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Title: The validity of register-data to identify children with atopic dermatitis, asthma or allergic rhinoconjunctivitis

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Authors' contributions:

LGS initiated and is guarantor of the study. LGS, LK, AH, SFT, JS planned the study. LK collected the data. LGS, AJ and JS analysed the data. LGS drafted the manuscript, and all authors read, critically revised and approved the final version of the manuscript.

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Conflicts of interests:

None declared.

Abstract

Journal: Ped All Immunol

Title: The validity of register-data to identify children with atopic dermatitis, asthma or allergic rhinoconjunctivitis

Authors: Stensballe LG, Klansø L, Jensen A, Hærskjold A, Thomsen SF, Simonsen J

Background

The incidence of atopic dermatitis, wheezing, asthma and allergic rhinoconjunctivitis have been increasing. Register-based studies are essential for research in subpopulations with specific diseases, and facilitate epidemiological studies to identify causes and evaluate interventions. Algorithms have been developed to identify children with atopic dermatitis, asthma or allergic rhinoconjunctivitis

using register information on disease-specific dispensed prescribed medication and hospital contacts, but the validity of the algorithms has not been evaluated. The present study validated the algorithms versus gold standard deep telephone interviews with the caretaker about physician-diagnosed atopic dermatitis, wheezing, asthma, or allergic rhinoconjunctivitis in the child.

Methods

The algorithms defined each of the three atopic diseases using register-based information on disease specific hospital contacts and/or filled prescriptions of disease specific medication. Confirmative answers to questions about physician-diagnosed atopic disease were used as the gold standard for the comparison with the algorithms, resulting in sensitivities and specificities and 95% confidence intervals. The interviews with the caretaker of the included 454 Danish children born 1997-2003 were carried out May-September 2015; the mean age of the children at the time of the interview being 15.2 years (standard deviation 1.3 years).

Results

For the algorithm capturing children with atopic dermatitis, the sensitivity was 74.1% (95%-confidence interval: 66.9-80.2%) and the specificity 73.0% (67.3-78.0%).

For the algorithm capturing children with asthma, both the sensitivity of 84.1% (78.0-88.8%) and the specificity of 81.6% (76.5-85.8%) were high compared with physician-diagnosed asthmatic bronchitis (recurrent wheezing). The sensitivity remained high when capturing physician-diagnosed asthma: 83.3% (74.3-89.6%), however, the specificity declined to 66.0% (60.9-70.8%).

For allergic rhino-conjunctivitis, the sensitivity was 84.4% (78.0-89.2) and the specificity 81.6% (75.0-84.4).

Conclusion

The algorithms are valid and valuable tools to identify children with atopic dermatitis, wheezing, asthma or allergic rhinoconjunctivitis on a population level using register data.

Keywords: Allergic rhinoconjunctivitis, asthma, atopic dermatitis, child, epidemiology, register-based research, register data, sensitivity, specificity, validation, wheezing.

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Introduction

The rates of atopic eczema, wheezing, asthma and allergic rhinoconjunctivitis, which have been increasing in high-income countries, appear to be stabilizing at a level of 20-40% of the population being affected (1;2), however the rates may still be increasing in low-income countries. (3) Large local variabilities in the prevalence of atopic diseases has been documented globally in the most recent report from The International Study of Asthma and Allergies in Childhood.(4) The causes of the variability and changes remain unclear; both genetics and environment have been found to be influential.(4-6)

As medicine increases its need to manage populations of individuals with specific diseases to improve care and prevention at the lowest cost, large scale epidemiological studies using register-based identification of subpopulations becomes increasingly valuable. Such studies can identify risk factors, and follow-up on disease rates and interventions.

In a recent study we developed methods, i.e. algorithms to identify children at a population level with atopic dermatitis, asthma or allergic rhinoconjunctivitis using data from public national health registers in Denmark and Sweden.(2) These algorithms used information on disease-specific

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dispensed prescribed medication and hospital contacts, and a criterion of repeated use of disease-specific medication within 12 months was used to secure the specificity.(2) However, sensitivity and specificity of the algorithms were not validated. Thus, the present study aims to validate the algorithms.

Methods

In short, the algorithms defining each of the three atopic diseases used register-based information on disease specific hospital contacts and/or filled prescriptions of disease specific medication. Each algorithm was generated in three steps: first, disease specific hospital diagnoses and disease specific medications were selected for each disease. Second, a criterion of repetition of the disease specific medication within twelve months was applied, since all three conditions are characterised by chronicity and recurrence. Third, other medical conditions known to lead to use of the medication types used as inclusion criteria in the first step were excluded. The algorithms used data from mandatory public health registers with 100% follow-up on all Danish citizens. Data on medication was obtained from The Danish National Prescription Registry (7) and data on hospital contacts was obtained from The Danish National Patient Register.(8) The study population consisted of 972,836 live born Danish children born from 1997 to 2011.(2)

The present study validated if children, who were captured by the algorithms as having atopic dermatitis, asthma or allergic rhinoconjunctivitis, also do/did have the conditions according to standardized telephone interviews with the caretaker. The validation study included Danish families only. The aim was to include at least 150 children in each of the three disease groups (as captured by the algorithms). Using random sampling from families participating in The Danish National Birth Cohort (from where we obtained contact information) we identified 250 children with atopic dermatitis, 250 children with asthma, and 250 children with allergic rhinoconjunctivitis according to

the algorithm.(9) The size of this initial sample was chosen to account for loss to contact. The sampling was done separately by disease and without replacement. It was possible for an identified child to suffer from more than one of the three diseases. However, the sampling without replacement ensured that no child appeared more than once in the sample. We invited the families by letter to participate in the study. The invitation contained a hyperlink to the study web site where the questions from the interview were presented. The invitation of 750 families was sufficient to obtain > 150 families in each disease group (as found by the algorithm) as desired in advance. For 284 families not contact was established, whilst 12 families declined to participate resulting in sample size of 454. The families were interviewed May-September 2015 by one expert research nurse, who was blinded to the result of the algorithm. The same interview, including questions from validated surveys for ascertaining atopic dermatitis, asthma and allergic rhinoconjunctivitis, was used for all families. The interview procedure started with the expert nurse calling the family to schedule the interview. When the family accepted to participate, the interview was scheduled and, again, the nurse referred to the questions at the web site for the family to be as prepared as possible for the interview. In order to reduce bias and increase specificity, we used confirmative answers to questions about physician-diagnosed disease as the gold standard for the comparison.(10)

In the analysis, all participants were pooled in one dataset (n=454). The results are presented as sensitivities (the proportion of “true cases” that register a positive test result) and specificities (the proportion of unaffected individuals found to be test negative), which are independent of the disease prevalence in the study population.(11) Further, positive and negative predictive values were calculated. However, since positive and negative predictive values depend on disease prevalence in the study population, value-added predictive values adjusted for the estimated prevalence were calculated as measures of the absolute improvement in diagnostic probability made by the test result. Further, the proportionate reductions in uncertainty scores were calculated as measures of the proportion by which a positive or negative test result reduces the diagnostic uncertainty.(11) 95-% confidence intervals were calculated using the Wilson score.(12) In order to

distinguish between recurrent wheezing and asthma, two comparisons were made for the algorithm developed to detect asthma: one where the algorithm was tested using the parent's confirmative answers to the question about whether the child had physician-diagnosed asthmatic bronchitis (recurrent wheezing) as the gold standard; and a second comparison using the parent's confirmative answer to the question about whether the child had physician-diagnosed asthma as gold standard. Further, sensitivity analyses were carried out to check if the algorithm might be optimized by applying less strict criteria for repeated use of disease-specific medication.

The Danish Data Protection Agency permitted the study. Upon inquiry The Regional Scientific Ethics Committee stated that the study did not need further ethical clearance.

Results

The nurse got in contact with 466 of 750 invited families (62%). 12 families declined participation and for 284 families no contact was established due to failing contact information. 454 families participated in the study. The mean age of the children included was 15.2 years (standard deviation 1.3 years, range 12.7 – 17.6 years).

For atopic dermatitis, the algorithm captured 74.1% (95-% confidence interval: 66.9-80.2%) of children who had/have had physician-diagnosed atopic dermatitis according to the caretaker, this figure representing the sensitivity (proportion of gold standard cases captured by the algorithm). The algorithm correctly identified 73.0% (67.3-78.0%) of children without physician-diagnosed atopic dermatitis according to the caretaker, this figure representing the specificity (proportion of unaffected children captured as unaffected by the algorithm) (Table 1).

For asthma, both sensitivity (84.1% (78.0-88.8%)) and specificity (81.6% (76.5-85.8%)) were high when compared to the parent's confirmative answers to the question regarding physician-diagnosed asthmatic bronchitis (recurrent wheezing) in the child.

The sensitivity remained high 83.3% (74.3-89.6%) when the algorithm to define asthma was compared with the parent's confirmative answer regarding physician-diagnosed asthma in the child, however, the specificity declined to 66.0% (60.9-70.8%) (Table 1).

For allergic rhino-conjunctivitis, the sensitivity was 84.4% (78.0-89.2) and the specificity 81.6% (75.0-84.4).

Not surprisingly, sensitivity analyses where algorithms with less strict criteria of repeated disease-specific medication was used showed increased sensitivities, but decreasing specificities (Table 2).

The algorithms yielded considerate proportionate reductions in uncertainty scores in the range of 21-56% for positive tests, and for negative tests in the range of 37-61%.

Discussion

To diagnose atopic dermatitis, asthma, or allergic rhinoconjunctivitis on a population level remains a challenge. Register-based research offers unique possibilities of epidemiologic and pharmaco-epidemiologic studies on atopic dermatitis, asthma and allergy;(2;13;14) however studies evaluating the validity of the methods used are clearly warranted.(15)

The present study validated algorithms developed to identify children with atopic dermatitis, asthma, or allergic rhinoconjunctivitis on a population level using register-based information on disease-specific dispensed prescribed medication and hospital contacts,(2) and found acceptable values of sensitivities, ranging from 74 to 84%, and specificities ranging from 66 to 81%, compared to information from the caretaker about physician-diagnosed disease.(16) Regarding asthma, the algorithm had a higher specificity (81.6%) of capturing individuals with asthmatic bronchitis (recurrent wheezing), than individuals with asthma (specificity 66.0%). This observation is in line with other studies from Denmark finding that wheezing is not the optimal predictor of asthma, since

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parents may have difficulties recognizing wheeze, consistency between parent and physician-reported wheeze may be low, and for physician diagnosed wheeze there may be significant inter-observer errors.(17) Moreover, despite the increased risk of asthma among infants and children with recurrent early wheeze, the majority of the children do not develop asthma.(18) Although sensitivities of the algorithms increased by using less strict criteria for repeated medication use, the specificities also decreased, so overall the result did not improve.

All children included in the study had at least one of the diseases under study according to the algorithm. The prevalence in the background population is approximately 42%.(2) However, sensitivity and specificity are independent of the disease prevalence.(11) Since positive and negative predictive values depend on disease prevalence in the study population, we calculated Proportionate Reduction in Uncertainty (PRU) scores, i.e. the proportion by which a positive or negative result reduces the uncertainty about the diagnosis. The motivation for introducing the PRU score is the following: in the presence of low prevalence (of a positive result), a large negative predictive value is not useful in itself – a negative test was already most likely due to the low prevalence. The absolute improvement of certainty (added-value negative predictive value) is compared to (i.e. divided by) the already known probability of a positive test (the prevalence) to obtain the PRU score for negative tests. Similarly the PRU score for positive tests is given by the ratio of the added-value of the PPV and the prior probability of a negative test. The PRU is the amount of uncertainty removed as a percentage of the amount of the remaining uncertainty present when taking the prevalence into account. A PRU with a value of zero means that the test does not increase certainty at all, whilst a PRU with a value of one means that all the remaining uncertainty has been removed. We found proportionate reductions in uncertainty scores from 20-60% and conclude that the algorithms considerably reduce the diagnostic uncertainty.(16)

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Register-based research poses a unique low-cost possibility to the development and evaluation of preventive measures and care of subpopulations of individuals with specific disease. However, it may be challenging to select which data to use for the diagnoses of specific diseases,(15) and to decide which accuracy is acceptable: whether one prefers a higher sensitivity but lower specificity, or *vice versa*.(16) If a population is to be identified for management, interventions, or recommendations, the sensitivity of the diagnosis should be high. On the other hand, to study the incidence of individuals with clinically significant disease, a high specificity of the diagnosis is essential.(19) The present study showed that the algorithms we developed to identify children with atopic dermatitis, asthma, or allergic rhinoconjunctivitis are valid. However, we also show how changes in the algorithms may increase the sensitivity, or the specificity of the diagnoses.

One prior study in Denmark evaluated the use of prescription data to identify children 6 to 14 years with asthma defined by hospitalization for asthma or physician-diagnosed asthma.(20) They found prescription of any anti-asthmatic drug (except from liquids containing beta2-agonists) within 12 months to yield the best values of sensitivity (66%) and specificity (86%).(20) A recent study from Sweden found asthma medication to be a suitable proxy for asthma in older children and adults with positive predictive values (PPV) ranging from 68% to 94%.(21) The study yielded a PPV of 45% of using atopic dermatitis specific medication to predict atopic dermatitis defined as hospital contacts (in- and out-patient) with the ICD-10 diagnosis of atopic dermatitis, L20, however not all children with atopic dermatitis may have hospital contacts. Thus, all three studies corroborate that register-information on asthma medication can be used to capture children with asthma. Regarding atopic dermatitis, our study showed acceptable sensitivity and specificity (>70%) when using register-based information on disease-specific dispensed prescribed medication and hospital contacts, and a criterion of repeated use of disease-specific medication within 12 months.

The study was limited by the overlap of child populations: the algorithms were generated among live born Danish children born from 1997 to 2011, and tested in The Danish National Birth Cohort of 100,000 Danish children born 1997-2003.⁽⁹⁾ The population under study consisted of Danish children only. To our knowledge, no validation of the algorithms has taken place among children from other countries yet. Positive and negative predictive values are dependent of disease prevalence in the population under study, so the crude positive and negative predictive values generated from the present study can only be applied to a population of children with at least one of the conditions under study. However, sensitivity and specificity are robust measures independent of the prevalence and we presented adjusted positive and negative predictive values using added-value predictive values and proportionate reductions in uncertainty scores.⁽¹¹⁾ Further, due to failing contact information, we got in contact with only 62% of the families invited since the addresses provided by The Danish National Birth Cohort were not updated since the establishment of the cohort.

In conclusion, the present study found good validity of using register-based information on disease-specific dispensed prescribed medication and hospital contacts, and a criterion of repeated use of disease-specific medication within 12 months, to identify children with atopic dermatitis, asthma, or allergic rhino-conjunctivitis on a population level. The results reinforce the value of population-based register linkages for the study of disease and the evaluation of interventions.

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Table 1

Positive and negative predictive values of diagnoses of atopic dermatitis, asthmatic bronchitis (recurrent wheezing), asthma, and allergic rhinoconjunctivitis defined by register-based information on disease-specific hospital contact(s) and/or ≥ 2 filled prescriptions of disease specific medication within one year, compared to "gold standard" information on physician-diagnosed disease in the child.

	Doctor's diagnosis of atopic dermatitis (gold standard)			
	Yes	No	Do not know	Total
Atopic dermatitis defined by disease-specific hospital contacts and/or ≥ 2 filled prescriptions within 12 months				
Yes	123	71	11	205 PPV ¹ 123/205=60.0% [53.2-66.5] Value added PPV ² =23.4% [16.6-29.9] PRU ³ =36.9% [26.2-47.1]
No	43	192	14	249 NPV ⁴ 192/249=77.1% [71.5-81.9] Value added NPV ³ =13.7% [8.1-18.5] PRU ⁶ =37.4% [22.1-50.5]
Total	166	263	25	454
Sensitivity 123/166=74.1% 95% confidence interval [66.9-80.2]				
Specificity 192/263=73.0% [67.3-78.0]				
	Doctor's diagnosis of asthmatic bronchitis (gold standard)			
	Yes	No	Do not know	Total
Asthma defined by disease-specific hospital contacts and/or ≥ 2 filled prescriptions within 12 months				
Yes	148	48	6	202 PPV 148/202=73.3% [66.8-78.9]

				Value added PPV=34.5% [28.0-40.1] PRU = 56.3% [45.7-65.5]
No	28	213	11	252 NPV 213/252=84.5% [79.5-88.5] Value added NPV=23.3% [18.3-27.2] PRU=60.1% [47.2-70.3]
Total	176	261	17	454
Sensitivity 148/176=84.1% [78.0-88.8]				
Specificity 213/261=81.6% [76.5-85.8]				
	Doctor's diagnosis of asthma (gold standard)			
	Yes	No	Do not know	Total
Asthma defined by disease-specific hospital contacts and/or ≥ 2 filled prescriptions within 12 months				
Yes	75	119	8	202 PPV 75/202=37.1% [30.8-44.0] Value added PPV=17.3% [10.9-24.1] PRU=21.6% [13.6-30.1]
No	15	231	6	252 NPV 231/252=91.7% [87.6-94.5] Value added NPV=11.5% [7.4-14.3] PRU=58.0% [37.4-72.2]
Total	90	350	14	454
Sensitivity 75/90=83.3% [74.3-89.6]				
Specificity 231/350=66.0% [60.9-70.8]				
	Doctor's diagnosis of allergic rhinoconjunctivitis (gold standard)			
	Yes	No	Do not know	Total
Allergic rhinoconjunctivitis defined by disease-specific hospital contacts and/or ≥ 2 filled prescriptions				
Yes	135	55	8	198 PPV 135/198=68.2% [61.4-74.3] Value added PPV ² = 32.9% [26.2-39.0] PRU = 50.9% [40.4-60.3]
No	25	221	10	256 NPV 221/256=86.3% [81.6-90.0] Value added NPV=21.6% [16.8-25.2] PRU=61.2% [47.7-71.6]
Total	160	276	18	454
Sensitivity 135/160=84.4% [78.0-89.2]				
Specificity 221/276=80.1% [75.0-84.4]				

¹ PPV Positive predictive value. ² PPV minus the prevalence (of positive tests). ³ Proportionate reduction in uncertainty score = (PPV minus prevalence)/(1 minus prevalence). ⁴ NPV Negative predictive value ⁵NPV minus (1 minus prevalence) ⁶ Proportionate reduction in uncertainty score = (NPV minus (1 minus prevalence))/prevalence

Table 2

Sensitivity analyses using other definitions of atopic dermatitis, asthmatic bronchitis, asthma, and allergic rhinoconjunctivitis. Positive and negative predictive values, compared to “gold standard” information on physician-diagnosed disease in the child.

Sensitivity analysis 1: any disease-specific hospital contact(s) and/or *at least one* filled prescription *at any time*.

Sensitivity analysis 2: any disease-specific hospital contact(s) and/or *at least two* filled prescriptions *at any time*.

Sensitivity analysis 1: any disease-specific hospital contact(s) and/or <i>at least one</i> filled prescription <i>at any time</i>				
	Doctor's diagnosis of atopic dermatitis (gold standard)			
	Yes	No	Do not know	Total
Atopic dermatitis defined by disease-specific hospital contacts and/or ≥ 1 filled prescription <i>at any time</i>				
Yes	151	158	18	327 PPV ¹ 151/327=46.2% [40.8-51.6] Value added PPV ² =9.6% [4.3-15.0] PRU ³ =15.2% [6.8-23.7]
No	15	105	7	127 NPV ⁴ 105/127=82.7% [75.2-88.3] Value added NPV ⁵ =19.2% [11.7-24.8] PRU ⁶ =52.6% [32.1-67.9]
Total	166	263	25	454
Sensitivity 151/166=91.0% 95% confidence interval [85.6-94.4]				
Specificity 105/263=39.9% [34.2-45.9]				
	Doctor's diagnosis of asthmatic bronchitis (gold standard)			
	Yes	No	Do not know	Total
Asthma defined by disease-specific hospital contacts and/or ≥ 1 filled				

prescription at any time				
Yes	153	57	8	218 PPV 153/218=70.2% [63.8-75.9] Value added PPV=31.4% [25.0-37.1] PRU=51.3% [40.9-60.6]
No	23	204	9	236 NPV 204/236=86.4% [81.5-90.2] Value added NPV=25.2% [20.3-29.0] PRU=65.0% [52.2-74.8]
Total	176	261	17	454
Sensitivity 153/176=86.9% [81.2-91.1]				
Specificity 204/261=78.2% [72.8-82.7]				
	Doctor's diagnosis of asthma (gold standard)			
	Yes	No	Do not know	Total
Asthma defined by disease-specific hospital contacts and/or ≥ 1 filled prescription at any time				
Yes	79	129	10	218 PPV 79/218=36.2% [30.1-42.8] Value added PPV=16.4% [10.3-23.0] PRU=20.5% [12.9-28.7]
No	11	221	4	236 NPV 221/236=93.6% [89.8-96.1] Value added NPV=13.5% [9.6-15.9] PRU=67.9% [48.4-80.4]
Total	90	350	14	454
Sensitivity 79/90=87.8% [79.4-93.0]				
Specificity 221/350=63.1% [58.0-68.0]				
	Doctor's diagnosis of allergic rhinoconjunctivitis (gold standard)			
	Yes	No	Do not know	Total
Allergic rhinoconjunctivitis defined by disease-specific hospital contacts and/or ≥ 1 filled prescription at any time				
Yes	144	114	13	271 PPV 144/271=53.1% [47.2-59.0] Value added PPV=17.9% [12.0-23.8] PRU=27.6% [18.5-36.7]
No	16	162	5	183 NPV 162/183=88.5% [83.1-92.4] Value added NPV=23.8% [18.3-27.6]

				PRU=67.4% [52.0-78.4]
Total	160	276	18	454
Sensitivity 144/160=90.0% [84.4-93.8]				
Specificity 162/276=58.7% [52.8-64.3]				
Sensitivity analysis 2: any disease-specific hospital contact(s) and/or <i>at least two</i> filled prescriptions <i>at any time</i>				
	Doctor's diagnosis of atopic dermatitis (gold standard)			
	Yes	No	Do not know	Total
Atopic dermatitis defined by disease-specific hospital contacts and/or ≥ 2 filled prescriptions <i>at any time</i>				
Yes	136	103	15	254 PPV 136/254=53.5% [47.4-59.6] Value added PPV=17.0% [10.8-23.0] PRU=26.8% [17.1-36.3]
No	30	160	10	200 NPV 160/200=80.0% [73.9-85.0] Value added NPV=16.6% [10.5-21.5] PRU=45.3% [28.7-58.9]
Total	166	263	25	454
Sensitivity 136/166=81.9% [75.4-87.0]				
Specificity 160/263=60.8% [54.8-66.5]				
	Doctor's diagnosis of asthmatic bronchitis (gold standard)			
	Yes	No	Do not know	Total
Asthma defined by disease-specific hospital contacts and/or ≥ 2 filled prescriptions <i>at any time</i>				
Yes	150	49	7	206 PPV 150/206=72.8% [66.4-78.4] Value added PPV=34.0% [27.6-39.7] PRU=55.6% [45.1-64.8]
No	26	212	10	248 NPV 212/248=85.5% [80.6-89.3] Value added NPV=24.3% [19.3-28.1] PRU=62.6% [49.8-72.5]
Total	176	261	17	454
Sensitivity 150/176=81.2% [79.2-89.7]				
Specificity 212/261=78.2% [76.0-85.5]				
	Doctor's diagnosis of asthma (gold standard)			

	Yes	No	Do not know	Total
Asthma defined by disease-specific hospital contacts and/or ≥ 2 filled prescriptions at any time				
Yes	77	119	10	206 PPV 77/206=37.4% [31.1-44.2] Value added PPV=17.6% [11.2-24.3] PRU=21.9% [14.0-30.4]
No	13	231	4	248 NPV 231/248=93.1% [89.3-95.7] Value added NPV=13.0% [9.1-15.5] PRU=65.4% [46.0-78.2]
Total	90	350	14	454
Sensitivity 77/90=85.6% [76.8-91.4]				
Specificity 231/350=66.0% [60.9-70.8]				
Doctor's diagnosis of allergic rhinoconjunctivitis (gold standard)				
	Yes	No	Do not know	Total
Allergic rhinoconjunctivitis defined by disease-specific hospital contacts and/or ≥ 2 filled prescriptions at any time				
Yes	138	65	9	212 PPV 138/212=65.1% [58.5-71.2] Value added PPV=29.9% [23.2-35.9] PRU=46.1% [35.9-55.5]
No	22	211	9	242 NPV 211/242=87.2% [82.4-90.8] Value added NPV=22.4% [17.6-26.1] PRU=63.7% [50.0-74.0]
Total	160	276	18	454
Sensitivity 77/90=85.6% [76.8-91.4]				
Specificity 231/350=66.0% [60.9-70.8]				

¹ PPV Positive predictive value. ² PPV minus the prevalence (of positive tests). ³ Proportionate reduction in uncertainty score = (PPV minus prevalence)/(1 minus prevalence). ⁴ NPV Negative predictive value ⁵NPV minus (1 minus prevalence) ⁶ Proportionate reduction in uncertainty score = (NPV minus (1 minus prevalence))/prevalence