosclerosis | |
| 4 5 | H86 | Deafness | |
| 6 | K01 | Heart pain | |
| 7 | K02 | Pressure/tightness of heart | |
| 8 | K04 | Palpitations/awareness of heart | |
| 9 10 | K05 | Irregular heartheat other | |
| 11 | K07 | Swollen ankles/oedema | |
| 12 | K29 | Cardiovascular sympt /complt_other | |
| 13 | K20 | Infection of circulatory system | |
| 14 | K71 | Rheumatic fever/heart disease | |
| 16 | K72 | Neoplasm cardiovascular | |
| 17 | K72 | Congenital anomaly cardiovascular | |
| 18 10 | K7J | | |
| 20 | K74 K75 | Acute myocardial infarction | |
| 21 | K75 K76 | | |
| 22 | | loget foilure | |
| 23 | K77 V70 | | |
| 24 | N70 | Atrial Infrination/Inutter | |
| 26 | K79 | | |
| 27 | K8U | | |
| 28 20 | K81 | Heart/arterial murmur NOS | |
| 30 | K82 | Pulmonary heart disease | |
| 31 | K83 | Heart valve disease NOS | |
| 32 | K84 | Heart disease other | |
| 33 | K85 | Elevated blood pressure | |
| 35 | K86 | Hypertension uncomplicated | |
| 36 | K87 | Hypertension complicated | |
| 37 | K88 | Postural hypotension | |
| 38 39 | K89 | Transient cerebral ischaemia | |
| 40 | K90 | Stroke/cerebrovascular accident | |
| 41 | K91 | Cerebrovascular disease | |
| 42 | K92 | Atherosclerosis/PVD | |
| 43 44 | K93 | Pulmonary embolism | |
| 45 | K94 | Phlebitis/thrombophlebitis | |
| 46 | K95 | Varicose veins of leg | |
| 47 49 | K96 | Haemorrhoids | |
| 40 49 | K99 | Cardiovascular disease other | |
| 50 | L01 | Neck symptom/complain | |
| 51 | L02 | Back symptom/complaint | |
| 52 53 | L03 | Low back symptom/complaint | |
| 54 | L04 | Chest symptom/complaint | |
| 55 | L05 | Flank symptom/complaint | |
| 56 57 | L06 | Axilla symptom/complaint | |
| ว <i>า</i> 58 | L07 | Jaw symptom/complaint | |
| 59 | | | |
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| 3 | L08 | Shoulder symptom/complaint |
|----------|-----|------------------------------------|
| 4 5 | L09 | Arm symptom/complaint |
| 6 | L10 | Elbow symptom/complaint |
| 7 | L11 | Wrist symptom/complaint |
| 8 | 112 | Hand/finger symptom/complaint |
| 9 10 | 113 | Hin symptom/complaint |
| 10 | 114 | |
| 12 | | Leg/trigh symptom/complaint |
| 13 | | knee symptom/complaint |
| 14 | L16 | Ankle symptom/complaint |
| 15 16 | L17 | Foot/toe symptom/complaint |
| 10 | L18 | Muscle pain |
| 18 | L19 | Muscle symptom/complaint NOS |
| 19 | L20 | Joint symptom/complaint NOS |
| 20 | L70 | Infections musculoskeletal system |
| 21 | L71 | Malignant neoplasm musculoskeletal |
| 22 | L82 | Congenital anomaly musculoskeletal |
| 23 | L83 | Neck syndrome |
| 25 | 184 | Back syndrome w/o radiating pain |
| 26 | 185 | Acquired deformity of spine |
| 27 | 196 | Acquired deforming of spine |
| 28 29 | | Back syndrome with radiating pain |
| 30 | L87 | Bursitis/tendinitis/synovitis NOS |
| 31 | L88 | Rheumatoid/seropositive arthritis |
| 32 | L92 | Shoulder syndrome |
| 33 | L93 | Tennis elbow |
| 34 35 | L94 | Osteochondrosis |
| 36 | L95 | Osteoporosis |
| 37 | L97 | Neoplasm benign/unspec musculo. |
| 38 | L98 | Acquired deformity of limb |
| 39 | L99 | Musculoskeletal disease, other |
| 40 41 | N01 | Headache |
| 42 | N02 | Tension headache |
| 43 | N03 | Pain face |
| 44 | N04 | Restless lens |
| 45 46 | NO5 | Tingling fingers /feet /tees |
| 40 47 | NOS | Sensation disturbance other |
| 48 | | Sensation disturbance other |
| 49 | NU7 | Convuision/seizure |
| 50 | N16 | Disturbance of smell/taste |
| 51 52 | N17 | Vertigo/dizziness |
| 52 53 | N18 | Paralysis/weakness |
| 54 | N19 | Speech disorder |
| 55 | N70 | Poliomyelitis |
| 56 | N71 | Meningitis/encephalitis |
| 57 59 | N72 | Tetanus |
| 50 59 | | |
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|----------|-----|---|
| 3 | N73 | Neurological infection other |
| 4 5 | N74 | Malignant neoplasm nervous system |
| 6 | N75 | Benign neoplasm nervous system |
| 7 | N76 | Neoplasm nervous system unspec. |
| 8 | N85 | Congenital anomaly neurological |
| 9 10 | N86 | Multiple sclerosis |
| 11 | N87 | Parkinsonism |
| 12 | N88 | Fnilensy |
| 13 14 | N89 | Migraine |
| 14 | N90 | Cluster headache |
| 16 | N91 | Facial naralysis/hell's nalsy |
| 17 | N92 | |
| 18 10 | NGS | |
| 20 | N93 | |
| 21 | N00 | Neurological disease other |
| 22 | N99 | Neurological disease, other |
| 23 | P01 | Feeling anxious/nervous/tense |
| 24 25 | P02 | Acute stress reaction |
| 26 | P03 | Feeling depressed |
| 27 | P04 | Feeling/behaving irritable/angry |
| 28 | P06 | Sleep disturbance |
| 29 30 | P10 | Stammering/stuttering/tic |
| 31 | P11 | Eating problem in child |
| 32 | P12 | Bedwetting/enuresis |
| 33 | P13 | Encopresis/bowel training problem |
| 34 35 | P20 | Memory disturbance |
| 36 | P21 | ADHD |
| 37 | P22 | Child behaviour symptom/complaint |
| 38 | P23 | Adolescent behav. Symptom/complt. |
| 39 40 | P24 | Specific learning problem |
| 41 | P71 | Organic psychosis other |
| 42 | P72 | Schizophrenia |
| 43 | P73 | Affective psychosis |
| 44 45 | P74 | Anxiety disorder/anxiety state |
| 46 | P75 | Somatization disorder |
| 47 | P76 | Depressive disorder |
| 48 | P78 | Neuraesthenia/surmenage |
| 49 50 | P79 | Phobia/compulsive disorder |
| 51 | P85 | Mental retardation |
| 52 | P98 | Psychosis NOS/other |
| 53 | PQQ | Psychological disorders other |
| 54 55 | R01 | Dain rechiratory system |
| 55 56 | DUJ | Fail respiratory system Shortness of broath dynamosa |
| 57 | | |
| 58 | KU3 | wneezing |
| 59 | | |

| 3 | R04 | Breathing problem, other |
|----------|------------|--|
| 4 5 | R05 | Cough |
| 6 | R06 | Nose bleed/epistaxis |
| 7 | R07 | Sneezing/nasal congestion |
| 8 0 | R08 | Nose symptom/complaint other |
| 9 10 | R09 | Sinus symptom/complaint |
| 11 | R21 | Throat symptom/complaint |
| 12 | R22 | Tonsils symptom/complaint |
| 13 14 | R23 | Voice symptom/complaint |
| 14 | R24 | Haemontysis |
| 16 | R25 | Sputum/phlegm abnormal |
| 17 | R29 | Respiratory symptom/complaint oth |
| 18 19 | R70 | Tuberculosis airways |
| 20 | R71 | Whooping cough |
| 21 | R72 | Stren throat |
| 22 | R73 | Boil/abscess nose |
| 23 24 | R7/ | Linner respiratory infection acute |
| 25 | R75 | Sinusitic acuto/chronic |
| 26 | P76 | Toncillitic acute |
| 27 | R70 P77 | |
| 28 29 | П// D70 | |
| 30 | | |
| 31 | | Innuenza De sum suite |
| 32 | ROL | Pheumonia Disuring (alound offusion |
| 33 34 | K82 | Pleurisy/pleural effusion |
| 35 | K83 | Respiratory infection other |
| 36 | R84 | Malignant neoplasm bronchus/lung |
| 37 | R85 | Malinant neoplasm respiratory, other |
| 30 39 | R86 | Benign neoplasm respiratory |
| 40 | R87 | Foreign body nose/larynx/bronch |
| 41 | R89 | Congenital anomaly respiratory |
| 42 | R90 | Hypertrophy tonsils/adenoids |
| 43 44 | R91 | Chronic bronchitis |
| 45 | R93 | Pleural effusion |
| 46 | R95 | Chronic obstructive pulmonary dis |
| 47 48 | R96 | Asthma |
| 40 49 | R97 | Allergic rhinitis |
| 50 | R98 | Hyperventilation syndrome |
| 51 | R99 | Respiratory disease other |
| 52 53 | S01 | Pain/tenderness of skin |
| 54 | S02 | Pruritus |
| 55 | S03 | Warts |
| 56 | S04 | Lump/swelling localized |
| 57 58 | S05 | Lumps/swellings generalized |
| 59 | | |
| 60 | | |
| 2 | | |
|----------|------------|------------------------------------|
| 3 | S06 | Rash localized |
| 4 5 | S07 | Rash generalized |
| 6 | S08 | Skin colour change |
| 7 | S09 | Infected finger/toe |
| 8 | S10 | Boil/carbuncle |
| 9 10 | S10 S11 | Skin infaction post traumatic |
| 10 | S11 S12 | |
| 12 | 512 | |
| 13 | 515 | Animai/numan bite |
| 14 | 514 | Burn/scald |
| 15 16 | 515 | Foreign body in skin |
| 17 | \$20 | Corn/callosity |
| 18 | S21 | Skin texture symptom/complaint |
| 19 | S22 | Nail symptom/complaint |
| 20 | S23 | Hair loss/baldness |
| 21 | S24 | Hair/scalp symptom/complaint |
| 23 | S70 | Herpes zoster |
| 24 | S71 | Herpes simplex |
| 25 | S72 | Scabies/other acariasis |
| 20 27 | S73 | Pediculosis/skin infestation other |
| 28 | S74 | Dermatophytosis |
| 29 | S75 | Moniliasis/candidiasis skin |
| 30 | S76 | Skin infection other |
| 31 | S77 | Malignant neonlasm of skin |
| 33 | 578 | |
| 34 | 579 | Neonlasm skin benign/unspecified |
| 35 | 580 | Solar koratosis (sunhurn |
| 36 27 | S00 SQ1 | |
| 38 38 | 501 | Nacinal giolina/ iyinpitaligiolina |
| 39 | 502 | |
| 40 | 585 | Congenital skin anomaly other |
| 41 | S84 | Impetigo |
| 42 43 | S85 | Pilonidal cyst/fistula |
| 44 | S86 | Dermatitis seborrhoeic |
| 45 | S87 | Dermatitis/atopic eczema |
| 46 | S89 | Diaper rash |
| 47 | S90 | Pityriasis rosea |
| 40 49 | S91 | Psoriasis |
| 50 | S92 | Sweat gland disease |
| 51 | S93 | Sebaceous cyst |
| 52 | S94 | Ingrowing nail |
| 53 54 | S95 | Molluscum contagiosum |
| 55 | S96 | Acne |
| 56 | S97 | Chronic ulcer skin |
| 57 | S98 | Urticaria |
| 58 50 | | |
| 60 | | |

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|----------|-----|------------------------------------|
| 3 4 | S99 | Skin disease, other |
| 5 | T01 | Excessive thirst |
| 6 | т02 | Excessive appetite |
| 7 | т03 | Loss of appetite |
| 8 | Т04 | Feeding problem of infant/child |
| 9 10 | T05 | Feeding problem of adult |
| 11 | T06 | |
| 12 | | |
| 13 | 107 | weight gain |
| 14 | 108 | Weight loss |
| 15 16 | 110 | Growth delay |
| 17 | T11 | Dehydration |
| 18 | T15 | Tumor thyroid |
| 19 | Т70 | Endocrine infection |
| 20 | T71 | Malignant neoplasm thyroid |
| 21 | Т72 | Benign neoplasm thyroid |
| 22 | Т73 | Neoplasm endocrine oth/unspecified |
| 24 | Т78 | Thyroglossal duct/cvs |
| 25 | т80 | Congenital anom endocrine/metab |
| 26 | T81 | Goitre |
| 27 | | Obecity |
| 20 29 | 102 | Obesity |
| 30 | 183 | Overweight |
| 31 | 185 | Hyperthyroidism/thyrotoxicosis |
| 32 | Т86 | Hypothyroidism/myxoedema |
| 33 | Т87 | Hypoglycaemia |
| 34 35 | Т88 | Renal glycosuria |
| 36 | Т89 | Diabetes insulin dependent |
| 37 | Т90 | Diabetes non-insulin dependent |
| 38 | T91 | Vitamin/nutritional deficiency |
| 39 | Т92 | Gout |
| 40 41 | Т93 | Lipid disorder |
| 42 | Т99 | Endocrine/metab/nutrit dis other |
| 43 | 101 | Dysuria/painful urination |
| 44 | | |
| 45 | 002 | |
| 46 47 | 004 | Incontinence urine |
| 48 | 005 | Urination problems other |
| 49 | 006 | Haematuria |
| 50 | U07 | Urine symptom/complaint other |
| 51 | U13 | Bladder symptom/complaint other |
| 52 | U14 | Kidney symptom/complaint |
| 54 | U70 | Pyelonephritis/pyelitis |
| 55 | U71 | Cystitis/urinary infection other |
| 56 | U72 | Urethritis |
| 57 | U75 | Malignant neoplasm of kidney |
| 58 50 | - | |
| 60 | | |
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| 2 | | |
|----------|-----|-----------------------------------|
| 3 | U76 | Malignant neoplasm of bladder |
| 4 5 | U77 | Malignant neoplasm urinary other |
| 6 | U78 | Benign neoplasm urinary tract |
| 7 | U79 | Neoplasm urinary tract NOS |
| 8 | U85 | Congenital anomaly urinary tract |
| 9 10 | U88 | Glomerulonephritis/nephrosis |
| 11 | U90 | Orthostatic albumin/proteinuria |
| 12 | U95 | Urinary calculus |
| 13 14 | U98 | Abnormal urine test NOS |
| 15 | U99 | Urinary disease, other |
| 16 | X83 | Congenital anomaly genital female |
| 17 | X84 | Vaginitis/vulvitis NOS |
| 19 | X85 | Cervical disease NOS |
| 20 | X99 | Genital disease female, other |
| 21 | Y74 | Orchitis/epididymitis |
| 22 23 | Y75 | Balanitis |
| 24 | Y81 | Phimosis/redundant prepuce |
| 25 | Y82 | Hypospadias |
| 26 27 | Y83 | Undescended testicle |
| 28 | Y84 | Congenital genl anomaly (m) other |
| 29 | 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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| | |



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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 nonatopic 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

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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.

<text>

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

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| 3 4 | 63 | not diagnosed. To study possible associations between atopic disorders and 404 different symptoms and |
| 5 6 7 | 64 | diseases, an extensive and representative nationwide general practice database is explored using a cross- |
| 7 8 9 | 65 | sectional design. The design of this study allows new hypotheses to be generated, providing valuable input for |
| 10 11 | 66 | future research. |
| $\begin{array}{c}12\\3\\1\\1\\1\\1\\1\\1\\1\\2\\2\\2\\2\\2\\2\\2\\2\\2\\2\\2$ | 67 | |

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 (<u>www.nivel.nl/en/dossier/nivel-primary-care-database</u>), 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).

B7 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 guarter 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.

13 Atopic triad

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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.

19 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).

9 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.

9 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 $p \le 0.001$ were considered statistically significant. All associations were tested for the modifying effects of age and gender. In case of a significant effect ($p \le 0.01$), 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.

149 Ethical approval

46 150 Dutch law allows the use of EHRs for research purposes under certain conditions. According to this legislation,
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48 151 it is not necessary to obtain informed consent from patients or approval from a medical ethics committee for
50 152 this type of observational study that contains no directly identifiable data (Dutch Civil Law, Article 7: 458).
52 153 153 Therefore, no waiver of ethical approval was obtained from an Institutional Review Board (IRB) or ethics
54 55 154 committee. The authors had no access to any identifying information at any moment during the analysis of the
57 155 data.

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Results

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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.

66 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).

177 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).

6 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.

8 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

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| 2 3 4 | 201 | considered high (OR 17.8). Allergic conjunctivitis (OR 6.8) is also frequently seen in children with all three atopic |
| 5678911123456789222222222222222222222222222222222222 | 202 | disorders. |

1 2 3 4 203 5 6 7 8 204 9 10 12 13 14 15 17 19 20 21 22 24 26 28 29 31 33 35 36 37 38 40 42 44 45 47 49 51 52 53 54 223 55 56 57 58 59 60

Discussion

Main findings

11 205 The present study used an extensive and representative general practice database (22). The large number of 206 children gives the study substantial power and generalizability. This could also allow evaluation of possible links 16 207 between atopic disorders and rare childhood diseases. This study showed that atopic children have an 18 208 increased risk for the development of both atopic and non-atopic diseases and symptoms. Children diagnosed 209 with one atopic disorder were frequently diagnosed by their GP with symptoms associated with one of the 23 210 (other) atopic disorder(s). This suggests that GPs are not always fully aware of relevant atopic comorbidity, or 25 211 at least do not label it correctly. Two examples support this hypothesis. First of all, a child diagnosed with ²⁷ 212 atopic eczema is also diagnosed with pruritus, suggesting possible misclassification. Secondly, a child with $\frac{-3}{30}$ 213 atopic eczema that presents with 'wheeze' or 'dyspnea' is at a higher risk for the development of asthma 32 214 compared to a child without atopic eczema. A GP should be aware of this increased risk, since it could result in 34 215 insufficient treatment of a child. However, a GP could also use symptom-related ICPC-codes deliberately when 216 the purpose is to record a provisional diagnosis (e.g. wheeze as the provisional diagnosis of asthma). Regarding 39 217 non-atopic co-morbidity, strong associations were found between the atopic disorder and diseases and 41 218 symptoms related to the same organ system. For example, children with atopic eczema are at increased risk for ⁴³ 219 the development of other skin diseases, asthmatic children are at risk of other airway diseases, and children ₄₆ 220 with allergic rhinitis are at risk of ear-nose-throat-related symptoms and diseases. Gastro-intestinal and 48 221 musculoskeletal diseases and symptoms were also seen more frequently in atopic children. When exploring ⁵⁰ 222 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

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2 3 224 Children with atopic eczema had an increased risk of developing infectious skin diseases such as warts, 4 5 6 225 impetigo, dermatophytosis and molluscum contagiosum. The common etiology could be the barrier 7 8 226 dysfunction of the skin in children with atopic eczema. This barrier dysfunction is also seen in psoriasis, a 9 10 227 disease that, according to the present study, is associated with atopic eczema (OR 3.4). They share some 11 12 13 228 common pathological backgrounds such as barrier dysfunction and enhanced IL-22 expression (31). Although 14 15 229 the clinical pictures of these two diseases can be very different, the observed association could also suggests 16 17 ₂₃₀ misclassification among these two chronic skin diseases that are often confused for one another. Otitis externa 18 19 231 and blepharitis both had significant ORs. These disorders could in fact be an expression of atopic eczema. 20 21 22 23²³² Children with asthma seem to have consulted their GP more frequently for airway-related infections such as 24 25 233 acute laryngitis/tracheitis, acute upper respiratory infection, pneumonia and bronchitis. This is in agreement 26 ²⁷ 234 with another primary healthcare study (2). An explanation for this could be that airway infections increase 28 29 235 asthma symptoms or vice versa, that asthma resulted in increased susceptibility for infection, which increased 30 31 32 236 their motivation to visit the GP. Furthermore, the awareness of parents is likely to be increased when a child 33 34 237 suffers from asthma, since such an infection could predispose for an asthma exacerbation. 35 36 37 ₂₃₈ Children with allergic rhinitis consulted their GPs more frequently for ear-nose-throat-related symptoms and 38 39 40²³⁹ diseases. However, even more striking are the asthma-related symptoms. Both shortness of breath (OR 2.7) 41 42 240 and wheeze (OR 4.3) were frequently seen in children with allergic rhinitis. There is strong evidence that 43 ⁴⁴ 241 allergic rhinitis has an adverse impact on asthma severity (32). Because allergic rhinitis can provoke asthma 45 46 242 symptoms, allergic rhinitis symptoms should be taken more seriously by GPs to reduce insufficient treatment. 47 48 49 50 243 Gastrointestinal-related symptoms are also frequently diagnosed by GPs in atopic children. This is in 51 52 244 accordance with a study in adults in a primary care setting (33). These symptoms could be related to IgE-53 ⁵⁴ 245 mediated food allergies or in rare cases even to eosinophilic esophagitis that are associated with atopic 55 56 57 246 disorders (34); however, in children, abdominal pains can also be a general expression of not feeling well. 58 59 60

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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.

254 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

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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).

82 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.

90 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

| 1 2 3 4 | 293 | comorbidity. In children known to have at least one atopic disorder, specific attention is required to avoid |
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| 5 | 294 | possible insufficient treatment and unnecessary loss of quality of life. |
| $egin{array}{c} 6 \\ 7 \\ 8 \\ 9 \\ 10 \\ 11 \\ 21 \\ 13 \\ 4 \\ 15 \\ 16 \\ 17 \\ 18 \\ 19 \\ 20 \\ 22 \\ 22 \\ 22 \\ 22 \\ 22 \\ 22 \\ 2$ | 294 | possible insufficient treatment and unnecessary loss of quality of life. |

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Competing Interests 14 298

18 299 We have read and understood BMJ policy on declaration of interests and declare that we have no competing

interests.

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Contributions 24 301

28 302 Study conception and design: DP, MN, JK, PB, AB

31 303 32 ³⁰³ Acquisition of data: DP, MN

Analysis and interpretation of data: DP, MN

38 305 Drafting of manuscript: DP

41 306 Critical revision: MN, JK, PB, AB

44 307 Guarantor: MN, AB

48 308 Funding

52 309 This research received no specific grant from any funding agency in the public, commercial or not-for-profit

54 310 sectors.

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| 3 | Data sharing statement |
| 4 511 5 | Data sharing statement |
| 6 7 | |
| , 8 312 | Data will be available from the repository of Data Archiving and Networked Services (DANS; |
| 9 10 24 2 | |
| 10 313 | www.dans.knaw.nl). |
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Figure legends

- Table 1. General characteristics of the total study population
- **Table 2.** Significantly ($p \le 0.001$) associated comorbidity in children diagnosed with only atopic eczema (Ec) and
- 15 426 at least three year follow-up versus controls (non-atopic children) (n=31,060)
- 18 427 **Table 3.** Significantly ($p \le 0.001$) associated comorbidity in children diagnosed with only asthma (As) and at least
- 20 428 three year follow-up versus controls (non-atopic children) (n=15,774)
- 23 ₄₂₉ **Table 4.** Significantly ($p \le 0.001$) associated comorbidity in children diagnosed with only allergic rhinitis (AR) and
- 26⁴³⁰ at least three year follow-up versus controls (non-atopic children) (n=13,670)
- 29 431 **Table 5.** Significantly (p≤0.001) associated comorbidity in children diagnosed with Atopic Triad (AT) and at least
- 31 432 three year follow-up versus controls (non-atopic children) (n= 1,118)

| | n | Age in years (SD) | Male |
|-------------------------|--------------------|----------------------|-----------------------|
| nly 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% |
| Atonic triad | 559 | 116(40) | 61.4% |
| NB Children in the firs | t three gro | 11.0 (4.0) | $\frac{01.470}{0100}$ |
| mentioned, but none c | of the othe | er disorders, wi | nereas cl |
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Table 2. Significantly ($p \le 0.001$) 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 | Preva | alence | OR sex | | OR age | | e |
|------------|---|---------------|----------------------------|---------------|--------------|--------|------|--------|------|-------|
| | | | | Ec | No Ec | boy | girl | 2-6 | 7-12 | 13-18 |
| Skin-r | elated 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 | | | | | |
| Airwa | y-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-n | ose-throat-related diseases and syn | nptoms | | | | | | | | |
| 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 | | | | | |
| Gastr | o-intestinal-related diseases and sy | mptom | S | | | | | | | |
| 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 | | | | | |
| Musc | uloskeletal | 2.20 | 1.51 5.11 | 0.10 | 0.21 | | | | | |
| 117 | Foot/toe symptom/complaint | 1 30 | 1 15 – 1 48 | 3 50 | 2 71 | | | | | |
| 198 | Acquired deformity of limb | 1 39 | 1.10 - 1.40 | 2 90 | 2.71 | | | | | |
| Misce | | 1.55 | 1.20 1.00 | 2.50 | 2.11 | | | | | |
| A04 | Weakness/tiredness general | 1 25 | 1 09 - 1 44 | 3 07 | 2 47 | | | | | |
| S12 | Insect hite / sting | 1 / 1 | 1 19 - 1 66 | 2.07 | 1.60 | | | | | |
| 512 | Plonharitic/styp/chalazion ² | 1 5 2 | 1.13 1.00 | 1 20 | 0.70 | | | 0.96 | 2 79 | 1 76 |
| F72 | | 1.55 | 1.22 - 1.95 1.20 - 1.91 | 1.20 2.10 | 0.79 | | | 0.50 | 2.75 | 1.70 |
| F7U VQ1 | Phimosis /redundant propuse | 1.35 1.02 | 1.23 - 1.01 | 2.10 1.40 | 1.44 0 00 | | | | | |
| 101 F71 | Conjunctivitis allergic | 1.05 1.00 | 1.47 - 2.72 | 1.49 | 0.05 | | | | | |
| r/⊥ ∧1⊃ | Allorgy | 1.99 2 1 1 | 1.33 - 2.49 | 1.45 2 / 1 | 0.75 | | | | | |
| ATT | Allergy | 5.11 | 2.02 - 3.09 | 5.42 | 1.13 | | | | | |

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

57 440 **Italics**: Overall model not significant

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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 | Prev | alence | OR | sex | OR age | | е |
|--------------|---|--------|---------------------------|--------------|--------------|------|------|--------|------|----|
| | | | | As | No As | boy | girl | 2-6 | 7-12 | 13 |
| Skin-r | elated diseases and symptoms | | | | | | | | | |
| S98 | Urtiacaria | 2.10 | 1.61 – 2.73 | 2.21 | 1.07 | | | | | |
| Airwa | y-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 | |
| R91 | Chronic bronchitis | 5.66 | 3.14-10.23 | 0.93 | 0.16 | | | | | |
| R02 | Shortness of breath/dysphoea | 7.74 | 5.05-11.87 | 2.31 | 0.30 | | | | | |
| R03 | Wheezing | 10.30 | 4.73-22.42 | 0.90 | 0.09 | | | | | |
| Ear-no | ose-throat-related diseases and syn | nptoms | | | | | | | | |
| 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 | p-intestinal-related diseases and sy | mptoms | | | | | | | | |
| 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 | | | | | |
| Musci | uloskeletal | - | | | | | | | | |
| 115 | Knee symptom/complaint ² | 1.11 | 0.90 - 1.37 | 2.42 | 2.18 | | | 1.34 | 1.49 | |
| 112 | Hand symptom/complaint ¹ | 1 37 | 1.09 - 1.71 | 2 27 | 1.67 | 1.00 | 2.13 | - | _ | |
| 198 | Acquired deformity of limb | 1.37 | 1 16 - 1 68 | 3 54 | 2 56 | | 0 | | | |
| 100 | Musculoskeletal disease other | 1.40 | 1.10 1.00 | 2.54 | 1 78 | | | | | |
| 111 | Wrist symptom/complaint | 1.92 | 1.22 1.05 | 2.00 | 0.87 | | | | | |
| Misce | | 1.50 | 1.40 2.05 | 1.71 | 0.07 | | | | | |
| P21 | | 1 34 | 1 13 – 1 58 | 4 18 | 3 17 | - | | | | |
| Δ <u>Ω</u> Λ | Weakness/tiredness general | 1 20 | 1.13 1.50 1.17 - 1.65 | 4.10 | 2 97 | | | | | |
| N01 | Headache | 1.55 | 1.17 1.05 | 7.04 2.49 | 1.66 | | | | | |
| F70 | Conjunctivitis infectious | 1 72 | 1.21 1.05 1.31 - 2.27 | 1 78 | 1.00 | | | | | |
| T10 | Growth delay | 1.72 | 1.51 2.27 1.35 - 2.44 | 1.60 | 1.04 0 80 | | | | | |
| T83 | Overweight | 2 09 | 1 41 - 3 10 | 0.98 | 0.05 | | | | | |
| T82 | Ohesity | 2.05 | 1.41 5.10 1.50 - 4.05 | 0.50 | 0.78 | | | | | |
| .02 | C S C S C S C S C S C S C S C S C S C S | 2.7/ | 1.30 4.03 | 0.00 | 0.20 | | | | | |
| F71 | Conjunctivitis allergic | 2 5 5 | 1 85 – 3 49 | 1 7 2 | 0 68 | | | | | |

1. significant ($p \le 0.01$) influence of gender; 2. significant ($p \le 0.01$) influence of age

55444Italics: Overall model not significant

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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 ag | 9 |
|---------|---|------|-------------|------------|-------|------|------|------|-------|-------|
| | • | | | 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 | | | | | |
| Airwa | ay-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-n | ose-throat-related diseases and sympt | oms | | | | | | | | |
| 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 | | | | | |
| Gastr | o-intestinal-related diseases and symp | toms | | | | | | | | |
| 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 | | | |
| Musc | uloskeletal | | | | | | | | | |
| 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 | | | | | |
| Misce | ellaneous | | | | | | | | | |
| 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 | 1 | | |
| 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 | | | | | |
| · · · ± | | 3.44 | | 25 | 0.02 | | | | | |

53 448 1. significant ($p \le 0.01$) influence of gender; 2. significant ($p \le 0.01$) influence of age

54 449 *Italics*: Overall model not significant

55 450

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)

| R05 L17 R74 | Cough Foot/toe symptom/complaint | 2.42 | | 3/0 | CI | Prevalence | | |
|-------------------|-------------------------------------|-------|------|-----|-------|------------|-------------|--|
| R05 L17 R74 | Cough Foot/toe symptom/complaint | 2.42 | | | | A. triad | No A. triad | |
| L17 R74 | Foot/toe symptom/complaint | | 1.43 | - | 4.10 | 8.59 | 3.76 | |
| R74 | | 3.25 | 1.63 | - | 6.50 | 6.08 | 1.97 | |
| -74 | Upper respiratory infection acute | 3.75 | 2.33 | - | 6.04 | 14.13 | 4.29 | |
| F/1 | 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 |

| 2 | | |
|----------|------------|--------------------------------------|
| 3 | B84 | Unexplained abnormal white cells |
| 4 | B87 | Splenomegaly |
| 6 | B90 | HIV-infection/aids |
| 7 | D01 | Abdominal pain/cramps general |
| 8 | D02 | Abdominal pain engastric |
| 9 10 | 0 003 | Hearthurn |
| 11 | | Rectal/anal nain |
| 12 | 2 D05 | |
| 13 | | Abdominal nain localized other |
| 14 | , D00 | |
| 16 | | Elatulance/gas/holching |
| 17 | 7 000 | Flatulence/gas/belching |
| 18 | B D09 | Nausea |
| 15 | | vomiting |
| 21 | | Diarrhoea |
| 22 | D12 | Constipation |
| 23 | 3 D13 | Jaundice |
| 24 | 1 D22 | Parasites |
| 26 | D70 | Gastrointestinal infection |
| 27 | , D71 | Mumps |
| 28 | 3 D72 | Viral hepatitis |
| 29 | D73 | Gastroenteritis presumed infection |
| 30 | D74 | Malignant neoplasm stomach |
| 32 | 2 D75 | Malignant neoplasm colon/rectum |
| 33 | B D76 | Malignant neoplasm pancreas |
| 34 | 1 D77 | Malig. neoplasm digest other/NOS |
| 36 | D78 | Neoplasm digest benign/uncertain |
| 37 | 7 D79 | Foreign body digestive system |
| 38 | B D81 | Congen. anomaly digestive system |
| 39 | D83 | Mouth/tongue/lip disease |
| 40 | D84 | Oesophagus disease |
| 42 | 2 D85 | Duodenal ulcer |
| 43 | B D86 | Peptic ulcer other |
| 44 75 | 1 5 D87 | Stomach function disorder |
| 46 | , 5 D88 | Appendicitis |
| 47 | 7 D89 | Inguinal hernia |
| 48 | B D90 | Hiatus hernia |
| 49 | D D91 | Abdominal hernia other |
| 51 | , I D92 | Diverticular disease |
| 52 | 2 D93 | Irritable bowel syndrome |
| 53 | B D94 | Chronic enteritis/ulcerative colitis |
| 54 | | Anal fissure/nerianal abscess |
| 56 | | Morms other parasites |
| 57 | 7 7 | liver disease NOS |
| 58 | 3 | |
| 59 | 9 | |
| OU | , | |

| 2 | | |
|----------|-----|----------------------------------|
| 3 | D98 | Cholecystitis/cholelithiasis |
| 4 5 | D99 | Disease digestive system, other |
| 6 | F01 | Eye pain |
| 7 | F02 | Red eve |
| 8 | F03 | Eve discharge |
| 9 10 | F04 | Visual floaters/spots |
| 11 | F05 | Visual disturbance other |
| 12 | F70 | Conjunctivitis infectious |
| 13 14 | F71 | Conjunctivitis allergic |
| 15 | F72 | Blepharitis/stve/chalazion |
| 16 | F73 | Eve infection/inflammation other |
| 17 | F74 | Neoplasm of eve/adnexa |
| 10 19 | F75 | Contusion/haemorrhage eve |
| 20 | F76 | Foreign hody in eve |
| 21 | F80 | Blocked lacrimal duct of infant |
| 22 | F81 | Congenital anomaly eve other |
| 23 24 | F82 | Detached retina |
| 25 | F83 | Betinonathy |
| 26 | F84 | Macular degeneration |
| 27 | F85 | Corpeal ulcer |
| 20 29 | F86 | Trachoma |
| 30 | F91 | Refractive error |
| 31 | FQ2 | Cataract |
| 32 33 | FQ3 | Glaucoma |
| 34 | FQ/ | Blindness |
| 35 | FQ5 | Strahiemus |
| 36 27 | F00 | Strabisinus |
| 38 | H01 | Eye/autiexa disease, ottiei |
| 39 | | |
| 40 | | |
| 41 42 | | For discharge |
| 43 | | Edi discharge |
| 44 | | Bleeding ear |
| 45 | H70 | Otitis externa |
| 46 47 | | Acute otitis media/myringitis |
| 48 | H72 | Serous otitis media |
| 49 | H73 | Eustachian salpingitis |
| 50 | H/4 | Chronic otitis media |
| 51 52 | H75 | Neoplasm of ear |
| 53 | H/6 | Foreign body in ear |
| 54 | H// | Perforation ear drum |
| 55 56 | H80 | Congenital anomaly of ear |
| 50 57 | H81 | Excessive ear wax |
| 58 | H82 | Vertiginous syndrome |
| 59 | | |

| 2 | | |
|----------|-----------|---|
| 3 | H83 | Otosclerosis |
| 4 5 | H86 | Deafness |
| 6 | K01 | Heart pain |
| 7 | К02 | Pressure/tightness of heart |
| 8 | К04 | Palpitations/awareness of heart |
| 9 10 | к05 | Irregular heartbeat other |
| 11 | К07 | Swollen ankles/oedema |
| 12 | K29 | Cardiovascular sympt /complt_other |
| 13 | K70 | Infection of circulatory system |
| 14 | K71 | Rheumatic fever/heart disease |
| 16 | к72 | Neonlasm cardiovascular |
| 17 | к73 | Congenital anomaly cardiovascular |
| 18 10 | K74 | Ischaemic heart disease w. angina |
| 20 | K75 | Acute myocardial infarction |
| 21 | K75 | Acute myocardiar marchon |
| 22 | К70 77 | lisense w/o angina |
| 23 | K77 | |
| 24 25 | K78 | Atrial fibrillation/flutter |
| 26 | к79 | Paroxysmal tachycardia |
| 27 | K8U | Cardiac arrhythmia NOS |
| 28 | K81 | Heart/arterial murmur NOS |
| 29 30 | K82 | Pulmonary heart disease |
| 31 | K83 | Heart valve disease NOS |
| 32 | K84 | Heart disease other |
| 33 | K85 | Elevated blood pressure |
| 34 35 | K86 | Hypertension uncomplicated |
| 36 | K87 | Hypertension complicated |
| 37 | K88 | Postural hypotension |
| 38 | K89 | Transient cerebral ischaemia |
| 39 40 | К90 | Stroke/cerebrovascular accident |
| 41 | К91 | Cerebrovascular disease |
| 42 | К92 | Atherosclerosis/PVD |
| 43 44 | К93 | Pulmonary embolism |
| 45 | К94 | Phlebitis/thrombophlebitis |
| 46 | K95 | Varicose veins of leg |
| 47 | K96 | Haemorrhoids |
| 48 ⊿9 | К99 | Cardiovascular disease other |
| 50 | L01 | Neck symptom/complain |
| 51 | L02 | Back symptom/complaint |
| 52 | L03 | Low back symptom/complaint |
| 53 54 | L04 | Chest symptom/complaint |
| 55 | L05 | Flank symptom/complaint |
| 56 | L06 | Axilla symptom/complaint |
| 57 59 | L07 | Jaw symptom/complaint |
| วช 59 | | , |
| 60 | | |

1
| 2 | | |
|----------|------------|------------------------------------|
| 3 | L08 | Shoulder symptom/complaint |
| 4 5 | L09 | Arm symptom/complaint |
| 6 | 110 | Flbow symptom/complaint |
| 7 | 111 | Wrist symptom/complaint |
| 8 | 112 | Hand/finger symptom/complaint |
| 9 | 112 | |
| 10 | 114 | Hip symptom/complaint |
| 12 | | Leg/thigh symptom/complaint |
| 13 | LIS | Knee symptom/complaint |
| 14 | | Ankle symptom/complaint |
| 15 16 | L1/ | Foot/toe symptom/complaint |
| 17 | L18 | Muscle pain |
| 18 | L19 | Muscle symptom/complaint NOS |
| 19 | L20 | Joint symptom/complaint NOS |
| 20 | L70 | Infections musculoskeletal system |
| 21 | L71 | Malignant neoplasm musculoskeletal |
| 23 | L82 | Congenital anomaly musculoskeletal |
| 24 | L83 | Neck syndrome |
| 25 | L84 | Back syndrome w/o radiating pain |
| 26 27 | L85 | Acquired deformity of spine |
| 28 | L86 | Back syndrome with radiating pain |
| 29 | L87 | Bursitis/tendinitis/synovitis NOS |
| 30 | L88 | Rheumatoid/seropositive arthritis |
| 31 32 | L92 | Shoulder syndrome |
| 33 | 193 | Tennis elbow |
| 34 | 194 | Osteochondrosis |
| 35 | 195 | Osteoporosis |
| 36 | 197 | Neoplasm benign/unspec musculo |
| 38 | 108 | Acquired deformity of limb |
| 39 | 100 | Acquired deforming of mind |
| 40 | L99 NO1 | Widsculoskeletal disease, other |
| 41 | NOT | Headache |
| 42 43 | NU2 | l'ension headache |
| 44 | NU3 | Pain face |
| 45 | N04 | Restless legs |
| 46 | N05 | Tingling fingers/feet/toes |
| 47 48 | N06 | Sensation disturbance other |
| 49 | N07 | Convulsion/seizure |
| 50 | N16 | Disturbance of smell/taste |
| 51 | N17 | Vertigo/dizziness |
| 52 53 | N18 | Paralysis/weakness |
| 53 54 | N19 | Speech disorder |
| 55 | N70 | Poliomyelitis |
| 56 | N71 | Meningitis/encephalitis |
| 57 59 | N72 | Tetanus |
| 59 | | |
| 60 | | |

| 2 | | |
|----------|------------|-----------------------------------|
| 3 | N73 | Neurological infection other |
| 4 5 | N74 | Malignant neoplasm nervous system |
| 6 | N75 | Benign neoplasm nervous system |
| 7 | N76 | Neoplasm nervous system unspec |
| 8 | N85 | Congenital anomaly neurological |
| 9 10 | N86 | Multiple sclerosis |
| 10 | NQ7 | Darkinconism |
| 12 | N07 | |
| 13 | | Epilepsy |
| 14 | N89 | Migraine |
| 15 16 | N90 | Cluster headache |
| 17 | N91 | Facial paralysis/bell's palsy |
| 18 | N92 | Trigeminal neuralgia |
| 19 | N93 | Carpal tunnel syndrome |
| 20 21 | N94 | Peripheral neuritis/neuropathy |
| 22 | N99 | Neurological disease, other |
| 23 | P01 | Feeling anxious/nervous/tense |
| 24 | P02 | Acute stress reaction |
| 25 26 | P03 | Feeling depressed |
| 20 27 | P04 | Feeling/behaving irritable/angry |
| 28 | P06 | Sleep disturbance |
| 29 | P10 | Stammering/stuttering/tic |
| 30 | P11 | Eating problem in child |
| 31 | P12 | Bedwetting/enuresis |
| 33 | P13 | Encopresis/bowel training problem |
| 34 | P20 | Memory disturbance |
| 35 | P21 | |
| 30 37 | P22 | Child behaviour symptom/complaint |
| 38 | P23 | Adolescent behav, Symptom/complet |
| 39 | P24 | Specific learning problem |
| 40 | D71 | Organic neuchosic other |
| 41 42 | F71 D72 | Sebises branie |
| 42 | P72 | Schizophrenia |
| 44 | P73 | Affective psychosis |
| 45 | P74 | Anxiety disorder/anxiety state |
| 46 47 | P75 | Somatization disorder |
| 47 48 | P76 | Depressive disorder |
| 49 | P78 | Neuraesthenia/surmenage |
| 50 | P79 | Phobia/compulsive disorder |
| 51 | P85 | Mental retardation |
| 52 53 | P98 | Psychosis NOS/other |
| 54 | P99 | Psychological disorders, other |
| 55 | R01 | Pain respiratory system |
| 56 | R02 | Shortness of breath/dyspnoea |
| 57 58 | R03 | Wheezing |
| 50 59 | | - |
| 60 | | |

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| 1 | | |
|----------|-----|---|
| 2 | | |
| 4 | R04 | Breathing problem, other |
| 5 | R05 | Cough |
| 6 7 | R06 | Nose bleed/epistaxis |
| 8 | R07 | Sneezing/nasal congestion |
| 9 | R08 | Nose symptom/complaint other |
| 10 | R09 | Sinus symptom/complaint |
| 11 | R21 | Throat symptom/complaint |
| 12 | R22 | Tonsils symptom/complaint |
| 14 | R23 | Voice symptom/complaint |
| 15 | R24 | Haemoptysis |
| 16 | R25 | Sputum/phlegm abnormal |
| 17 | R29 | Respiratory symptom/complaint oth. |
| 19 | R70 | Tuberculosis airways |
| 20 | R71 | Whooping cough |
| 21 | R72 | Strep throat |
| 22 | R73 | Boil/abscess nose |
| 24 | R74 | Upper respiratory infection acute |
| 25 | R75 | Sinusitis acute/chronic |
| 26 27 | R76 | Tonsillitis acute |
| 27 | R77 | Larvngitis/tracheitis acute |
| 29 | R78 | Acute bronchitis/bronchiolitis |
| 30 | R80 | Influenza |
| 31 | R81 | Pneumonia |
| 32 33 | R82 | |
| 34 | R83 | Picurisy/picural enusion Bospiratory infaction other |
| 35 | R85 | Malignant noonlasm bronchus (lung |
| 36 | | Malignant neoplasm receivatory, other |
| 37 38 | ROJ | Panian neoplasm respiratory, other |
| 39 | R80 | Benign heoplasm respiratory |
| 40 | K87 | Foreign body nose/larynx/bronch |
| 41 | R89 | Congenital anomaly respiratory |
| 42 43 | R90 | Hypertrophy tonsils/adenoids |
| 44 | R91 | Chronic bronchitis |
| 45 | R93 | Pleural effusion |
| 46 | R95 | Chronic obstructive pulmonary dis |
| 47 48 | R96 | Asthma |
| 49 | R97 | Allergic rhinitis |
| 50 | R98 | Hyperventilation syndrome |
| 51 52 | R99 | Respiratory disease other |
| 52 53 | S01 | Pain/tenderness of skin |
| 54 | S02 | Pruritus |
| 55 | S03 | Warts |
| 56 | S04 | Lump/swelling localized |
| 57 58 | S05 | Lumps/swellings generalized |
| 59 | | |
| 60 | | |

| 2 | | |
|----------|------|------------------------------------|
| 3 | S06 | Rash localized |
| 4 5 | S07 | Rash generalized |
| 6 | S08 | Skin colour change |
| 7 | S09 | Infected finger/toe |
| 8 | S10 | Boil/carbuncle |
| 9 10 | S11 | Skin infection post-traumatic |
| 10 | S12 | Insort hito/sting |
| 12 | S12 | Animal/human hita |
| 13 | 513 | |
| 14 15 | 514 | Burriyscalu |
| 16 | 515 | Foreign body in skin |
| 17 | S20 | Corn/callosity |
| 18 | \$21 | Skin texture symptom/complaint |
| 19 | S22 | Nail symptom/complaint |
| 20 21 | S23 | Hair loss/baldness |
| 22 | S24 | Hair/scalp symptom/complaint |
| 23 | S70 | Herpes zoster |
| 24 | S71 | Herpes simplex |
| 25 26 | S72 | Scabies/other acariasis |
| 20 | S73 | Pediculosis/skin infestation other |
| 28 | S74 | Dermatophytosis |
| 29 | S75 | Moniliasis/candidiasis skin |
| 30 31 | S76 | Skin infection other |
| 32 | S77 | Malignant neoplasm of skin |
| 33 | S78 | Lipoma |
| 34 | S79 | Neoplasm skin benign/unspecified |
| 35 | S80 | Solar keratosis/sunburn |
| 30 37 | S81 | Haemangioma/lymphangioma |
| 38 | S82 | Naevus/mole |
| 39 | S83 | Congenital skin anomaly other |
| 40 41 | S84 | Impetigo |
| 41 | 585 | Pilonidal cyst/fistula |
| 43 | 586 | Dermatitis seborrhoeic |
| 44 | 580 | Dermatitis /atonic oczema |
| 45 46 | 580 | Dianor rash |
| 40 47 | 500 | |
| 48 | 590 | Pityriasis rosea |
| 49 | 291 | |
| 50 | 592 | Sweat gland disease |
| วา 52 | 293 | Sebaceous cyst |
| 53 | 594 | Ingrowing nail |
| 54 | 595 | Molluscum contagiosum |
| 55 50 | S96 | Acne |
| 50 57 | S97 | Chronic ulcer skin |
| 58 | S98 | Urticaria |
| 59 | | |

| 2 | | |
|----------|------------|------------------------------------|
| 3 | S99 | Skin disease, other |
| 4 5 | T01 | Excessive thirst |
| 6 | T02 | Excessive appetite |
| 7 | T03 | Loss of appetite |
| 8 | T04 | Feeding problem of infant/child |
| 9 10 | T05 | Feeding problem of adult |
| 11 | T06 | Anorexia nervosa |
| 12 | T07 | Weight gain |
| 13 14 | T08 | Weight loss |
| 15 | T10 | Growth delay |
| 16 | T11 | Dehydration |
| 17 | T15 | Tumor thyroid |
| 18 19 | T70 | Endocrine infection |
| 20 | T71 | Malignant neonlasm thyroid |
| 21 | T72 | Benign neonlasm thyroid |
| 22 | T73 | Neonlasm endocrine oth/unspecified |
| 23 24 | T78 | Thyrogloscal duct/ovs |
| 25 | T20 | Congonital anom ondesting (motoh |
| 26 | T00 T01 | Coitro |
| 27 | 101 | Obesity |
| 28 29 | 102 T02 | Obesity |
| 30 | TOS | Overweight |
| 31 | | Hyperthyroidism/thyrotoxicosis |
| 32 | | Hypothyroidism/myxoedema |
| 33 34 | 187 | Hypogiycaemia |
| 35 | 188 | Renal giycosuria |
| 36 | 189 | Diabetes insulin dependent |
| 37 | 190 | Diabetes non-insulin dependent |
| 39 | 191 | Vitamin/nutritional deficiency |
| 40 | 192 | Gout |
| 41 | 193 | Lipid disorder |
| 42 43 | 199 | Endocrine/metab/nutrit. dis. other |
| 44 | 001 | Dysuria/paintul urination |
| 45 | 002 | Urinary frequency/urgency |
| 46 | U04 | Incontinence urine |
| 47 48 | U05 | Urination problems other |
| 49 | U06 | Haematuria |
| 50 | U07 | Urine symptom/complaint other |
| 51 52 | U13 | Bladder symptom/complaint other |
| 5∠ 53 | U14 | Kidney symptom/complaint |
| 54 | U70 | Pyelonephritis/pyelitis |
| 55 | U71 | Cystitis/urinary infection other |
| 56 57 | U72 | Urethritis |
| 57 58 | U75 | Malignant neoplasm of kidney |
| 59 | | |
| 60 | | |

| 3 | 1176 | |
|--|------|-----------------------------------|
| 4 | 076 | Malignant neoplasm of bladder |
| 5 | 077 | Malignant neoplasm urinary other |
| 6 7 | U78 | Benign neoplasm urinary tract |
| 8 | U79 | Neoplasm urinary tract NOS |
| 9 | U85 | Congenital anomaly urinary tract |
| 10 | U88 | Glomerulonephritis/nephrosis |
| 11 | U90 | Orthostatic albumin/proteinuria |
| 12 | U95 | Urinary calculus |
| 14 | U98 | Abnormal urine test NOS |
| 15 | U99 | Urinary disease, other |
| 16 | X83 | Congenital anomaly genital female |
| 17 18 | X84 | Vaginitis/vulvitis NOS |
| 19 | X85 | Cervical disease NOS |
| 20 | X99 | Genital disease female, other |
| 21 | Y74 | Orchitis/epididymitis |
| 22 | Y75 | Balanitis |
| 24 | Y81 | Phimosis/redundant prepuce |
| 25 | Y82 | Hypospadias |
| 26 27 | Y83 | Undescended testicle |
| 28 | Y84 | Congenital genl anomaly (m) other |
| 29 | Y99 | Genital disease male, other |
| 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 | | |
| 46 47 | | |

 BMJ Open

| 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 | |
| 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 | |
| Bias | 9 | Describe any efforts to address potential sources of bias | |
| Study size | 10 | Explain how the study size was arrived at | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | |
| 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 | 8-9 |

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| | | 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 | (<i>a</i>) 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.

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