Phenotyping asthma, rhinitis, and eczema in MeDALL population-based birth cohorts: an allergic comorbidity cluster

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ABSTRACT

BACKGROUND: Asthma, rhinitis, and eczema often co-occur in children but their interrelationships at the population level have been poorly addressed. We assessed co-occurrence of childhood asthma, rhinitis, and eczema using unsupervised statistical techniques.

METHODS: We included 17,209 children at 4 years and 14,585 at 8 years from seven European-population-based birth cohorts (MeDALL project). At each age period, children were grouped, using partitioning cluster analysis, according to the distribution of 23 variables covering symptoms "ever" and "in the last 12 months", doctor diagnosis, age of onset, and treatments of asthma, rhinitis, and eczema, IgE sensitisation, weight, and height. We tested the sensitivity of our estimates to subject and variable selections, and to different statistical approaches, including latent class analysis and self-organising maps.

RESULTS: Two groups were identified as the optimal way to cluster the data at both age periods and in all sensitivity analyses. The first (reference) group at 4 and 8 years (including 70 and 79% of children, respectively) was characterised by a low prevalence of symptoms and sensitisation, whereas the second (symptomatic) group exhibited more frequent symptoms and sensitisation. 99% children with comorbidities (co-occurrence of asthma, rhinitis, and/or eczema) were included in the symptomatic group at both ages. The children's characteristics in both groups were consistent in all sensitivity analyses.

CONCLUSION: At 4 and 8 years, at the population level, asthma, rhinitis, and eczema can be classified together as an allergic comorbidity cluster. Future research including time-repeated assessments and biological data will help understanding the interrelationships between these diseases.

Abstract word count: 250

Keywords: allergy; asthma; cluster analysis; eczema; rhinitis

Abbreviations used:

BAMSE: Children, Asthma, Milieu, Stockholm, Epidemiological Study

DARC: The Danish Allergy Research Centre

GINIplus: German Infant Study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy development study

IgE: Immunoglobulin E

LISAplus: The Influence of Life-style factors on the development of the Immune System and Allergies in West Germany plus the influence of environment and genetics study

MAS: Multicentre Allergy Study

MeDALL: Mechanisms of the Development of Allergy

PARIS: Pollution and Asthma Risk: an Infant Study

PIAMA: Prevention and Incidence of Asthma and Mite Allergy

INTRODUCTION

Allergy-related diseases, including asthma, rhinitis, and eczema, are very common.[1] Their characteristics and management are well established, but gaps exist in their causes, mechanisms, diagnosis, and prevention.[2-4] Allergy-related diseases often co-occur in the same subjects as comorbidities[2] but this co-occurrence has been seldom studied at the population level. Firstly, using a classical approach defining the diseases by experts on symptom-based definitions and self-reported diagnoses, we studied 17,000 children from 12 ongoing European birth cohort studies participating in MeDALL (Mechanisms of the Development of ALLergy).[5] We showed that co-occurrence of asthma, rhinitis, and eczema is more common (50% higher) than expected by chance, both in the presence and absence of IgE sensitisation.[6] Another approach applies unsupervised machine learning methods to several characteristics including symptoms to identify their distribution in a population. In the PARIS birth cohort, latent class and transition analyses at 4 years revealed four distinct phenotypes: 'transient rhinitis', 'transient wheeze', 'persistent cough/rhinitis' and 'persistent dermatitis', the two latter associated with IgE sensitisation.[7-8] Most comorbidity of asthma, rhinitis, and eczema was observed in the 'cough/rhinitis' phenotype. Another study assessed repeatedly 9801 children in two population-based British birth cohorts (ALSPAC and MAAS) using Bayesian machine learning methods to identify developmental profiles of symptoms over time.[9] The study revealed eight latent classes, four of which (accounting for 16% of children) included comorbidity of asthma, rhinitis and/or eczema. However, the authors concluded that this comorbidity was likely due to chance, while IgE sensitisation, the most frequently considered common mechanism of allergy-related diseases, was not assessed.

To further advance the understanding of comorbidities of allergy-related diseases at the population level, we assessed the presence of different allergic phenotypes using unsupervised (hypothesis-free) statistical techniques in children at 4 and 8 years of age from seven European population-based birth cohorts as part of the MeDALL project. Additionally, we tested if IgE sensitisation modified the classification of allergy-related symptoms in these children.

METHODS

Design and study population

A cross-sectional analysis of birth cohort studies was done at 4 years (ranging from 3 to 5) and 8 years (ranging from 8 to 10). The children were selected from seven MeDALL cohorts (BAMSE,[11] Sweden; DARC,[11-12] Denmark; GINIplus,[13] LISAplus,[14] and MAS,[15] Germany; PARIS,[16] France; and PIAMA,[17] The Netherlands). Inclusion and exclusion criteria are presented in Online Supplement. The sample size for each cohort and period ranged from 505 to 4299 children (Online Supplement). In all participating cohorts, parents gave written informed consent and local ethics review boards approved the studies.

Measurements

We pooled and harmonised the data collected from questionnaires on 20 variables covering symptoms "ever" and "in the last 12 months", doctor diagnosis, age of onset, and treatment of allergy-related diseases (asthma, rhinitis, and eczema) (Table E1, Online Supplement). Children's weight and height were obtained from physical examination. Sensitisation was defined by serum specific IgE ≥0.35 kUA/l against at least one of the following aero- and food allergens: house dust mite, cat dander, birch pollens, grass pollens, cow's milk, and egg.[6] We also defined current asthma, rhinitis, and eczema using the classical definitions.[6] Asthma, rhinitis, and eczema comorbidities were defined as the co-occurrence of two or three of these diseases in the same child (Online Supplement).

Statistical analysis

The number of subjects available was greater than required according to sample size calculations (Online Supplement). We assessed the presence and patterns of missing values and, assuming the missing-at-random hypothesis,[18] we used multiple imputation (20 imputed datasets) with the method of chained equations.[19] We compared the characteristics of children in the complete case to the imputed datasets (Online Supplement). For the unsupervised analysis, we included 23 variables: all 20 features of allergy-related diseases, weight, height, and IgE sensitisation. All variables were standardised using Z-scores; in a secondary analysis, variables were scaled from 0 to 1. We did not perform any data reduction (e.g., factor analysis) prior to clustering (i) because there was not a high degree of colinearity in our variables (Figure E2, Online

Supplement), (ii) to avoid losing the amount of variance that is not explained in such pre-processing, and (iii) to facilitate the interpretation of clusters.[20]

Primarily, we used k-means partitioning cluster analysis, which groups subjects according to the Euclidean distance between the included variables.[21] This analysis was performed at both time periods, 4 and 8 years, for each of the 20 datasets generated by the multiple imputation method, following a method previously reported to integrate multiple imputation in cluster analyses.[22] We selected the number of groups (clusters) that maximised the Calinski-Harabasz stopping rule if and only if it was in agreement with another stopping rule (the Average silhouette width) and with consensus measures, and it could not be attributed to chance (Online Supplement). To test the longitudinal stability of the identified clusters, we compared the groups to which children belonged between 4 and 8 years using cross-tabulation. We evaluated the role of IgE sensitisation in the cluster analysis by performing all analyses both including and excluding IgE from the cluster model, and by stratifying the cluster analysis according to IgE sensitisation.

As part of our sensitivity analysis, we tested whether alternative hypothesis-free grouping methods could have yielded different results, repeating all analyses using (i) hierarchical clustering with Ward's method, (ii) latent class analysis, and (iii) self-organising maps (Online Supplement). We also performed several secondary analyses to assess the sensitivity of our estimates against our assumptions regarding selection bias and information bias, as well as to test for model misspecification (Online Supplement).

For the graphical description of the groups identified by cluster analysis, we plotted the prevalence of each variable in each group with a colour intensity scale spanning from white (prevalence of 0%) to red (prevalence of 100%). We compared the distribution of all 23 variables across groups and calculated the relative relevance of each variable to the separation in cluster groups using F values (the ratio of the variance of the group means [between-group variance] over the overall variance of the variable, where higher values indicate higher relevance of the variable for separating cluster groups). We also assessed the distribution of the classical definitions of current asthma, rhinitis, and eczema, as well as their comorbidity, according to cluster groups.

All analyses were performed using Stata 12 (Stata Statistical Software: Release 12. College Station, TX: StataCorp LP) and R 2.14.2 (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org/).

RESULTS

17,209 children were included at 4 years (49% female, mean (SD) 46.9 (5.0) months) and 14,585 at 8 years (48% female, 106.4 (12.1) months) (Table 1, Table E4 Online Supplement). Lifetime (ever) prevalences of asthma, rhinitis, and eczema were 8.2%, 3.8%, and 26.8% at 4 years, and 15.4%, 15.9%, and 34.8% at 8 years.

Both the Calinski-Harabasz and the average silhouette width stopping rules (Figure 1), as well as the consensus matrix (Figure E3, Online Supplement) showed that two groups was the most effective classification of children and was not due to chance; this is, that the separation in two clusters resulted in groups of children homogeneous within- and heterogeneous between them, while the classification in more than two groups provided mixed groups that moreover were poorly reproducible.

Figure 2 and Table E5 (Online Supplement) show how the 20 symptoms were distributed in the two cluster groups. At 4 years, Group 1 included 12,052 (70.0%) children with low symptoms prevalence; Group 2 included 30.0% children exhibiting a higher prevalence of most symptoms (22.9% of asthma ever, 10.4% of allergic rhinitis ever, 64.5% of eczema ever). IgE sensitisation occurred in 16.6% of children in Group 1 and 31.2% of children in Group 2. At 8 years, the results were similar although fewer children (21.5%) were classified in Group 2. 10,835 (75.3%) of 14,383 children belonged to the same group at both 4 and 8 years but Group 1 was more stable than Group 2 (Table 2).

The prevalences of current asthma, rhinitis, and eczema according to classical definitions were higher in Group 2 than in Group 1 (at 8 years: 36.9%, 49.0%, and 27.5%, *versus* 1.1%, 1.8%, and 8.0%) (Figure 3; Table E6, Online Supplement). Almost all children with comorbidity of asthma, rhinitis, and eczema were included in Group 2 at both 4 and 8 years.

The classification in three groups (Figure E4, Online Supplement) showed a similar Group 1 (59.7% of children) with a low prevalence of symptoms and sensitisation, a Group 2 (15.6%) with a higher prevalence of symptoms of asthma and rhinitis, and a Group 3 (24.7%) with higher proportions of eczema symptoms. The prevalences of symptoms in Groups 1 and 2 were almost identical with and without including IgE sensitisation in the cluster analysis. After stratifying the cluster analysis according to IgE sensitisation, the pattern of differences between Groups 1 and 2 was maintained, although prevalences of symptoms and diseases were higher in the IgE sensitised children. (Figure 4; Figures E5-E6, and Tables E7-E8, Online Supplement).

Sensitivity analyses showed little change in response to changes in assumptions regarding statistical models, as well as selection and information biases (Figure 5; Figures E7-E20 and Tables E9-E19, Online Supplement). Alternative hypothesis-free grouping methods (hierarchical clustering with Ward's method, latent class analysis, and self-organising maps) also showed the organisation of children into two groups as the best option. The same classification was obtained after considering variables with potential problems of measurement error, that is, after excluding "itchy rash ever" and "food allergy ever" (one at a time), using a higher cut-off for IgE sensitisation (≥3.5 kUA/l), and using body mass index instead of weight and height separately. Likewise, the inclusion of additional variables (spirometry, bronchial responsiveness, airway resistance (Rint), skin prick test, exhaled nitric oxide (FeNO), and others; Online Supplement) in a subset of two birth cohorts (PIAMA and BAMSE) also supported two groups, as well as did the stratification by birth cohort or by the proportion of missing data. In all sensitivity analyses Group 2 showed a higher prevalence of allergy-related diseases and sensitisation.

DISCUSSION

Using hypothesis-free statistical analyses, we identified two groups of children at 4 and 8 years of age from seven population-based birth cohorts: a reference group (70.0% at 4 years and 78.5% at 8 years) with low frequencies of asthma, rhinitis, and eczema symptoms, and a symptomatic group (30.0% at 4 years and 21.5% at 8 years) with high frequencies of symptoms of the three diseases. The symptomatic group presented 99% comorbidity. While IgE sensitisation was more prevalent in the symptomatic group (31.2% *vs* 16.6% at 4 years; 71.7% *vs* 30.0% at 8 years), the distribution of symptoms across cluster groups did not change according to the inclusion or exclusion of IgE sensitisation in the model. The sensitivity analysis showed that classification in two groups was very stable in relation to changes in the selection of subjects and variables and the use of different clustering methods.

Strengths and limitations

Our study is based on a large network of European birth cohorts[7] including a large sample size, a wide geographical and environmental variability, and the harmonisation of standardised questionnaires. To avoid losing information due to missing values, we performed multiple imputations, a valid solution in cluster analysis.[22] Information bias during questionnaire-based symptom assessment cannot be excluded although

we do not expect this bias differentially distributed across cluster groups. Input data are restricted to information available in all seven cohorts, but our results did not change in the sensitivity analyses including lung function and biomarkers. Having only two time points and lacking data from the first year of life might have hampered the study of the development over time of such complex diseases, as elegantly performed in the unsupervised analysis of the ALSPAC and MAAS cohorts.[9] Nevertheless, our assessment of changes in group membership from 4 to 8 years suggested substantial temporal stability. Unsupervised methods for the classification of subjects may differ according to the type of modelling and stopping rules, and are conditional to a number of assumptions and analytical decisions. We used a wide range of models and tested our assumptions in the sensitivity analyses, which indicated that our results are very stable.

Consistency with previous studies

Most previous studies using unsupervised methods have focused on a single allergic disease.[23-36] Based on these results it was expected that our study would identify several groups, separating asthma, rhinitis, and eczema symptoms. However, our results show that, at the population level, most children with symptoms of asthma, rhinitis, and eczema are better classified together, in a single symptomatic group. Moreover, 99% children with comorbidity were classified in this symptomatic group. Overall, results strongly suggest the existence of an allergic comorbidity cluster. Some studies focusing on wheezing/asthma in children, applying unsupervised methods, found similar prevalences of the other allergy-related diseases (rhinitis and eczema) among all identified wheezing groups, which is consistent with our results.[25,30]

Conversely, two previous unsupervised studies that assessed the joint distribution of asthma, rhinitis, and eczema obtained several groups.[7-9] Relevant methodological differences could explain the diverse results. First, previous studies included a reduced number of allergy-related symptoms or diseases diagnostics while our analysis used a large diversity of the diagnostic signs, symptoms, and biomarkers of three different organ-related diseases (lungs, nose, and skin). Second, and as a consequence of the first, they used longitudinal clustering techniques (feasible for small number of variables) while we performed cross-sectional clustering at two time points. Interestingly, in our three-group solution, children with a high prevalence of rhinitis and asthma symptoms tended to remain in the same group, whereas a third group of children with the highest prevalence of eczema symptoms emerged. However, this separation was largely driven (according to F values, see Methods) by the symptom “itchy rash ever”, a variable with known

potential problems of missclassification. Remarkably, our sensitivity analyses confirmed that two-group classification is a better option than classification into a larger number of groups. The additional analysis with the p-values of stopping rules showed that it is very unlikely to find such two groups clustering structure by chance. Therefore, and although unexpected, we conclude that childhood symptoms of asthma, rhinitis, and eczema can be classified in two groups at the population level, which requires replication in further studies.

The influence of IgE sensitisation appeared to be minor, since the classification was similar after stratification by IgE sensitisation, as well as after including or excluding the IgE sensitisation variable. The PARIS study had shown that the two persistent phenotypes (cough/rhinitis and dermatitis) were associated with IgE sensitisation whereas the two transient phenotypes (rhinitis and wheeze) were not.[7] However the two studies are not directly comparable due to dissimilar study design and analytical approaches. By contrast, the present findings are consistent with results from our previous MeDALL study which examined a larger number of birth cohorts and showed that the strong tendency of asthma, rhinitis, and eczema to co-occur in the same children was independent of IgE sensitisation.[6] Both the present unsupervised and the previous supervised MeDALL studies strongly suggest that specific IgE contributes to the comorbidity cluster of asthma, rhinitis, and eczema but should no longer be considered its dominant mechanism.

Several mechanisms other than IgE can be proposed as responsible for the identified comorbidity cluster. Some studies have reported common genetic determinants of asthma, rhinitis, and eczema, such as the filaggrin gene[37], the Leucine Rich Repeat Containing 32 gene (*LRRC32*)[38], and the 17q21 locus.[39] Comorbidity cluster could also be the clinical expression of the effects of common environmental factors, but few studies have focused on environmental determinants of allergy-related comorbidity. A bioinformatics approach to analysing allergy-related diseases in European children combined feature selection and machine learning to show that combinations of environmental and lifestyle factors were more frequently related to allergy-related diseases than combinations solely involving genes.[40] However, the study did not assess comorbidity determinants. Overall, understanding the mechanisms of the identified allergic comorbidity cluster warrants further reserach.

Implications

The current emphasis on assessing the heterogeneity of allergy-related entities and searching for meaningful subgroups should be balanced with increased efforts to understand their interrelationships.[41] Although comorbidities of allergy-related diseases are well known, the cluster found in the present paper suggests that undisclosed mechanisms underlying the three diseases need to be investigated using new research approaches and concepts, such as the diseasome[42] or the integrative systems biology models.[43] At the clinical level, the present study supports an integration of care pathways in children with allergy-related diseases.

Conclusion

Our study has shown that, at the population level, childhood asthma, rhinitis, and eczema are more accurately classified together as an allergic comorbidity cluster, than as three independent diseases. Future research including time-repeated assessments and biological data will help understanding the interrelationships between these diseases.

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Authors' contribution

JG-A wrote the initial draft. MB prepared the common database. MB and YS carried out statistical analysis. JG-A, MB, MP, XB, and JMA had full access to the data and participated in the interpretation of the findings. MW, EM, IK, JH (BAMSE), CBJ, EE (DARC), JH, SK, CGT, DB (GINIplus and LISAplus), TK, CH, SL, UW (MAS), IM, FR, JJ (PARIS), and HAS, MK, UG, GK (PIAMA) provided data. All authors (i) provided substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work, (ii) revised the manuscript for important intellectual content, (iii) approved the final version, and (iv) agreed to be accountable for all aspects of the work. JB and JMA coordinate the MeDALL project.

Conflicts of interest

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Table 1. Characteristics and symptoms of asthma, rhinitis, and eczema in participating children at 4 and 8 years.

	4 years n=17,209 n (%)	8 years n=14,585 n (%)
Sex: female	8354 (48.5)	7060 (48.4)
Age (months), m (SD)	46.9 (5.0)	106.4 (12.1)
Wheezing ever	5641 (32.8)	5767 (39.5)
Wheezing attacks in the last 12 months		
None	15309 (89.0)	13112 (89.9)
1-3 times	1289 (7.5)	1005 (6.9)
4-12 times	482 (2.8)	358 (2.5)
> 12 times	129 (0.8)	110 (0.8)
Wheezing after exercise ever	1346 (7.8)	2345 (16.1)
Asthma ever	1410 (8.2)	2243 (15.4)
Asthma treatment in the last 12 months	1936 (11.3)	1371 (9.4)
Asthma onset before 2 years of age	924 (5.4)	879 (6.0)
Bronchitis or Bronchiolitis ever	5794 (33.7)	5760 (39.5)
Cough at night (when no cold) ever	4948 (28.8)	6189 (42.4)
Sneezing or runny or blocked nose (when no cold) ever	5607 (32.6)	6392 (43.8)
Sneezing or runny or blocked nose (when no cold) in the last 12 months	2474 (14.4)	3400 (23.3)
Itchy watery eyes (when no cold) in the last 12 months	831 (4.8)	1845 (12.7)
Allergic rhinitis ever	648 (3.8)	2326 (15.9)
Rhinitis onset before 2 years of age	876 (5.1)	345 (2.4)
Itchy rash (coming and going for at least six months) ever	6290 (36.6)	6921 (47.5)
Itchy rash (coming and going for at least six months) in the last 12 months	3353 (19.5)	2126 (14.6)
Itchy rash affecting common areas	4820 (28.0)	1657 (11.4)
Itchy rash onset before 2 years of age	3734 (21.7)	3477 (23.8)
Eczema ever	4614 (26.8)	5049 (34.6)
Urticaria ever	3403 (19.8)	3043 (20.9)
Food allergy ever	1850 (10.7)	2699 (18.5)
IgE sensitisation	3611 (21.0)	5680 (38.9)
Weight (kg), m (SD)	17.0 (2.7)	32.3 (7.7)
Height (cm), m (SD)	103.8 (6.0)	137.9 (9.4)

* A total of 14383 children had data available at both age periods.

Table 2. Stability of group membership of children at 4 and 8 years.

			Cluster analysis at 8 years		
			Group 1	**Group 2**	total
Cluster analysis at 4 years	**Group 1**	n	8891	924	9815
		*row %**	*90.6*	*9.4*	
		total %†	*61.8*	*6.4*	*68.2*
	Group 2	*n*	2624	1944	4568
		*row %**	*57.4*	*42.6*	
		total %†	*18.2*	*13.5*	*31.8*
	total	n	11515	2868	14383
		total %	*80.1*	*19·9*	*100*

* Proportion of children belonging to Groups 1 or 2 at 8 years taking into account their belonging at 4 years.

† Total proportion of children assigned to each combination of cluster Groups at 4 and 8 years.

FIGURE LEGENDS

Figure 1. Distribution of values over 20 imputed datasets of the Calinski-Harabasz and Average silhouette width stopping rules* across 2 to 10 cluster groups at 4 and 8 years.

* Higher values indicate higher separation between groups and similarity within groups. The p-values for the observed values of both stopping rules being generated by their background distributions are 0, so not likely to be observed by chance.

Figure 2. Prevalence* of symptoms of asthma, rhinitis, and eczema according to the two groups identified in cluster analysis, at 4 and 8 years.

* Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

Figure 3. Distribution of classical definitions of current asthma, rhinitis, eczema, and their comorbidity, according to the two groups identified in cluster analysis, at 4 and 8 years.

Figure 4. Prevalence* of symptoms of asthma, rhinitis, and eczema according to the two groups identified in cluster analysis at 8 years, according to IgE sensitisation.

* Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

Figure 5. Prevalence* of symptoms of asthma, rhinitis, and eczema according to the two groups identified in cluster analysis, at 4 and 8 years, in sensitivity analyses.

Online Supplement

Phenotyping asthma, rhinitis, and eczema in MeDALL population-based birth cohorts: an allergic comorbidity cluster

METHODS

Design and study population

This study involves cross-sectional analyses of birth cohort studies at two age periods: 4 years of age (ranging from 3 to 5 years) and 8 years of age (ranging from 8 to 10 years). From all birth cohorts involved in MeDALL, we included those for whom information on asthma, rhinitis, and eczema symptoms and IgE sensitisation was available at any time during both age periods. We excluded children who did not participate in the 4 and/or 8-year follow-ups and those with all variables missing, leaving a total of 17209 children at 4 years and 14585 at 8 years, from which 14383 were coincident in both age periods. The children in the study came from seven MeDALL birth cohorts: BAMSE, The Stockholm Children Allergy and Environmental Prospective Birth Cohort Study,[E1] Sweden; DARC, The Danish Allergy Research Centre,[E2,E3] Denmark; GINIplus, German Infant Study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy development,[E4] Germany; LISAplus, The Influence of Life-style factors on the development of the Immune System and Allergies in East and West Germany plus the influence of environment and genetics,[E5] Germany; MAS, Multicentre Allergy Study,[E6] Germany; PARIS, Pollution Asthma Risk an Infant Study,[E7] France; and PIAMA, Prevention and Incidence of Asthma and Mite Allergy,[E8] The Netherlands. The sample size for each cohort and period ranged from 505 to 4299 children. In all participating cohorts, parents gave written informed consent and the studies were approved by local ethics review boards.

132

133 **Table E1. List of questions of allergy-related diseases**

Respiratory Symptoms
Has your child ever had wheezing or whistling in the chest at any time in the past?
How many attacks of wheezing has your child had in the last 12 months?
In the last 12 months, has your child's chest sounded wheezy during or after exercise?
Has your child ever been diagnosed by a doctor as having asthma?
Has your child taken any medicines for asthma or breathing difficulties (wheezing, chest tightness, shortness of breath) in the last 12 months? (include any inhalers, nebulisers, tablets or liquid medicines)
Age of asthma onset
Has your child had bronchitis or bronchiolitis?
Has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?
Rhinitis, Nose & Eyes
Has your child ever had a problem with sneezing, or a runny or blocked nose when he/she did not have a cold or the flu?
In the last 12 months, has your child had problems with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or flu?
In the last 12 months, has this nose problem been accompanied by itchy-watery eyes?
Has your child ever been diagnosed by a doctor as having hay fever or allergic rhinitis?
Age of rhinitis onset
Skin
Has your child ever had an itchy rash which was coming and going for at least 6 months?
Has your child had an itchy rash which was coming and going (intermittently) at any time in the last 12 months?
Has this itchy rash at any time affected any of the following places (You may choose several answers)? Please tick all that apply: – the folds of the elbows – behind the knees – in front of the ankles – under the buttocks, or – around the neck, ears or face
Age of itchy rash onset
Has your child ever been diagnosed by a doctor as having eczema /atopic dermatitis?
Has your child ever had a rash characterised by pale itchy bumps similar to mosquito bites or blisters, that appeared and disappeared again within a day or two (i.e. nettle rash)?
Drugs and Food Allergy
Has your child ever had an allergic reaction to food?

134

135

"Classical" definitions of asthma, rhinitis, and eczema

Information about asthma, rhinitis, and eczema outcomes was obtained through questionnaires from each of the cohorts. We used definitions of these diseases that were agreed by a panel of experts, comprising participants of MeDALL and invited external participants, which aimed at re-defining the current definitions of asthma, rhinitis, and eczema as well as their phenotypes from childhood to young adulthood using a modified version of the GA^{2}LEN questionnaire for current asthma definition and ISAAC questions to define current rhinitis and current eczema. To apply the MeDALL definitions, harmonising decisions were taken by a panel of co-authors. Such definitions[E9] and accompanying documents are also available upon request.

Current asthma: Asthma definition was based on a modified version of the GA^{2}LEN questionnaire.[E10] Asthma was defined as a positive answer to at least two of the three following questions: *Doctor-diagnosed asthma ever*: "Has your child ever been diagnosed by a doctor as having asthma?"; *Asthma medication in the last 12 months*: "Has your child taken any medicines for asthma (including inhalers, nebulisers, tablets, or liquid medicines) or breathing difficulties (chest tightness, shortness of breath) in the last 12 months?"; and *Wheezing in the last 12 months according to ISAAC parental core questionnaire*[E11] *AND/OR breathing difficulties (chest tightness and shortness of breath) in the last 12 months*: "Have you had wheezing or whistling in your chest at any time in the last 12 months?" AND/OR "Has your child had breathing difficulties (chest tightness, shortness of breath) in the last 12 months?".

Current rhinitis: Rhinitis was defined as a positive answer to the following ISAAC questions[E12,E13] "Has your child had problems with sneezing, or a runny, or blocked nose when s/he did not have a cold or flu?" If yes "In the last 12 months, has this nose problem been accompanied by itchy-watery eyes?".

Current eczema: Eczema was defined as a positive answer to the following three questions from ISAAC[E11]: "Has your child ever had an itchy rash which was coming and going for at least six months?"; "Has your child had this itchy rash at any time in the last 12 months?" and "Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?".

164

165 **Sample size calculations**

166 Although the use of clustering methods has become widespread, there are no sample size calculation
167 formulas for cluster analysis.[E14-E16] In the context of high-dimension low-sample size data, such as in
168 microarray data analysis, the ratio of number of subjects to number of variables is often as low as 0.01.[E17] In
169 our study, the number of subjects was greater than the number of variables in all analyses (main analysis,
170 stratifications, and sensitivity analysis).

171 **Assessment and treatment of missing data**

172 We assessed the presence and patterns of missing values according to variables, subjects, periods, and
173 cohorts (Table E2 and Figure E1). Then, assuming the missing at random hypothesis, i.e. that the probability
174 of data being missing does not depend on the unobserved data, conditional on the observed data,[E18] we used
175 multiple imputation (20 imputed datasets) with the method of chained equations, defining the appropriate
176 distribution (e.g. Gaussian, logistic, Poisson) for every variable.[E19] We compared the characteristics of
177 children between the complete case and the imputed datasets (Table E3).

178

179 **Table E2. Number and proportion of missing values per variable, cohort and period**

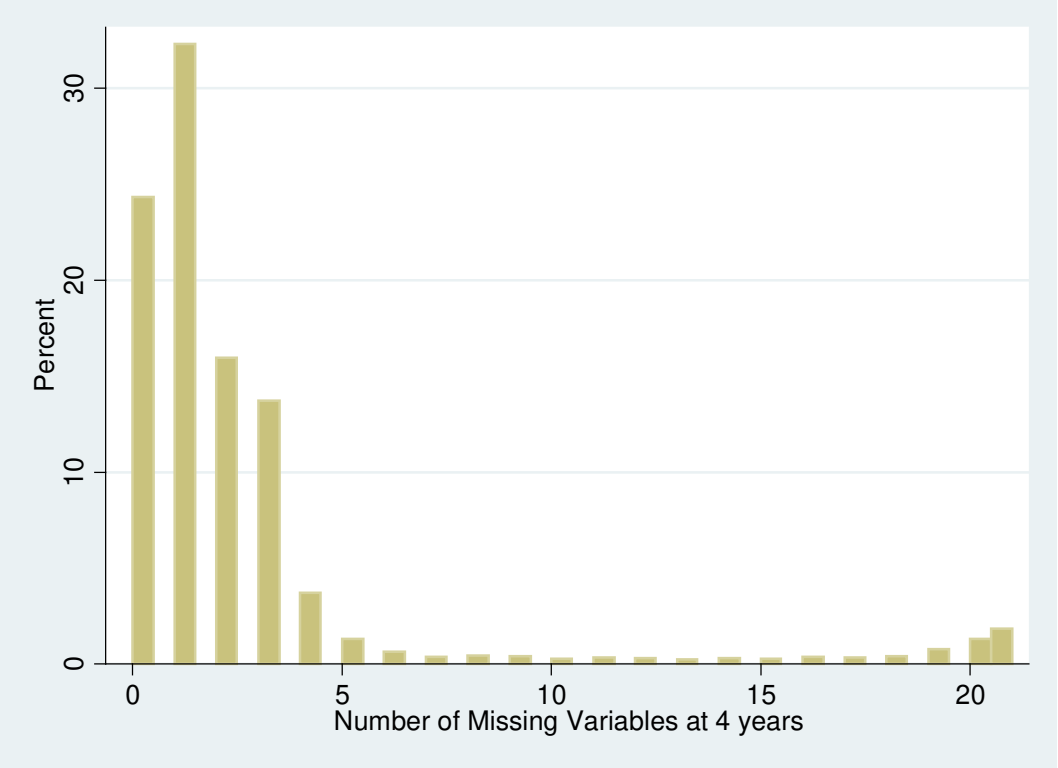
	BAMSE		DARC		GINI		LISA		MAS		PARIS		PIAMA*	
	4y	8y	4y	8y	4y	8y	4y	8y	4y	8y	4y	8y	4y	8y
N of children	**3993**	**4011**	**505**	**NA**	**4299**	**4118**	**1899**	**1779**	**1097**	**1109**	**1781**	**NA**	**3635**	**3568**
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Respiratory Symptoms														
Wheezing ever	302 (7.6)	743 (18.5)	15 (3.0)	NA	351 (8.2)	749 (18.2)	152 (8.0)	319 (17.9)	64 (5.8)	252 (22.7)	0 (0)	NA	93 (2.6)	314 (8.8)
Number of wheezing attacks in the last 12 months	284 (7.1)	612 (15.3)	38 (7.5)	NA	341 (7.9)	836 (20.3)	154 (8.1)	499 (28.1)	115 (10.5)	257 (23.2)	18 (1.0)	NA	94 (2.6)	305 (8.6)
Wheezing after exercise ever	368 (9.2)	713 (17.8)	27 (5.4)	NA	546 (12.7)	1185 (28.8)	200 (10.5)	534 (30.0)	164 (15.0)	253 (22.8)	0 (0)	NA	153 (4.2)	527 (14.8)
Asthma ever	362 (9.1)	663 (16.5)	32 (6.3)	NA	542 (12.6)	1308 (31.8)	282 (14.9)	632 (35.5)	117 (10.7)	196 (17.7)	0 (0)	NA	86 (2.4)	307 (8.6)
Any Asthma treatment in the last 12 months	284 (7.1)	599 (14.9)	38 (7.5)	NA	288 (6.7)	839 (20.4)	166 (8.7)	501 (28.2)	264 (24.1)	274 (24.7)	0 (0)	NA	92 (2.5)	313 (8.8)
Age of asthma onset	384 (9.6)	758 (18.9)	47 (9.3)	NA	551 (12.8)	1349 (32.8)	285 (15.0)	646 (36.3)	39 (3.6)	37 (3.3)	0 (0)	NA	92 (2.5)	322 (9.0)
Bronchitis or Bronchiolitis ever	347 (8.7)	365 (9.1)	15 (3.0)	NA	376 (8.8)	125 (3.0)	135 (7.1)	42 (2.4)	1097 (100)	1109 (100)	0 (0)	NA	143 (3.9)	507 (14.2)
Cough at night (when no cold) ever	359 (9.0)	377 (9.4)	36 (7.1)	NA	453 (10.5)	841 (20.4)	197 (10.4)	424 (23.8)	64 (5.8)	252 (22.7)	0 (0)	NA	183 (5.0)	273 (7.7)
Rhinitis, Nose & Eyes														
Sneezing or runny or blocked nose (when no cold) ever	295 (7.4)	518 (12.9)	29 (5.7)	NA	346 (8.1)	759 (18.4)	157 (8.3)	359 (20.2)	64 (5.8)	252 (22.7)	0 (0)	NA	94 (2.6)	322 (9.0)

Sneezing or runny or blocked nose (when no cold) in the last 12 months	308 (7.7)	602 (15.0)	38 (7.5)	NA	305 (7.1)	871 (21.2)	139 (7.3)	504 (28.3)	64 (5.8)	506 (45.6)	0 (0)	NA	92 (2.5)	320 (9.0)
Itchy watery eyes (when no cold) in the last 12 months	309 (7.7)	611 (15.2)	38 (7.5)	NA	305 (7.1)	879 (21.4)	142 (7.5)	504 (28.3)	64 (5.8)	291 (26.2)	0 (0)	NA	98 (2.7)	536 (15.0)
Allergic Rhinitis ever	278 (7.0)	672 (16.8)	38 (7.5)	NA	540 (12.6)	1246 (30.3)	310 (16.3)	644 (36.2)	111 (10.1)	230 (20.7)	0 (0)	NA	104 (2.9)	318 (8.9)
Age of rhinitis onset	389 (9.7)	755 (18.8)	42 (8.3)	NA	557 (13.0)	1357 (33.0)	312 (16.4)	675 (37.9)	9 (0.8)	29 (2.6)	0 (0)	NA	113 (3.1)	332 (9.3)
Skin														
Itchy rash (coming and going for at least six months) ever?	1 (0.0)	13 (0.3)	20 (4.0)	NA	400 (9.3)	838 (20.4)	240 (12.6)	412 (23.2)	75 (6.8)	253 (22.8)	0 (0)	NA	156 (4.3)	283 (7.9)
Itchy rash (coming and going for at least six months) in the last 12 months?	270 (6.8)	602 (15.0)	38 (7.5)	NA	311 (7.2)	857 (20.8)	147 (7.7)	512 (28.8)	64 (5.8)	254 (22.9)	0 (0)	NA	87 (2.4)	317 (8.9)
Itchy rash affecting common areas	233 (5.8)	604 (15.1)	20 (4.0)	NA	628 (14.6)	860 (20.9)	249 (13.1)	515 (29.0)	104 (9.5)	355 (32.0)	2 (0.1)	NA	104 (2.9)	333 (9.3)
Age of itchy rash onset	1 (0.0)	13 (0.3)	122 (24.2)	NA	444 (10.3)	913 (22.2)	289 (15.2)	464 (26.1)	163 (14.9)	72 (6.5)	0 (0)	NA	1043 (28.7)	597 (16.7)
Eczema ever	318 (8.0)	597 (14.9)	32 (6.3)	NA	430 (10.0)	994 (24.1)	218 (11.5)	473 (26.6)	163 (14.5)	154 (13.9)	0 (0)	NA	146 (4.0)	332 (9.3)
Urticaria ever	311 (7.8)	329 (8.2)	37 (7.3)	NA	566 (13.2)	1290 (31.3)	275 (14.5)	611 (34.4)	64 (5.8)	329 (8.2)	1781 (100)	NA	134 (3.7)	802 (22.5)
Drugs and Food Allergy														
Food allergy ever	369 (9.2)	711 (17.7)	35 (6.9)	NA	531 (12.4)	1185 (28.8)	290 (15.3)	559 (31.4)	108 (9.9)	152 (13.7)	0 (0)	NA	90 (2.5)	321 (9.0)
Clinical data														
Weight	1056	1391	93	NA	1408	1130	629	622	78	399	134	NA	628	685

	(26.5)	(34.7)	(18.4)		(32.8)	(27.4)	(33.1)	(35.0)	(7.1)	(36.0)	(7.5)		(17.3)	(19.2)
Height	1060 (26.6)	1391 (34.7)	101 (20.0)	NA	1415 (32.9)	1140 (27.7)	628 (33.1)	623 (35.0)	80 (7.3)	401 (36.2)	185 (10.4)	NA	714 (19.6)	696 (19.5)
IgE sensitisation	1389 (34.8)	1560 (38.9)	217 (43.0)	NA	3197 (74.4)	2316 (56.2)	395 (20.8)	976 (54.9)	468 (42.7)	423 (38.1)	672 (37.7)	NA	2895 (79.6)	1873 (52.5)

* In the PIAMA study, variables of "symptoms ever" at 4 years were constructed from the variables "symptoms during the past 12 months" using data from surveys at 1, 2, 3, and 4 years. Similarly, variables of "symptoms ever" at 8 years were constructed from the variables "symptoms during the past 12 months" using data from surveys at 1, 2, 3, 4, 5, 6, 7 and 8 years. Therefore, the number of children with non-missing information for "symptoms ever" and consequently the number of children that were included in the present analysis exceeds the number of children with completed 4-year and/or 8-year questionnaires. // NA: Not available.

Figure E1. Distribution of the number of variables with missing values, per period



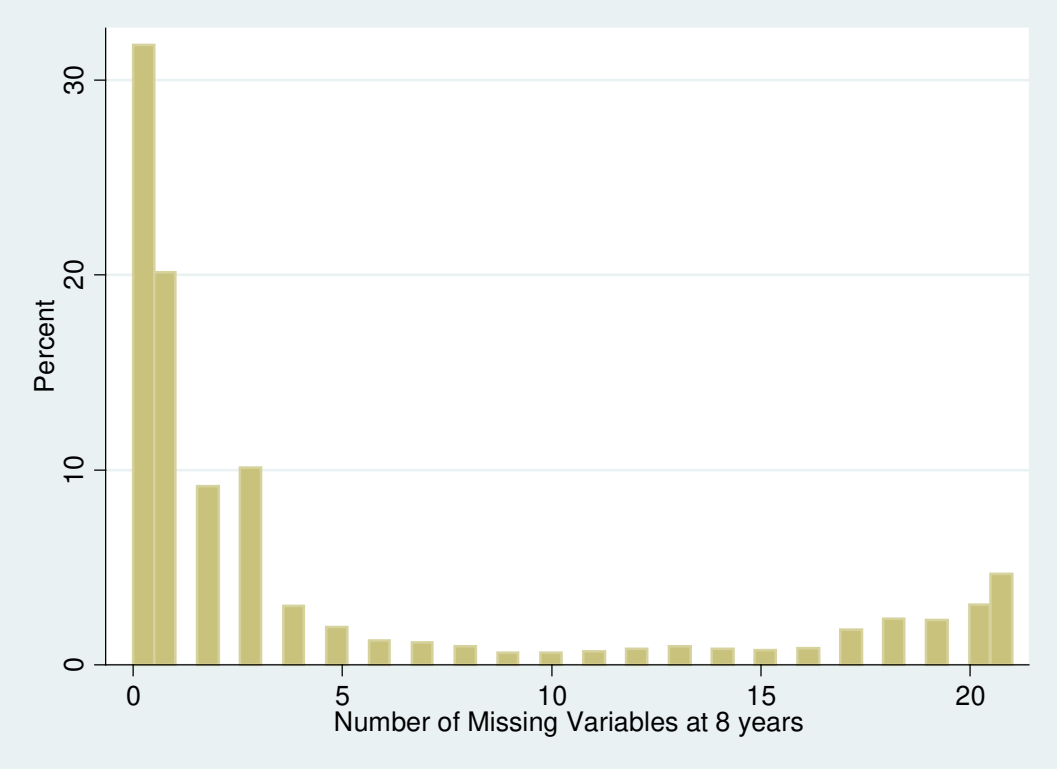


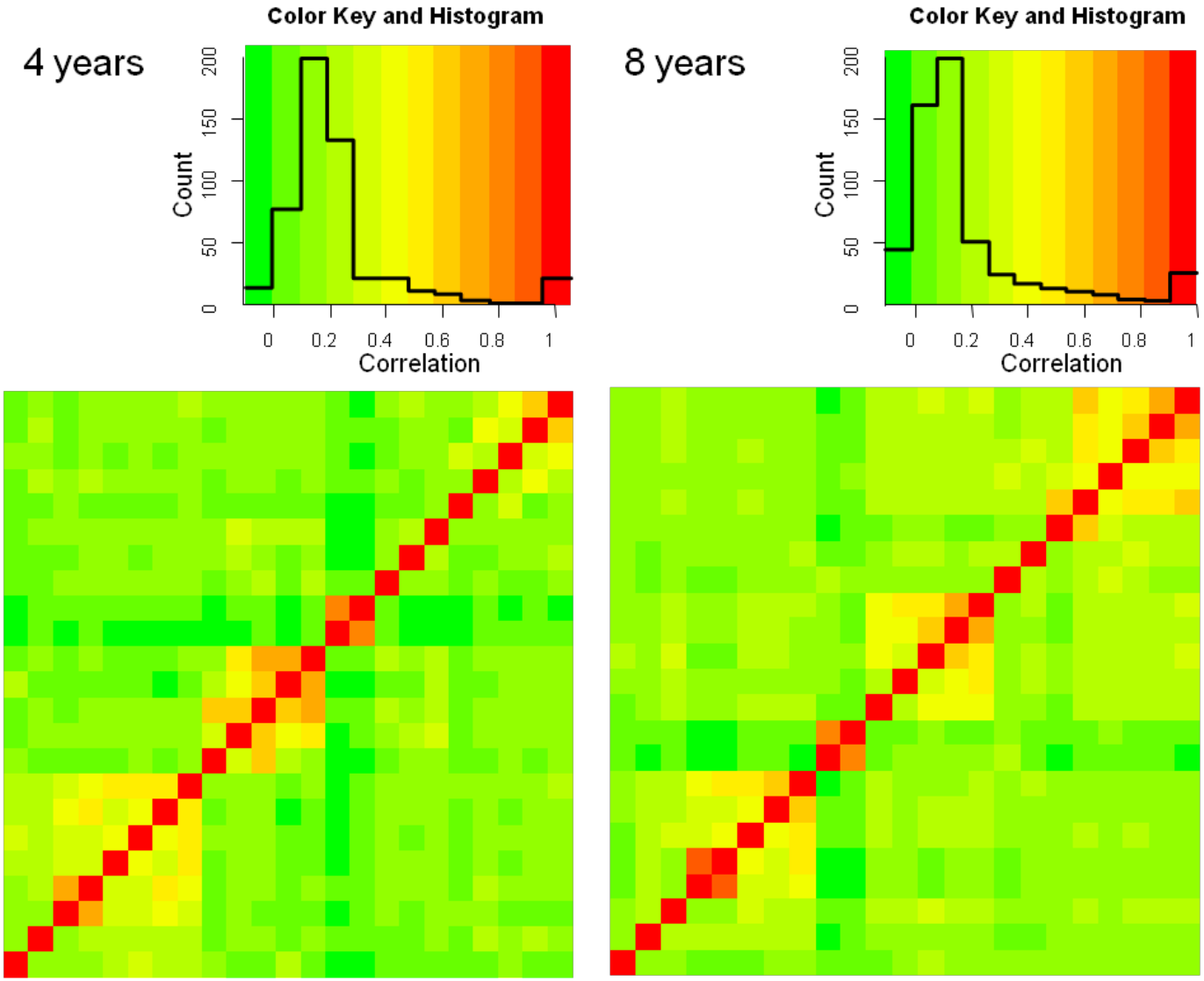
Table E3. Characteristics of participating children at 4 and 8 years, using complete cases and imputed datasets

	4 years		8 years	
	Complete cases N= 4187 n (%)	**Imputed data N= 17209 n (%)**	**Complete cases N= 4635 n (%)**	**Imputed data N= 14585 n (%)**
Sex: female *(variable not imputed)*	2004 (47.9)	8354 (48.5)	2278 (49.1)	7060 (48.4)
Age (months), m (SD)	47.8 (3.3)	46.9 (5.0)	104.8 (11.5)	106.4 (12.1)
Weight (kg), m (SD)	17.6 (2.4)	17.0 (2.7)	31.3 (6.1)	32.3 (7.7)
Height (cm), m (SD)	105.0 (4.8)	103.8 (6.0)	135.9 (7.9)	137.9 (9.4)
Wheezing ever	1343 (32.1)	5641 (32.8)	1537 (33.2)	5767 (39.5)
Wheezing attacks in the last 12 months				
None	3626 (86.6)	15309 (89.0)	4216 (91.0)	13112 (89.9)
1 - 3 times	381 (9.1)	1289 (7.5)	292 (6.3)	1005 (6.9)
4 - 12 times	141 (3.4)	482 (2.8)	95 (2.1)	358 (2.5)
> 12 times	39 (0.9)	129 (0.8)	32 (0.7)	110 (0.8)
Wheezing after exercise ever	304 (7.3)	1346 (7.8)	486 (10.5)	2345 (16.1)
Asthma ever	336 (8.0)	1410 (8.2)	525 (11.3)	2243 (15.4)
Asthma treatment in the last 12 months	806 (19.3)	1936 (11.3)	426 (9.2)	1371 (9.4)
Asthma onset before 2 years of age	228 (5.4)	924 (5.4)	183 (3.9)	879 (6.0)
Bronchitis or Bronchiolitis ever	1238 (29.6)	5794 (33.7)	1550 (33.4)	5760 (39.5)
Cough at night (when no cold) ever	965 (23.0)	4948 (28.8)	1508 (32.5)	6189 (42.4)
Sneezing or runny or blocked nose (when no cold) ever	1432 (34.2)	5607 (32.6)	1773 (38.3)	6392 (43.8)
Sneezing or runny or blocked nose (when no cold) in the last 12 months	516 (12.3)	2474 (14.4)	897 (19.4)	3400 (23.3)
Itchy watery eyes (when no cold) in the last 12 months	203 (4.8)	831 (4.8)	474 (10.2)	1845 (12.7)
Allergic rhinitis ever	111 (2.7)	648 (3.8)	492 (10.6)	2326 (15.9)
Rhinitis onset before 2 years of age	54 (1.3)	876 (5.1)	36 (0.8)	345 (2.4)
Itchy rash (coming and going for at least six months) ever	1358 (32.4)	6290 (36.6)	1939 (41.8)	6921 (47.5)
Itchy rash (coming and going for at least six months) in the last 12 months	801 (19.1)	3353 (19.5)	652 (14.1)	2126 (14.6)
Itchy rash affecting common areas	1271 (30.4)	4820 (28.0)	515 (11.1)	1657 (11.4)

Itchy rash onset before 2 years of age	681 (16.3)	3734 (21.7)	991 (21.4)	3477 (23.8)
Eczema ever	1043 (24.9)	4614 (26.8)	1391 (30.0)	5049 (34.6)
Urticaria ever	846 (20.2)	3403 (19.8)	907 (19.6)	3043 (20.9)
Food allergy ever	402 (9.6)	1850 (10.7)	640 (13.8)	2699 (18.5)
IgE sensitisation	879 (21.0)	3611 (21.0)	1634 (35.3)	5680 (38.9)

193

Figure E2. Correlations between the 23 variables included in the cluster analysis (20 features of allergy-related diseases, weight, height, and age)



197

198 **Selection of the number of cluster groups**

199 We determined the number of groups (clusters) using the Calinski-Harabasz stopping rule, if and only if the
200 suggested number of groups was in agreement with another stopping rule (the average silhouette width) and
201 with consensus measures, and it could not be attributed to chance. The Calinski and Harabasz index is a
202 measure of inter-cluster (dis)similarity over intra-cluster (dis)similarity.[E20] The average silhouette width is a
203 measure of how tightly grouped all the data in the cluster are.[E21] In both stopping rules, larger values indicate
204 better clustering (high between- and low within-cluster differences). We also calculated p-values for the
205 distributions of Calinsky-Harabasz and average silhouette width, assuming the null hypothesis (i.e., that there
206 are no clusters in our data), by comparing actual values with the background distributions built on a large
207 number (20000) of randomly permuted versions of the original dataset. Consensus measures assess the
208 confidence in the number of groups and the group memberships by bootstrapping the data and report the
209 consensus of these repetitions, which is robust relative to sampling variability.[E22]

210 **Sensitivity analysis**

211 We performed several secondary analyses to assess the sensitivity of our estimates to our assumptions
212 regarding selection bias and information bias, as well as to test for model misspecification.

213 First, to test if alternative hypothesis-free grouping methods could have yielded different results, we repeated
214 all analyses using hierarchical cluster with Wards method, latent class analysis, and self-organizing maps
215 (Sensitivity Analysis I). In hierarchical cluster analysis with Wards method, all observations begin as a single
216 cluster, and pairs of clusters are iteratively joined in a hierarchical way. In each step, the two pairs of clusters
217 that minimize the within-group variance are joined.[E23] Latent class analysis is probabilistic or model-based
218 clustering technique that identifies classes so that within a latent class all variables are assumed independent,
219 i.e. class membership accounts for the interrelationship between the original variables.[E24] Self-organizing
220 maps are an unsupervised type of neural network analysis often used for clustering and visualisation.[E25]

221 Second, to assess potential differences in cluster results according to each of the birth cohorts resulting from
222 different recruitment methods or characteristics of each specific population, we performed the cluster
223 analyses separately for each birth cohort (Sensitivity analysis II).

224 Third, to rule out the possibility that cluster results are influenced by variables with potential problems of
225 measurement error (and so, misclassification), we repeated cluster analysis excluding “itchy rash ever” and

226 “food allergy ever” (one at a time), using a higher cut-offs for IgE-sensitisation (≥ 3.5 kUA/l) and using body
227 mass index (BMI) instead of weight and height separately (Sensitivity analysis III).
228 Fourth, to explore if cluster results are limited by the availability of data common to the seven cohorts, we
229 repeated cluster analysis in a subset of two birth cohorts (PIAMA and BAMSE) including additional
230 variables. In PIAMA we included: (i) a broader list of symptoms, signs and triggers of the three allergy-
231 related diseases, (ii) detailed information on health services use and treatments related to the three diseases,
232 (iii) lung function including spirometry, bronchial responsiveness (only at 8 y), and airway resistance (Rint),
233 (iv) skin prick test (only at 8 y), and (v) inflammation by exhaled nitric oxide (FeNO). In BAMSE, we
234 included: (i) a broader list of symptoms, signs and triggers of the three allergy-related diseases, (ii) lung
235 function (only at 8 y), (iii) inflammation by exhaled nitric oxide (FeNO, only at 8 y), and (iv) detailed
236 information about sensitization (defined using up to 14 specific IgEs). (Sensitivity analysis IV).
237 Finally, to evaluate the uncertainty produced by the multiple imputation we repeated cluster analyses
238 stratifying children according to the proportion of missing data (Sensitivity analysis V).
239

MAIN RESULTS

Table E4. Characteristics of children at 4 and 8 years, by birth cohort.

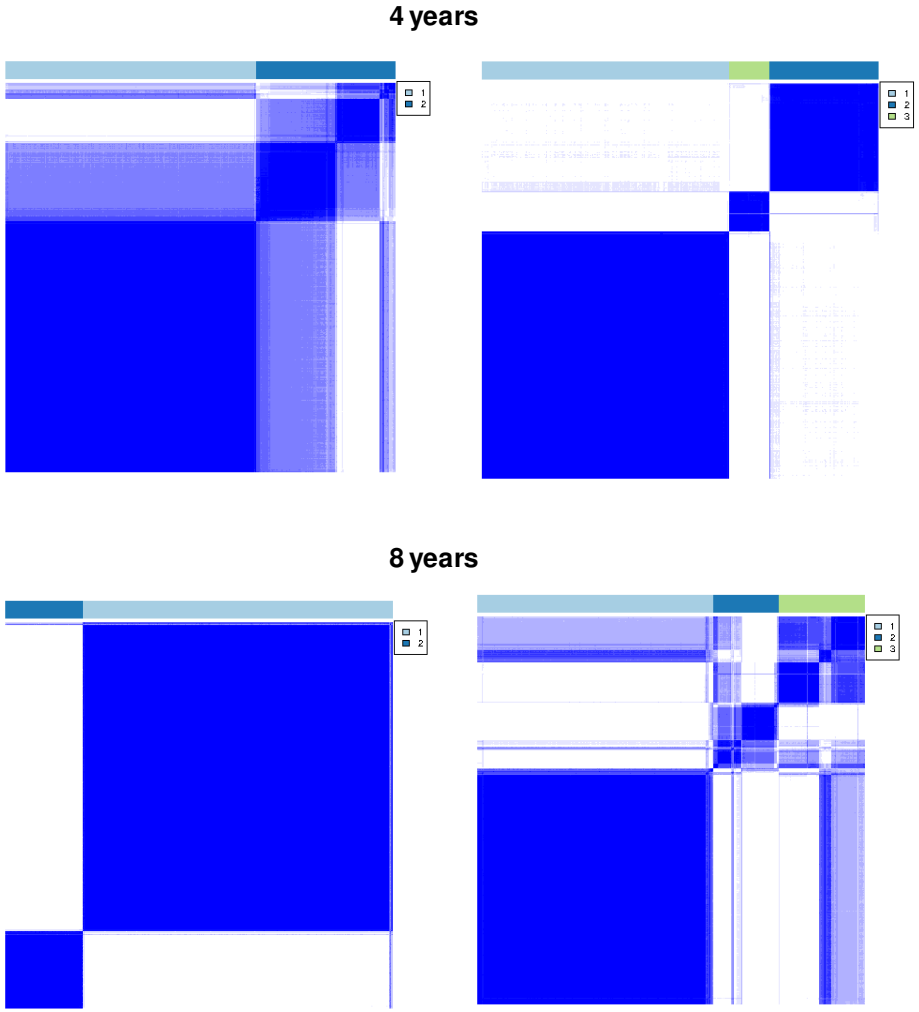
		BAMSE*	DARC	GINIplus*	LISAplus*	MAS*	PARIS	PIAMA*,†
Country		Sweden	Denmark	Germany	Germany	Germany	France	Netherlands
N at 4 years	17209¶	3993 (23.2)	505 (2.9)	4299 (25.0)	1899 (11.0)	1097 (6.4)	1781 (10.4)	3635 (21.1)
Sex: female, n (%)	8354 (48.5)	1973 (49.4)	245 (48.5)	2092 (48.7)	894 (47.1)	520 (47.4)	878 (49.3)	1752 (48.2)
Age (months), m (SD)	46.9 (5.0)	48.7 (3.0)	36.0 (0.0)	48.7 (1.1)	49.3 (1.5)	48.4 (0.9)	34.9 (2.0)	48.5 (1.4)
Weight (kg), m (SD)	17.0 (2.5)	18.3 (2.4)	14.8 (1.7)	17.0 (2.2)	17.0 (2.1)	17.1 (2.3)	14.3 (1.6)	17.4 (2.3)
Height (cm), m (SD)	103.7 (5.6)	106.0 (4.4)	95.7 (5.9)	104.7 (4.4)	104.5 (4.2)	104.5 (4.2)	95.4 (3.8)	105.2 (4.6)
N at 8 years	14585¶	4011 (27.5)		4118 (28.2)	1779 (12.2)	1109 (7.6)		3568 (24.5)
Sex: female, n (%)	7060 (48.4)	1982 (49.4)		2001 (48.6)	836 (47.0)	528 (47.6)		1713 (48.0)
Age (months), m (SD)	106.4 (12.1)	97.9 (5.6)		121.1 (2.9)	120.8 (2.5)	97.0 (2.8)		97.0 (2.4)
Weight (kg), m (SD)	32.2 (6.8)	30.2 (5.5)		35.1 (6.7)	34.7 (6.6)	36.7 (8.7)		28.8 (4.8)
Height (cm), m (SD)	137.9 (8.3)	132.2 (6.2)		143.8 (6.8)	143.3 (6.6)	142.6 (6.7)		133.5 (6.0)

* A total of 14383 children had data available at both age periods; 3882 in BAMSE, 3982 in GINIplus, 1777 in LISAplus, 1259 in MAS, and 3483 in PIAMA.

† In the PIAMA study, variables of "symptoms ever" at 4 years were constructed from the variables "symptoms during the past 12 months" using data from surveys at 1, 2, 3, and 4 years. Similarly, variables of "symptoms ever" at 8 years were constructed from the variables "symptoms during the past 12 months" using data from surveys at 1, 2, 3, 4, 5, 6, 7 and 8 years. Therefore, the number of children with non-missing information for "symptoms ever" and consequently the number of children that were included in the present analysis exceeds the number of children with completed 4-year and/or 8-year questionnaires.

¶ Some data is missing: at 4 years, age 1065/17209 (6.2%), weight 4026/17209 (23.4%), and height 4183/17209 (24.3%); at 8 years, age 2430/14585 (16.7%), weight 4227/14585 (29.0%), and height 4251/14585 (29.1%).

Figure E3. Consensus matrix* for 2 and 3 cluster groups, at 4 and 8 years



* Homogeneous blue blocks represent stable clusterings, indicating samples are consistently grouped over different bootstrap resamplings of the data.

255 **Table E5. Description of the two groups identified by cluster analysis at 4 and 8 years**

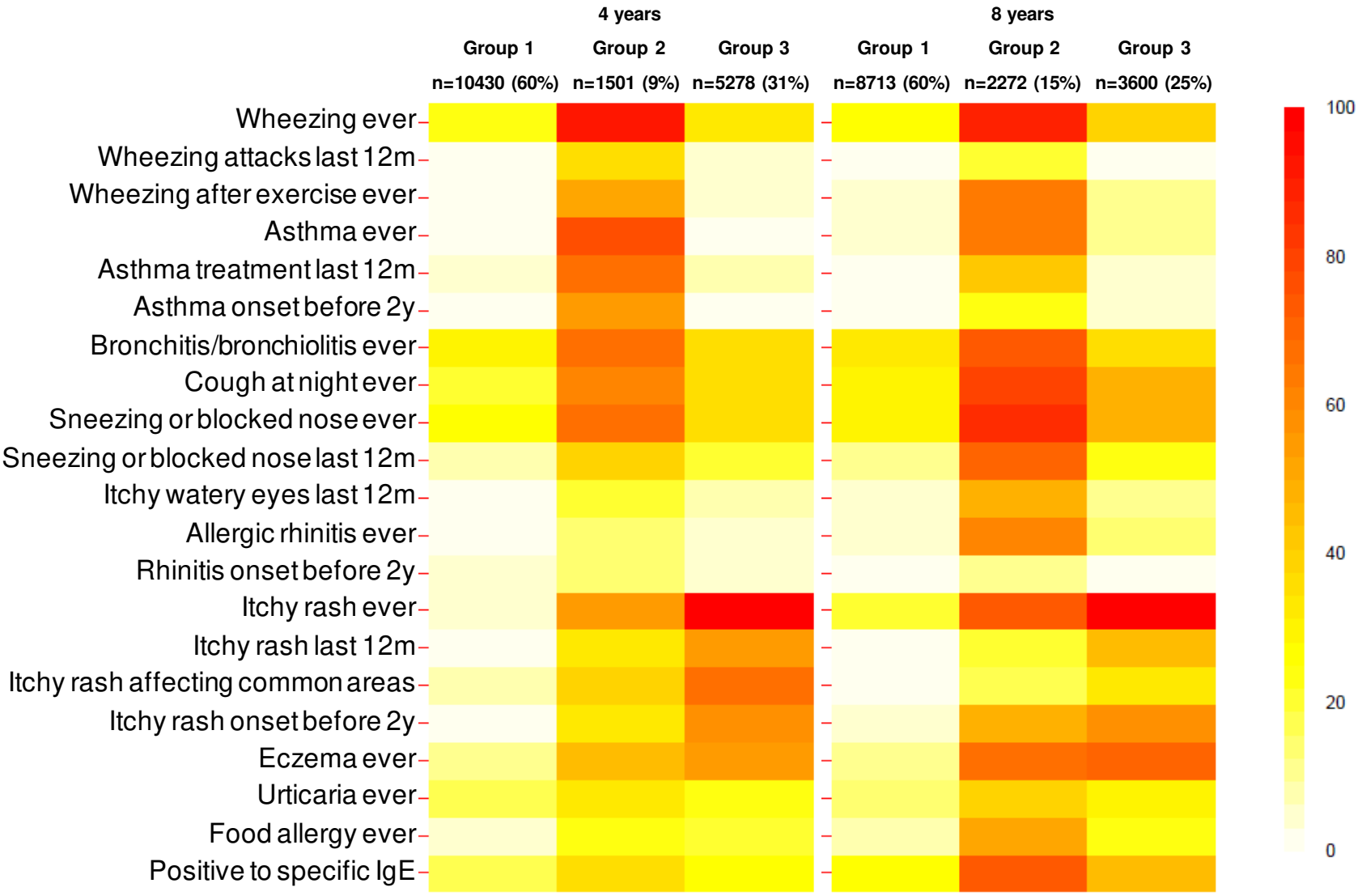
	4 years				8 years			
	All	**Group 1**	**Group 2**		**All**	**Group 1**	**Group 2**	
	N = 17209	**12052 (70.0)**	**5157 (30.0)**	**F***	**N = 14585**	**11456 (78.5)**	**3129 (21.5)**	**F***
	n (%)	**n (%)**	**n (%)**		**n (%)**	**n (%)**	**n (%)**	
Wheezing ever	5641 (32.8)	2666 (22.1)	2975 (57.7)	1753.7	5767 (39.5)	3263 (28.5)	2505 (80.1)	1661.0
Wheezing attacks in the last 12 months								
None	15309 (89.0)	11561 (95.9)	3748 (72.7)	366.8	13112 (89.9)	11099 (96.9)	2012 (64.3)	347.7
1 - 3 times	1289 (7.5)	438 (3.6)	851 (16.5)		1005 (6.9)	292 (2.5)	714 (22.8)	
4 - 12 times	482 (2.8)	45 (0.4)	437 (8.5)		358 (2.5)	48 (0.4)	310 (9.9)	
> 12 times	129 (0.8)	8 (0.1)	121 (2.4)		110 (0.8)	17 (0.2)	93 (3.0)	
Wheezing after exercise ever	1346 (7.8)	251 (2.1)	1095 (21.2)	1077.5	2345 (16.1)	701 (6.1)	1644 (52.6)	1869.0
Asthma ever	1410 (8.2)	230 (1.9)	1180 (22.9)	979.4	2243 (15.4)	614 (5.4)	1629 (52.1)	2019.2
Asthma treatment in the last 12 months	1936 (11.3)	624 (5.2)	1312 (25.4)	1092.2	1371 (9.4)	306 (2.7)	1065 (34.0)	1278.2
Asthma onset before 2 years of age	924 (5.4)	131 (1.1)	793 (15.4)	691.3	879 (6.0)	262 (2.3)	617 (19.7)	588.5
Bronchitis or Bronchiolitis ever	5794 (33.7)	3144 (26.1)	2651 (51.4)	831.1	5760 (39.5)	3734 (32.6)	2026 (64.8)	852.9
Cough at night (when no cold) ever	4948 (28.8)	2469 (20.5)	2479 (48.1)	1137.4	6189 (42.4)	3865 (33.7)	2324 (74.3)	1188.6
Sneezing or runny or blocked nose (when no cold) ever	5607 (32.6)	2825 (23.4)	2782 (53.9)	1306.8	6392 (43.8)	3700 (32.3)	2692 (86.0)	1361.9
Sneezing or runny or blocked nose (when no cold) in the last 12 months	2474 (14.4)	870 (7.2)	1603 (31.1)	1351.0	3400 (23.3)	1288 (11.2)	2112 (67.5)	1955.6
Itchy watery eyes (when no cold) in the last 12 months	831 (4.8)	122 (1.0)	709 (13.7)	686.0	1845 (12.7)	389 (3.4)	1456 (46.5)	1550.9

Allergic rhinitis ever	648 (3.8)	109 (0.9)	538 (10.4)	453.4	2326 (15.9)	569 (5.0)	1756 (56.1)	1688.1
Rhinitis onset before 2 years of age	876 (5.1)	349 (2.9)	527 (10.2)	309.9	345 (2.4)	75 (0.7)	270 (8.6)	259.8
Itchy rash (coming and going for at least six months) ever	6290 (36.6)	1934 (16.0)	4356 (84.5)	4842.9	6921 (47.5)	4498 (39.3)	2423 (77.4)	1020.1
Itchy rash (coming and going for at least six months) in the last 12 months	3353 (19.5)	591 (4.9)	2762 (53.6)	3495.0	2126 (14.6)	1287 (11.2)	839 (26.8)	326.2
Itchy rash affecting common areas	4820 (28.0)	1323 (11.0)	3497 (67.8)	4135.1	1657 (11.4)	936 (8.2)	721 (23.1)	378.2
Itchy rash onset before 2 years of age	3734 (21.7)	1023 (8.5)	2712 (52.6)	2688.8	3477 (23.8)	1831 (16.0)	1646 (52.6)	1344.3
Eczema ever	4614 (26.8)	1288 (10.7)	3327 (64.5)	3949.2	5049 (34.6)	2869 (25.0)	2181 (69.7)	1562.6
Urticaria ever	3403 (19.8)	1844 (15.3)	1559 (30.2)	331.4	3043 (20.9)	1806 (15.8)	1238 (39.6)	528.1
Food allergy ever	1850 (10.7)	517 (4.3)	1332 (25.8)	1227.5	2699 (18.5)	1187 (10.4)	1513 (48.3)	1476.2
IgE sensitisation	3611 (21.0)	2001 (16.6)	1610 (31.2)	319.2	5680 (38.9)	3437 (30.0)	2243 (71.7)	985.5
Weight (kg), m (SD)	17.0 (2.7)	17.1 (2.6)	16.9 (3.0)	18.5	32.3 (7.7)	32.0 (7.4)	33.4 (8.7)	66.9
Height (cm), m (SD)	103.8 (6.0)	104.1 (5.9)	103.2 (6.5)	61.4	137.9 (9.4)	137.5 (8.8)	139.5 (10.7)	95.6

256 * F values correspond to the ratio of the variance of the group means (between-group variance) over the overall variance of the variable (higher values meaning higher relevance of the
257 variable for separating cluster groups), and were obtained by means of linear regression models using each variable as the outcome, and the cluster group as the exposure.

258

Figure E4. Prevalence* of symptoms of asthma, rhinitis, and eczema according to three groups identified in cluster analysis, at 4 and 8 years.



* Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

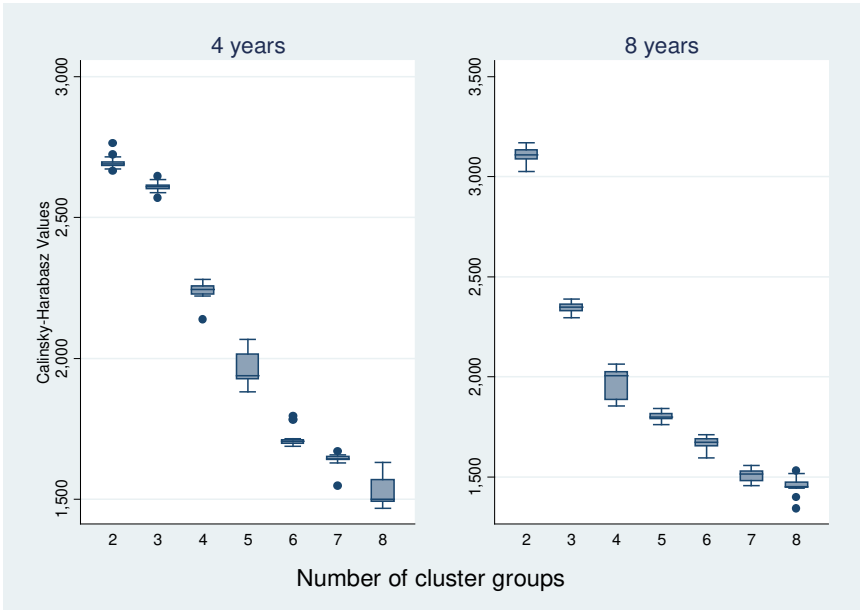
Table E6. Distribution of classical phenotypes of current asthma, rhinitis, eczema, and their comorbidity, according to the two groups identified in cluster analysis, at 4 and 8 years.

2A. 4 years	**4 years**				**8 years**			
	All	**Group 1**	**Group 2**		**All**	**Group 1**	**Group 2**	
	N= 17209	**12052 (70.0)**	**5157 (30.0)**	**p**	**N= 14585**	**11456 (78.5)**	**3129 (21.5)**	**p**
	n (%)	**n (%)**	**n (%)**		**n (%)**	**n (%)**	**n (%)**	
Sex, female n (%)	8354 (48.5)	6004 (49.8)	2350 (45.6)	<0.001	7060 (48.4)	5807 (50.7)	1253 (40.0)	<0.001
Age, months, mean (SD)	46.9 (5.0)	47.1 (4.8)	46.4 (5.5)	<0.001	106.4 (12.1)	106.1 (12.0)	107.9 (12.2)	<0.001
Classical phenotypes definitions	*n=15019*	*n=10855*	*n=4164*		*n=10673*	*n=9003*	*n=1670*	
None	11555 (76.9)	10306 (94.9)	1249 (30.0)	<0.001	8334 (78.1)	8017 (89.1)	317 (19.0)	<0.001
Asthma	736 (4.9)	190 (1.8)	546 (13.1)		356 (3.3)	98 (1.1)	258 (15.4)	
Rhinitis	290 (1.9)	91 (0.8)	199 (4.8)		630 (5.9)	164 (1.8)	466 (27.9)	
Eczema	1908 (12.7)	268 (2.5)	1640 (39.4)		878 (8.2)	718 (8.0)	160 (9.6)	
Asthma & Rhinitis	71 (0.5)	0 (0)	71 (1.7)		169 (1.6)	0 (0)	169 (10.1)	
Asthma & Eczema	235 (1.6)	0 (0)	235 (5.6)		120 (1.1)	4 (0.0)	116 (6.9)	
Rhinitis & Eczema	148 (1.0)	0 (0)	148 (3.6)		113 (1.1)	2 (0.0)	111 (6.7)	
Asthma & Rhinitis & Eczema	76 (0.5)	0 (0)	76 (1.8)		73 (0.7)	0 (0)	73 (4.4)	

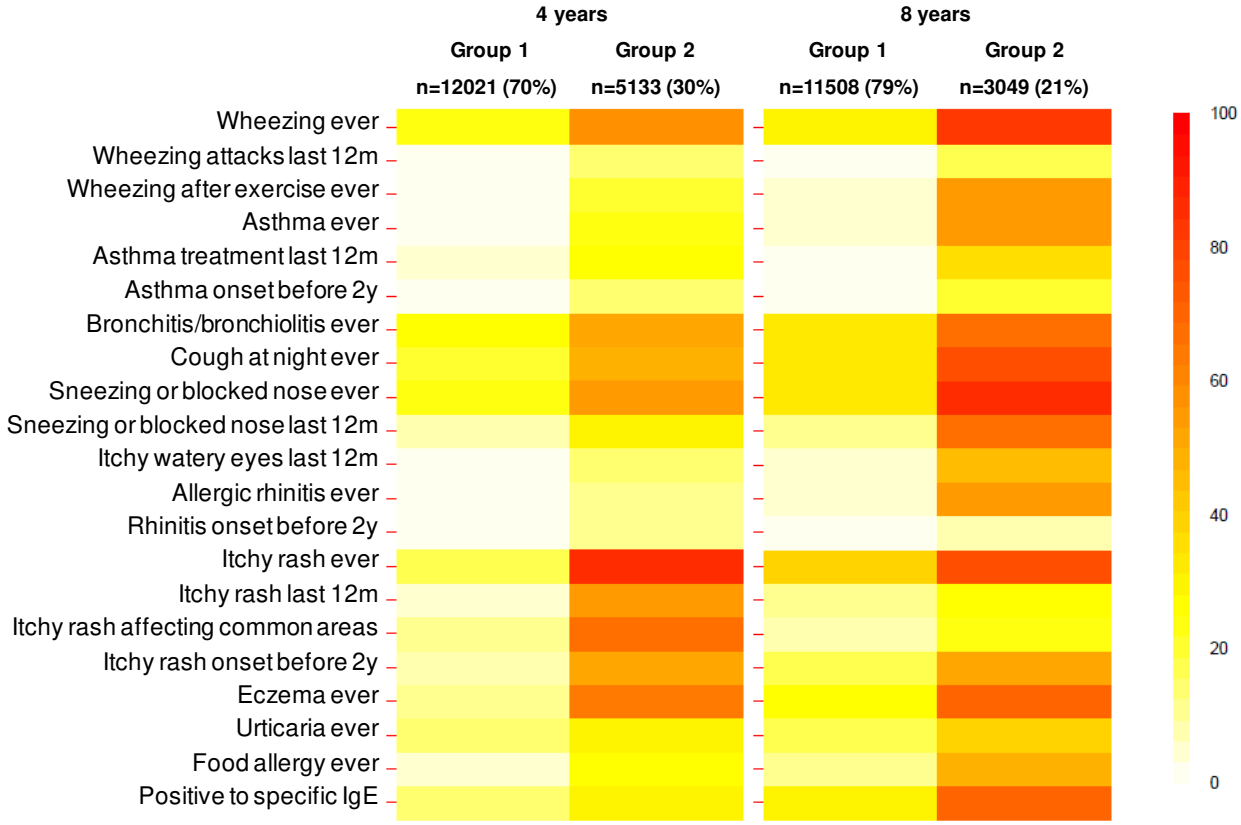
268

ROLE OF IGE

Figure E5. Distribution of Calinsky-Harabasz stopping rule* and graphical description† of the two groups identified by cluster analysis at 4 and 8 years, without including IgE sensitisation as a variable in the cluster analysis



* Higher values indicate higher separation between groups and similarity within groups.



† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

281 **Table E7. Description of the two groups identified by cluster analysis at 4 and 8 years, without including IgE sensitisation as a variable in the cluster analysis**

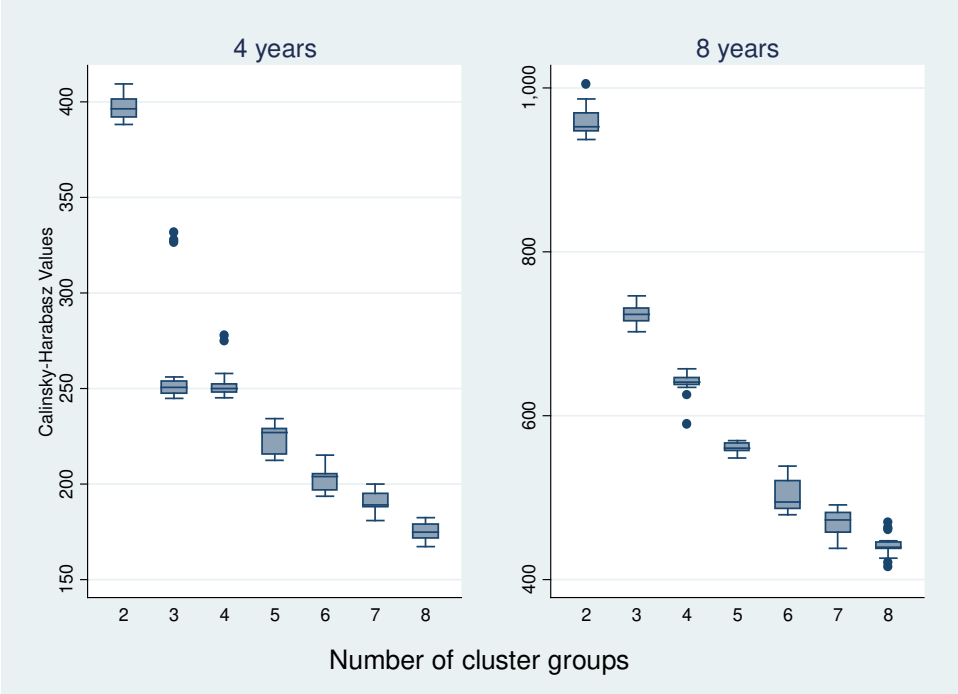
	4 years				8 years			
	All	**Group 1**	**Group 2**		**All**	**Group 1**	**Group 2**	
	N= 17154	**12021 (70.1)**	**5133 (29.9)**	**F***	**N= 14557**	**11508 (79.1)**	**3049 (20.9)**	**F***
	n (%)	**n (%)**	**n (%)**		**n (%)**	**n (%)**	**n (%)**	
Wheezing ever	5614 (32.7)	2657 (22.1)	2957 (57.6)	1809.3	5747 (39.5)	3240 (28.2)	2508 (82.2)	1755.1
Wheezing attacks in the last 12 months								
None	15260 (89.0)	11535 (96.0)	3726 (72.6)	338.3	13090 (89.9)	11164 (97.0)	1926 (63.2)	359.5
1 - 3 times	1282 (7.5)	433 (3.6)	848 (16.5)		1003 (6.9)	283 (2.5)	720 (23.6)	
4 - 12 times	484 (2.8)	45 (0.4)	439 (8.6)		353 (2.4)	44 (0.4)	309 (10.1)	
> 12 times	128 (0.7)	8 (0.1)	120 (2.3)		111 (0.8)	17 (0.1)	94 (3.1)	
Wheezing after exercise ever	1343 (7.8)	248 (2.1)	1094 (21.3)	1097.9	2333 (16.0)	671 (5.8)	1662 (54.5)	2286.4
Asthma ever	1411 (8.2)	229 (1.9)	1182 (23.0)	1211.6	2242 (15.4)	590 (5.1)	1652 (54.2)	2282.3
Asthma treatment in the last 12 months	1929 (11.2)	619 (5.1)	1310 (25.5)	1141.8	1354 (9.3)	289 (2.5)	1065 (34.9)	1199.0
Asthma onset before 2 years of age	925 (5.4)	127 (1.1)	797 (15.5)	763.3	874 (6.0)	247 (2.1)	628 (20.6)	734.4
Bronchitis or Bronchiolitis ever	5762 (33.6)	3129 (26.0)	2634 (51.3)	909.5	5733 (39.4)	3703 (32.2)	2031 (66.6)	883.5
Cough at night (when no cold) ever	4922 (28.7)	2474 (20.6)	2448 (47.7)	1103.6	6163 (42.3)	3865 (33.6)	2298 (75.4)	1145.0
Sneezing or runny or blocked nose (when no cold) ever	5581 (32.5)	2806 (23.3)	2776 (54.1)	1368.2	6374 (43.8)	3763 (32.7)	2611 (85.6)	1352.0
Sneezing or runny or blocked nose (when no cold) in the last 12 months	2465 (14.4)	865 (7.2)	1600 (31.2)	1335.8	3390 (23.3)	1360 (11.8)	2031 (66.6)	1933.1
Itchy watery eyes (when no cold) in the last 12 months	832 (4.9)	124 (1.0)	708 (13.8)	675.3	1848 (12.7)	461 (4.0)	1387 (45.5)	1886.0

Allergic rhinitis ever	645 (3.8)	107 (0.9)	538 (10.5)	480.1	2321 (15.9)	650 (5.6)	1671 (54.8)	2001.9
Rhinitis onset before 2 years of age	872 (5.1)	349 (2.9)	523 (10.2)	326.3	351 (2.4)	77 (0.7)	274 (9.0)	233.5
Itchy rash (coming and going for at least six months) ever	6255 (36.5)	1920 (16.0)	4334 (84.4)	5040.6	6902 (47.4)	4528 (39.3)	2374 (77.9)	986.7
Itchy rash (coming and going for at least six months) in the last 12 months	3321 (19.4)	564 (4.7)	2756 (53.7)	3607.2	2124 (14.6)	1286 (11.2)	838 (27.5)	369.1
Itchy rash affecting common areas	4787 (27.9)	1299 (10.8)	3488 (67.9)	4194.4	1653 (11.4)	935 (8.1)	719 (23.6)	398.1
Itchy rash onset before 2 years of age	3710 (21.6)	1027 (8.5)	2683 (52.3)	2968.6	3475 (23.9)	1864 (16.2)	1612 (52.9)	1183.8
Eczema ever	4588 (26.7)	1289 (10.7)	3299 (64.3)	3814.0	5033 (34.6)	2882 (25.0)	2151 (70.6)	1350.8
Urticaria ever	3404 (19.8)	1841 (15.3)	1563 (30.4)	288.3	3041 (20.9)	1812 (15.7)	1229 (40.3)	619.2
Food allergy ever	1836 (10.7)	513 (4.3)	1323 (25.8)	1245.9	2684 (18.4)	1216 (10.6)	1467 (48.1)	1438.4
Weight (kg), m (SD)	17.0 (3.0)	17.1 (2.9)	16.9 (3.0)	17.6	32.3 (8.0)	32.1 (7.1)	33.3 (9.7)	52.9
Height (cm), m (SD)	103.8 (6.6)	104.1 (6.4)	103.2 (6.5)	64.3	137.9 (9.5)	137.6 (8.9)	139.4 (10.4)	83.0
Variable not included in the cluster analysis:								
IgE sensitisation	1568 (19.8)	825 (15.4)	743 (29.0)	—	2773 (37.4)	1853 (30.5)	920 (69.2)	—

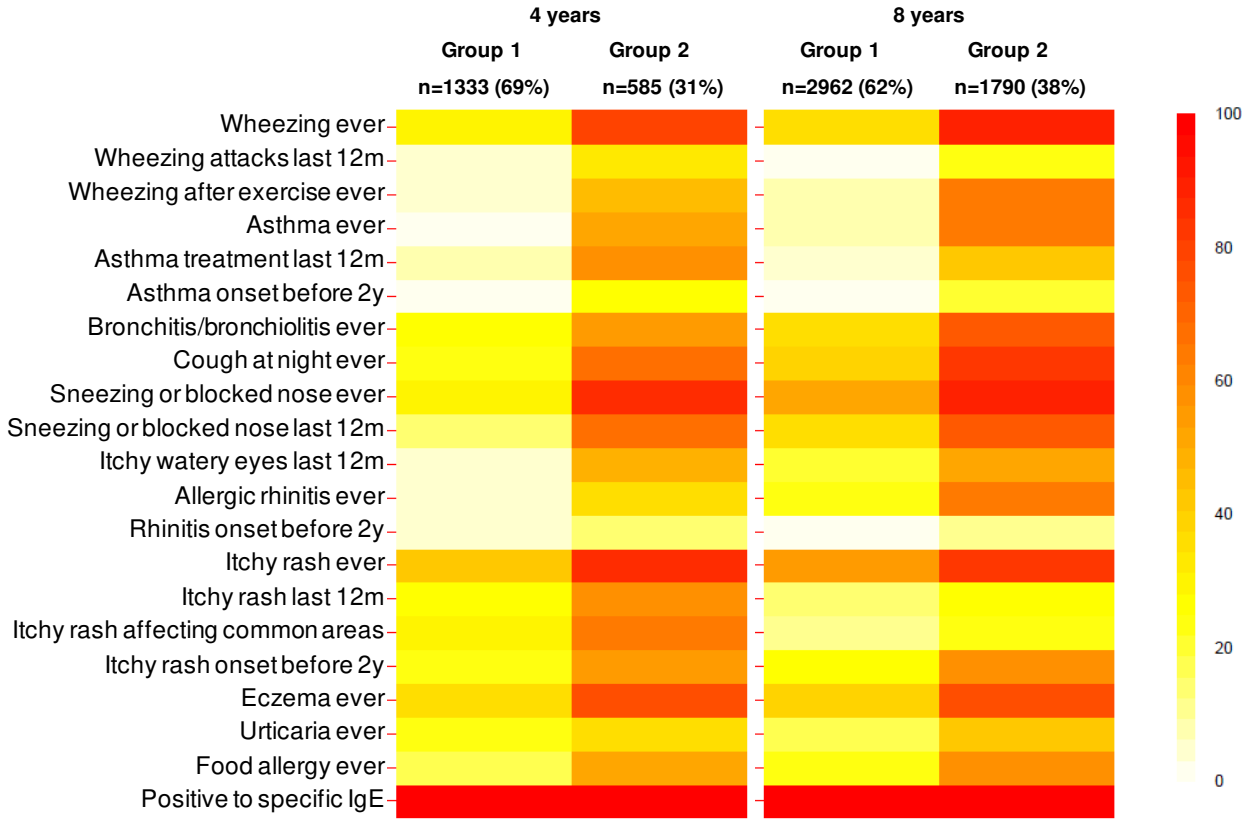
* F values correspond to the ratio of the variance of the group means (between-group variance) over the overall variance of the variable (higher values meaning higher relevance of the variable for separating cluster groups), and were obtained by means of linear regression models using each variable as the outcome, and the cluster group as the exposure.

Figure E6. Distribution of Calinsky-Harabasz stopping rule* and graphical description† of the two groups identified by cluster analysis at 4 and 8 years, after stratifying the cluster analysis according to IgE sensitisation

Sensitised – Positive to IgE

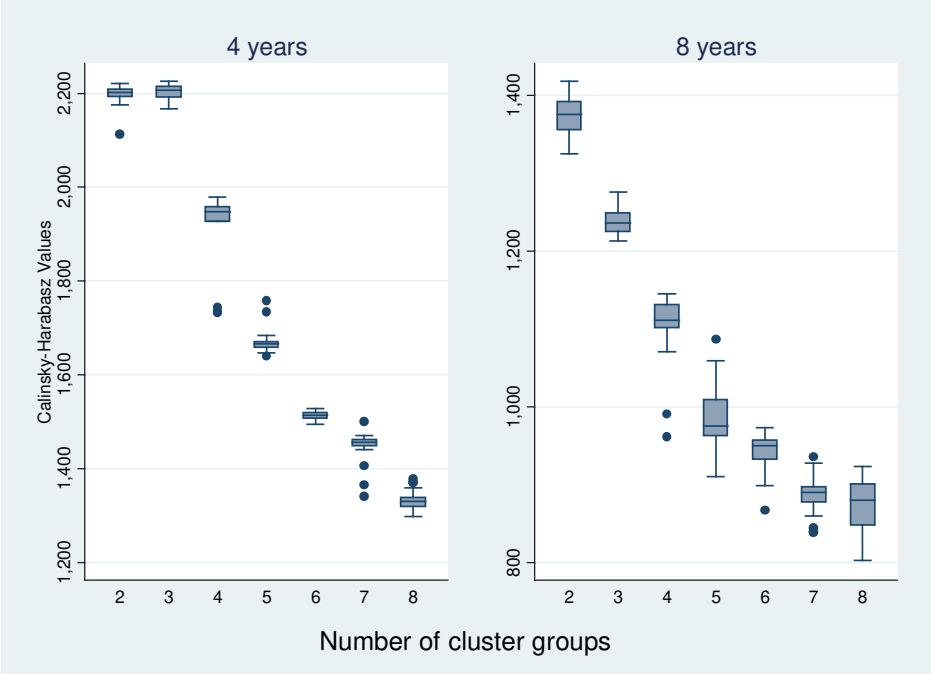


* Higher values indicate higher separation between groups and similarity within groups.

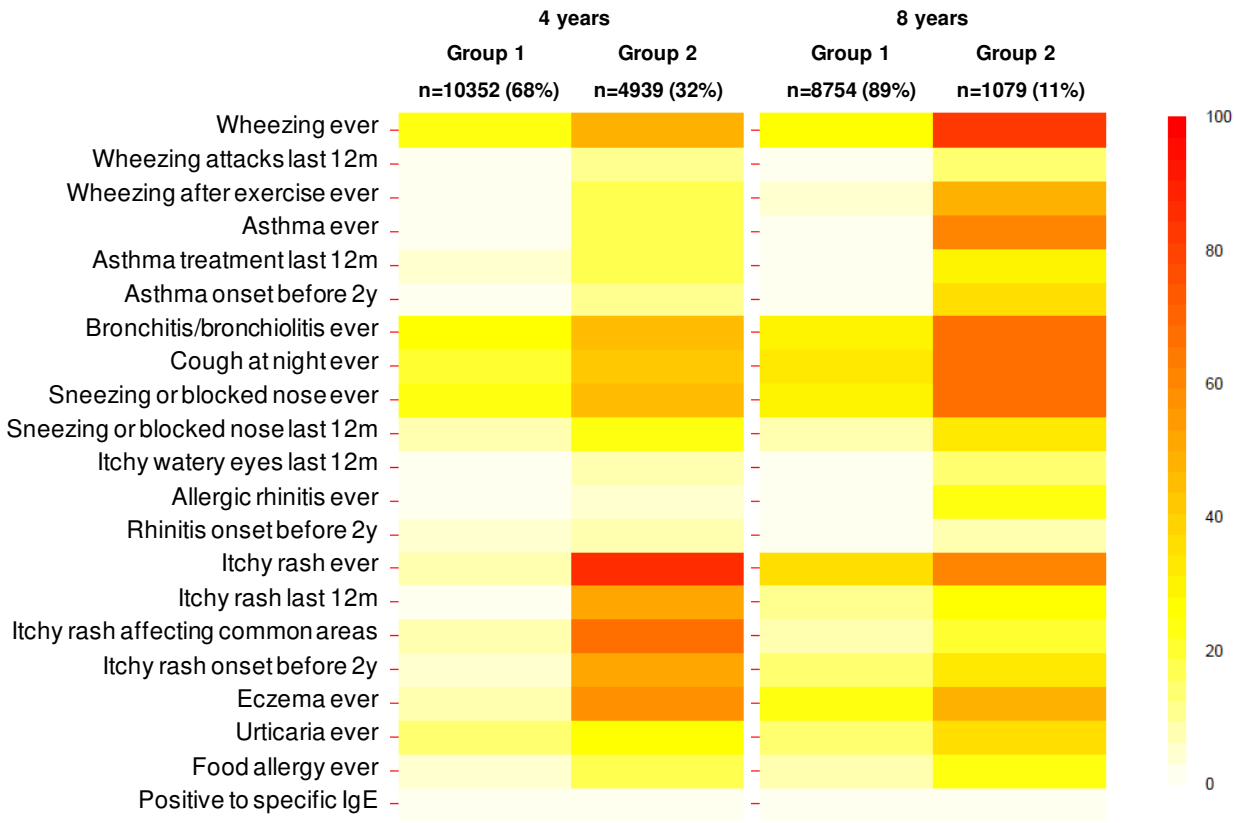


† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

Not sensitised - Negative to IgE



* Higher values indicate higher separation between groups and similarity within groups.



† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

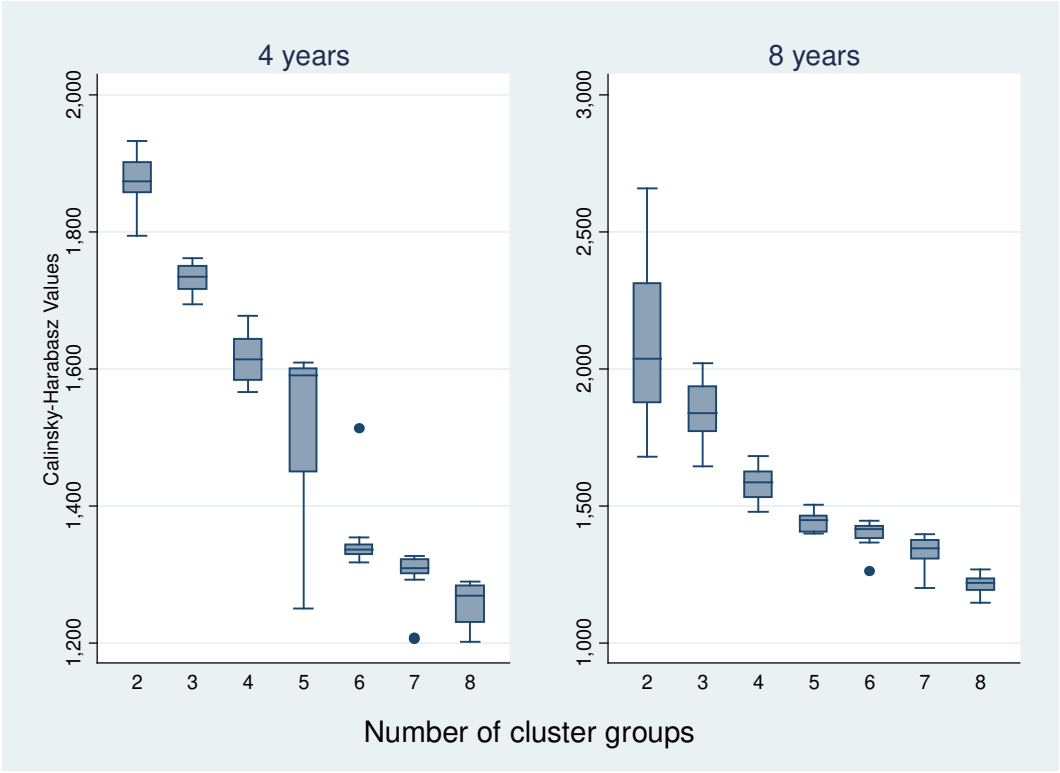
303 **Table E8. Description of the two groups identified by cluster analysis at 4 and 8 years, after stratifying the cluster analysis according to IgE sensitisation**

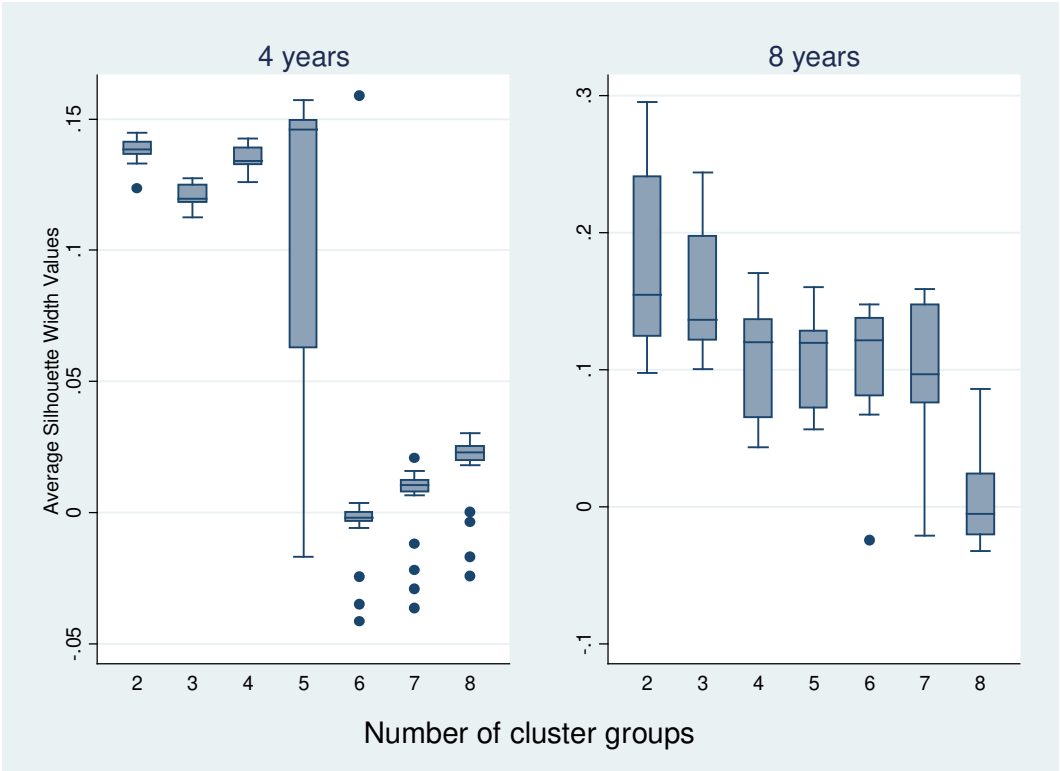
	4 years				8 years			
	Sensitised		Not sensitised		Sensitised		Not sensitised	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
	N=1333 (69.5)	N=585 (30.5)	N=10352 (67.7)	N=4939 (32.3)	N=2962 (62.3)	N=1790 (37.7)	N=8754 (89.0)	N=1079 (11.0)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Wheezing ever	399 (29.9)	471 (80.4)	2346 (22.7)	2426 (49.1)	1021 (34.5)	1609 (89.9)	2229 (25.5)	908 (84.1)
Wheezing attacks in the last 12 months								
None	1226 (92.0)	247 (42.1)	9909 (95.7)	3926 (79.5)	2784 (94.0)	978 (54.7)	8593 (98.2)	756 (70.1)
1 - 3 times	88 (6.6)	162 (27.7)	392 (3.8)	647 (13.1)	146 (4.9)	498 (27.8)	136 (1.6)	225 (20.9)
3 - 12 times	15 (1.2)	137 (23.5)	43 (0.4)	286 (5.8)	27 (0.9)	240 (13.4)	19 (0.2)	72 (6.7)
> 12 times	4 (0.3)	39 (6.6)	8 (0.1)	79 (1.6)	5 (0.2)	74 (4.1)	6 (0.1)	25 (2.4)
Wheezing after exercise ever	46 (3.5)	268 (45.9)	232 (2.2)	799 (16.2)	265 (9.0)	1162 (64.9)	397 (4.5)	522 (48.4)
Asthma ever	39 (2.9)	308 (52.6)	230 (2.2)	833 (16.9)	213 (7.2)	1129 (63.1)	234 (2.7)	666 (61.8)
Asthma treatment in the last 12 months	123 (9.2)	336 (57.5)	568 (5.5)	908 (18.4)	142 (4.8)	777 (43.4)	127 (1.4)	325 (30.2)
Asthma onset before 2 years of age	17 (1.3)	162 (27.7)	131 (1.3)	614 (12.4)	67 (2.3)	369 (20.6)	68 (0.8)	375 (34.8)
Bronchitis or Bronchiolitis ever	365 (27.4)	329 (56.2)	2791 (27.0)	2310 (46.8)	1036 (35.0)	1290 (72.0)	2725 (31.1)	709 (65.7)
Cough at night (when no cold) ever	309 (23.2)	399 (68.2)	2155 (20.8)	2085 (42.2)	1182 (39.9)	1459 (81.5)	2814 (32.1)	734 (68.0)
Sneezing or runny or blocked nose (when no cold) ever	408 (30.6)	498 (85.2)	2450 (23.7)	2250 (45.6)	1522 (51.4)	1591 (88.9)	2552 (29.2)	727 (67.4)

Sneezing or runny or blocked nose (when no cold) in the last 12 months	169 (12.7)	400 (68.5)	735 (7.1)	1170 (23.7)	1092 (36.9)	1300 (72.6)	641 (7.3)	367 (34.0)
Itchy watery eyes (when no cold) in the last 12 months	57 (4.3)	280 (47.9)	98 (0.9)	396 (8.0)	637 (21.5)	935 (52.2)	119 (1.4)	154 (14.3)
Allergic rhinitis ever	48 (3.6)	203 (34.7)	90 (0.9)	306 (6.2)	724 (24.5)	1151 (64.3)	213 (2.4)	237 (22.0)
Rhinitis onset before 2 years of age	44 (3.3)	77 (13.1)	327 (3.2)	428 (8.7)	38 (1.3)	179 (10.0)	37 (0.4)	91 (8.4)
Itchy rash (coming and going for at least six months) ever	580 (43.5)	498 (85.1)	936 (9.0)	4276 (86.6)	1613 (54.4)	1484 (82.9)	3169 (36.2)	655 (60.7)
Itchy rash (coming and going for at least six months) in the last 12 months	337 (25.3)	330 (56.5)	162 (1.6)	2524 (51.1)	462 (15.6)	488 (27.3)	902 (10.3)	274 (25.4)
Itchy rash affecting common areas	392 (29.4)	378 (64.6)	735 (7.1)	3316 (67.1)	350 (11.8)	427 (23.8)	657 (7.5)	223 (20.7)
Itchy rash onset before 2 years of age	321 (24.1)	312 (53.3)	512 (4.9)	2590 (52.4)	825 (27.8)	1055 (58.9)	1252 (14.3)	346 (32.0)
Eczema ever	475 (35.6)	452 (77.3)	896 (8.7)	2791 (56.5)	1158 (39.1)	1374 (76.8)	2004 (22.9)	513 (47.6)
Urticaria ever	308 (23.1)	218 (37.2)	1559 (15.1)	1319 (26.7)	552 (18.6)	773 (43.2)	1342 (15.3)	377 (34.9)
Food allergy ever	233 (17.5)	299 (51.1)	415 (4.0)	903 (18.3)	666 (22.5)	1024 (57.2)	744 (8.5)	266 (24.7)
Weight (kg), m (SD)	17.2 (2.7)	17.0 (2.7)	17.1 (2.6)	16.9 (2.9)	32.5 (7.9)	33.6 (9.2)	32.0 (7.3)	32.7 (8.1)
Height (cm), m (SD)	104.0 (6.0)	103.7 (5.8)	104.1 (5.8)	103.3 (6.3)	138.2 (9.3)	139.9 (11.2)	137.5 (8.8)	137.4 (9.6)

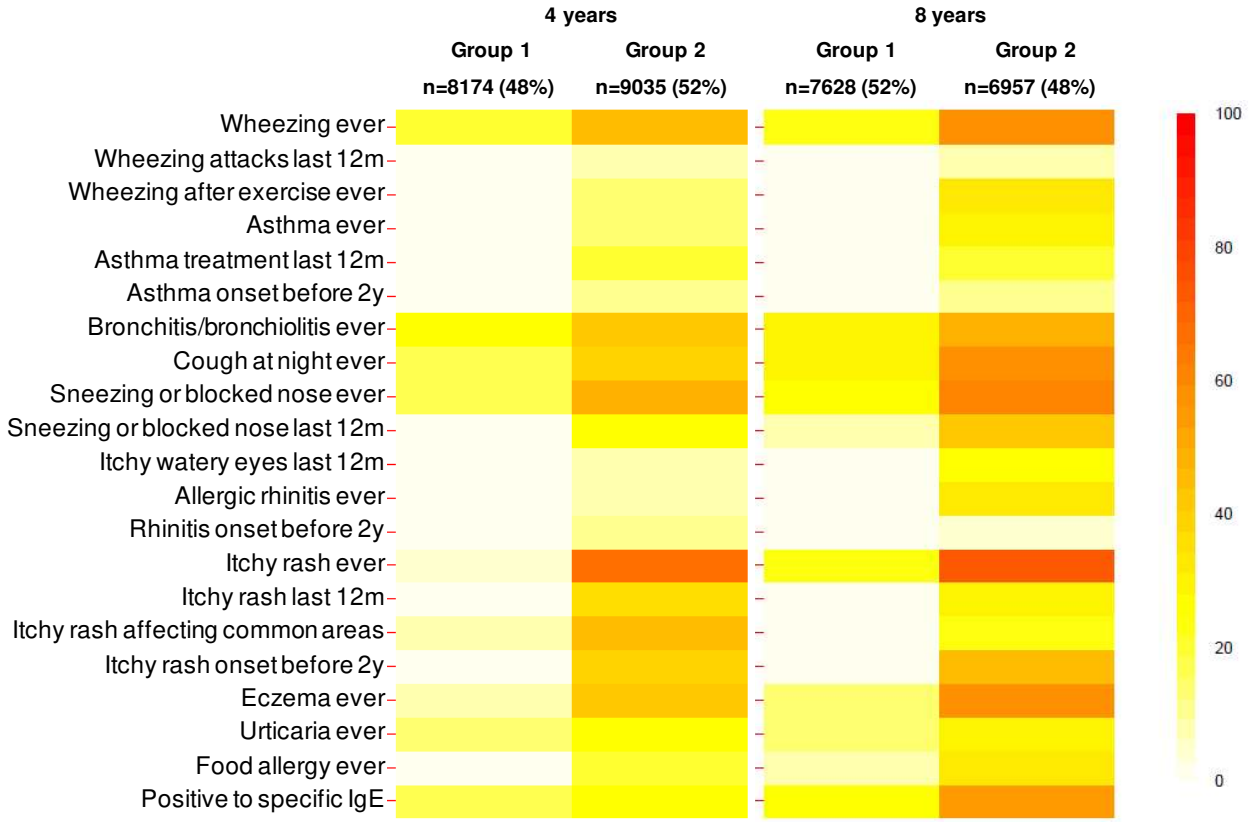
SENSITIVITY ANALYSIS I—alternative clustering methods

Figure E7. Distribution of Calinsky-Harabasz and Average silhouette width stopping rules*, and graphical description† of the two groups identified by hierarchical analysis at 4 and 8 years





* Higher values indicate higher separation between groups and similarity within groups.



† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

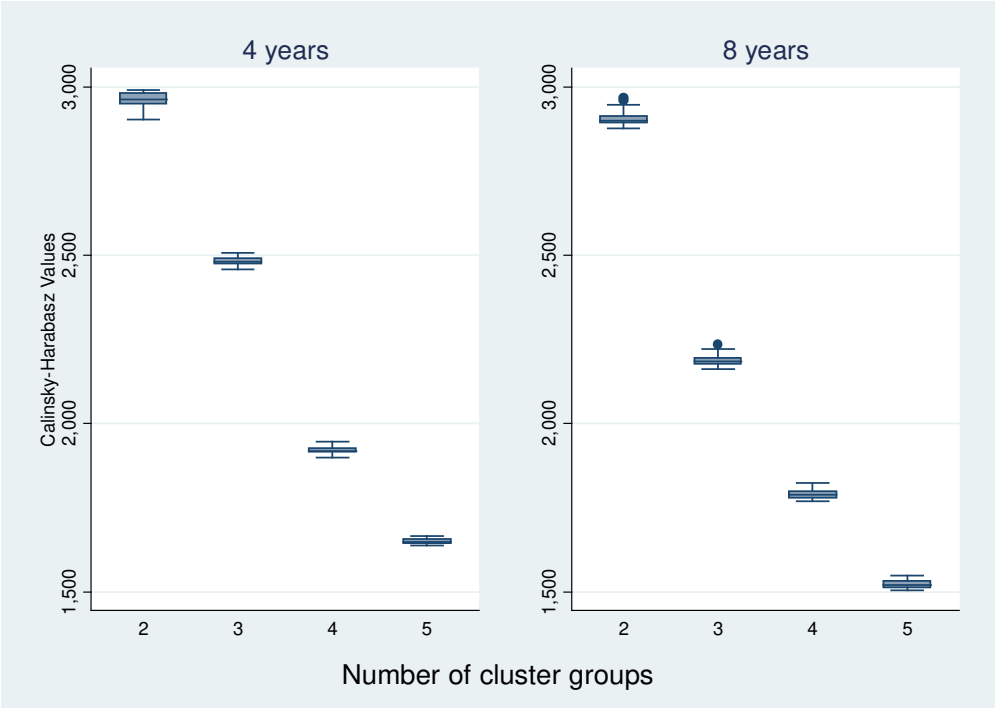
Table E9. Description of the two groups identified by cluster analysis at 4 and 8 years, using hierarchical analysis as the clustering method

	4 years				8 years			
	All	**Group 1**	**Group 2**		**All**	**Group 1**	**Group 2**	
	N = 17209	**8174 (47.5)**	**9035 (52.5)**	**F***	**N = 14585**	**7628 (52.3)**	**6957 (47.7)**	**F***
	n (%)	**n (%)**	**n (%)**		**n (%)**	**n (%)**	**n (%)**	
Wheezing ever	5641 (32.8)	1620 (19.8)	4021 (44.5)	1055.3	5767 (39.5)	1732 (22.7)	4035 (58.0)	1470.8
Wheezing attacks in the last 12 months								
None	15309 (89.0)	7972 (97.5)	7337 (81.2)	197.2	13112 (89.9)	7517 (98.6)	5594 (80.4)	149.7
1 - 3 times	1289 (7.5)	182 (2.2)	1107 (12.3)		1005 (6.9)	98 (1.3)	907 (13.0)	
4 - 12 times	482 (2.8)	18 (0.2)	464 (5.1)		358 (2.5)	9 (0.1)	349 (5.0)	
> 12 times	129 (0.8)	2 (0.0)	127 (1.4)		110 (0.8)	4 (0.0)	107 (1.5)	
Wheezing after exercise ever	1346 (7.8)	24 (0.3)	1322 (14.6)	199.4	2345 (16.1)	103 (1.3)	2243 (32.2)	518.5
Asthma ever	1410 (8.2)	20 (0.2)	1390 (15.4)	97.8	2243 (15.4)	82 (1.1)	2161 (31.1)	520.7
Asthma treatment in the last 12 months	1936 (11.3)	28 (0.3)	1908 (21.1)	221.2	1371 (9.4)	39 (0.5)	1332 (19.2)	286.7
Asthma onset before 2 years of age	924 (5.4)	11 (0.1)	913 (10.1)	96.3	879 (6.0)	37 (0.5)	842 (12.1)	184.6
Bronchitis or Bronchiolitis ever	5794 (33.7)	2080 (25.4)	3714 (41.1)	422.8	5760 (39.5)	2284 (29.9)	3476 (50.0)	518.8
Cough at night (when no cold) ever	4948 (28.8)	1399 (17.1)	3549 (39.3)	876.8	6189 (42.4)	2193 (28.7)	3996 (57.4)	992.8
Sneezing or runny or blocked nose (when no cold) ever	5607 (32.6)	1326 (16.2)	4281 (47.4)	1610.5	6392 (43.8)	2067 (27.1)	4325 (62.2)	1500.9
Sneezing or runny or blocked nose (when no cold) in the last 12 months	2474 (14.4)	23 (0.3)	2450 (27.1)	309.3	3400 (23.3)	499 (6.5)	2901 (41.7)	1300.9
Itchy watery eyes (when no cold) in the last 12 months	831 (4.8)	5 (0.1)	826 (9.1)	37.9	1845 (12.7)	47 (0.6)	1798 (25.8)	322.7

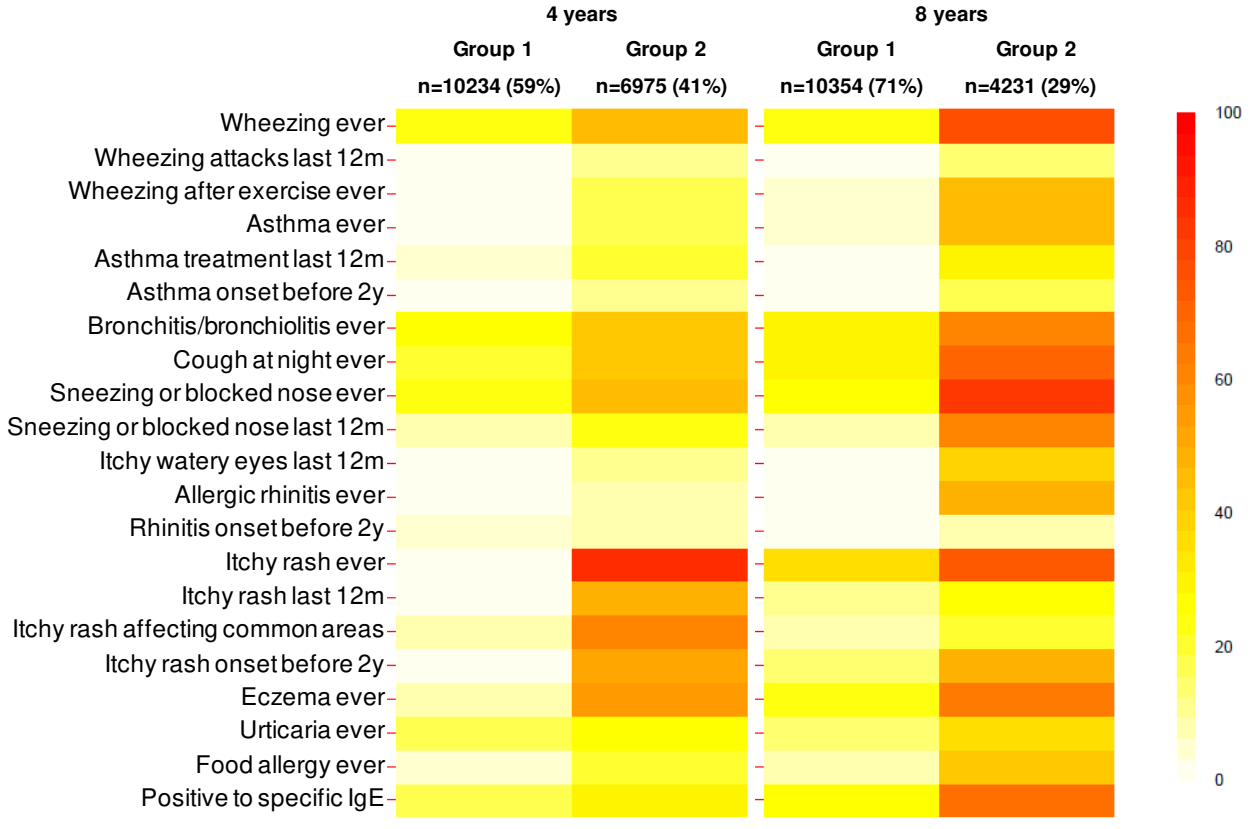
Allergic rhinitis ever	648 (3.8)	9 (0.1)	639 (7.1)	62.2	2326 (15.9)	93 (1.2)	2232 (32.1)	537.0
Rhinitis onset before 2 years of age	876 (5.1)	11 (0.1)	865 (9.6)	109.5	345 (2.4)	14 (0.2)	331 (4.8)	62.0
Itchy rash (coming and going for at least six months) ever	6290 (36.6)	335 (4.1)	5956 (65.9)	3425.0	6921 (47.5)	1726 (22.6)	5195 (74.7)	2958.8
Itchy rash (coming and going for at least six months) in the last 12 months	3353 (19.5)	10 (0.1)	3344 (37.0)	190.7	2126 (14.6)	39 (0.5)	2087 (30.0)	345.1
Itchy rash affecting common areas	4820 (28.0)	685 (8.4)	4135 (45.8)	2156.3	1657 (11.4)	28 (0.4)	1629 (23.4)	229.4
Itchy rash onset before 2 years of age	3734 (21.7)	64 (0.8)	3670 (40.6)	861.9	3477 (23.8)	216 (2.8)	3261 (46.9)	1571.8
Eczema ever	4614 (26.8)	741 (9.1)	3874 (42.9)	1875.9	5049 (34.6)	1095 (14.3)	3955 (56.8)	2244.8
Urticaria ever	3403 (19.8)	1046 (12.8)	2357 (26.1)	312.7	3043 (20.9)	996 (13.1)	2047 (29.4)	435.6
Food allergy ever	1850 (10.7)	34 (0.4)	1816 (20.1)	317.5	2699 (18.5)	516 (6.8)	2183 (31.4)	1066.8
IgE sensitisation	3611 (21.0)	1279 (15.6)	2332 (25.8)	201.6	5680 (38.9)	1944 (25.5)	3735 (53.7)	738.3
Weight (kg)· m (SD)	17.0 (2.7)	17.1 (2.6)	17.0 (2.8)	6.3	32.3 (7.7)	32.2 (7.4)	32.4 (8.3)	2.1
Height (cm)· m (SD)	103.8 (6.0)	104.2 (5.9)	103.5 (6.2)	47.3	137.9 (9.4)	137.9 (8.6)	138.0 (10.5)	1.0

* F values correspond to the ratio of the variance of the group means (between-group variance) over the overall variance of the variable (higher values meaning higher relevance of the variable for separating cluster groups), and were obtained by means of linear regression models using each variable as the outcome, and the cluster group as the exposure.

Figure E8. Distribution of Calinsky-Harabasz stopping rule*, and graphical description† of the two groups identified by latent class analysis at 4 and 8 years



* Higher values indicate higher separation between groups and similarity within groups.



† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

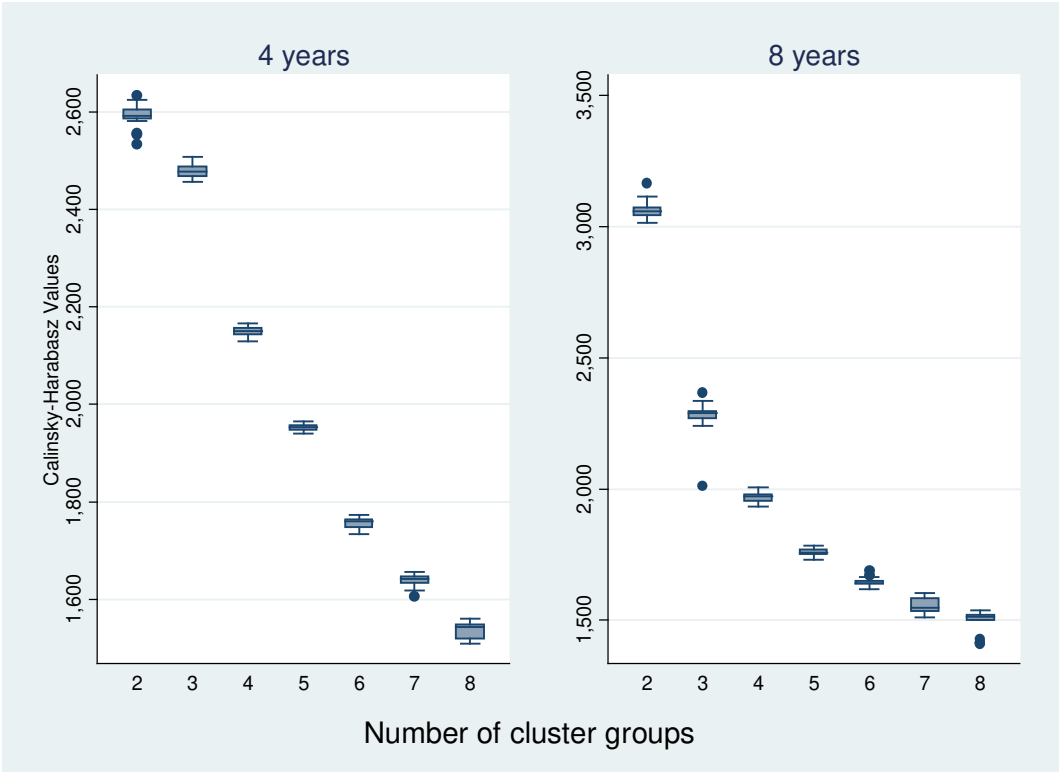
328 **Table E10. Description of the two groups identified by cluster analysis at 4 and 8 years, using latent class analysis as the clustering method**
329

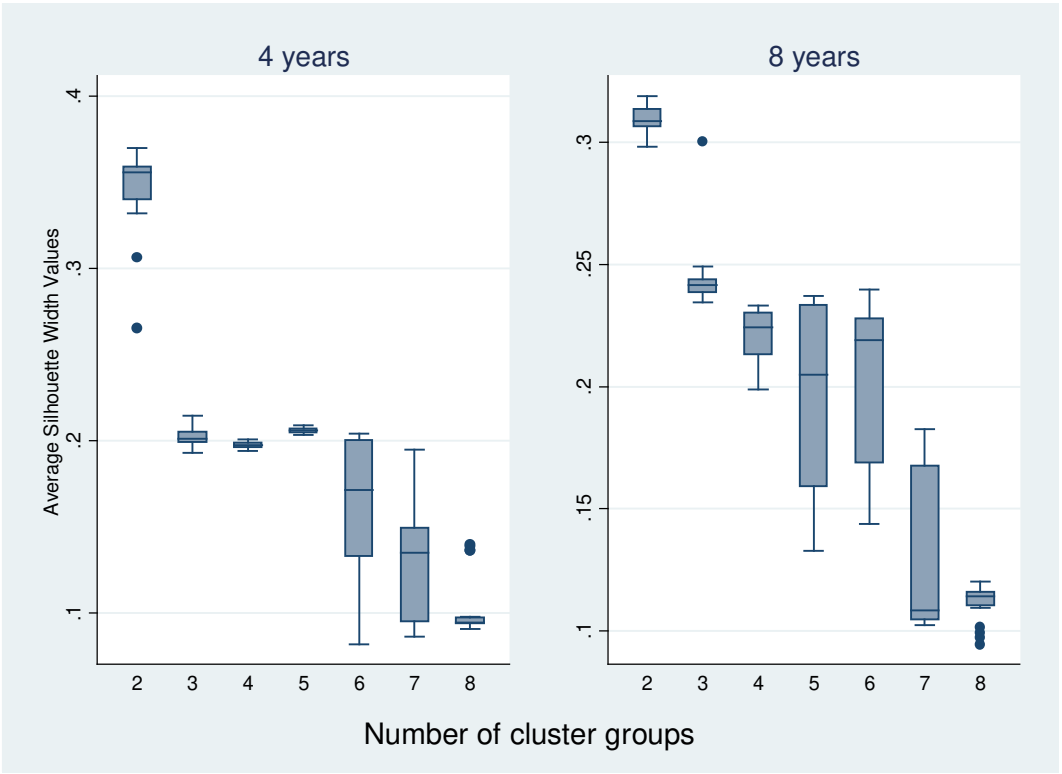
	4 years				8 years			
	All	**Group 1**	**Group 2**		**All**	**Group 1**	**Group 2**	
	N = 17209	**10234 (59.5)**	**6975 (40.5)**	**F***	**N = 14585**	**10354 (71.0)**	**4231 (29.0)**	**F***
	n (%)	**n (%)**	**n (%)**		**n (%)**	**n (%)**	**n (%)**	
Wheezing ever	5641 (32.8)	2428 (23.7)	3213 (46.1)	847.5	5767 (39.5)	2586 (25.0)	3182 (75.2)	2153.2
Wheezing attacks in the last 12 months								
None	15309 (89.0)	9781 (95.6)	5527 (79.2)		13112 (89.9)	10177 (98.3)	2934 (69.4)	
1 - 3 times	1289 (7.5)	407 (4.0)	882 (12.6)	234.6	1005 (6.9)	148 (1.4)	857 (20.3)	289.1
4 - 12 times	482 (2.8)	38 (0.4)	444 (6.4)		358 (2.5)	18 (0.2)	339 (8.0)	
> 12 times	129 (0.8)	8 (0.1)	122 (1.7)		110 (0.8)	10 (0.1)	100 (2.4)	
Wheezing after exercise ever	1346 (7.8)	237 (2.3)	1109 (15.9)	686.2	2345 (16.1)	438 (4.2)	1908 (45.1)	1619.1
Asthma ever	1410 (8.2)	238 (2.3)	1172 (16.8)	643.5	2243 (15.4)	377 (3.6)	1866 (44.1)	1862.3
Asthma treatment in the last 12 months	1936 (11.3)	602 (5.9)	1334 (19.1)	571.8	1371 (9.4)	164 (1.6)	1207 (28.5)	1034.6
Asthma onset before 2 years of age	924 (5.4)	138 (1.3)	786 (11.3)	458.1	879 (6.0)	160 (1.5)	719 (17.0)	543.9
Bronchitis or Bronchiolitis ever	5794 (33.7)	2858 (27.9)	2936 (42.1)	308.8	5760 (39.5)	3190 (30.8)	2570 (60.7)	933.4
Cough at night (when no cold) ever	4948 (28.8)	2074 (20.3)	2874 (41.2)	794.5	6189 (42.4)	3193 (30.8)	2996 (70.8)	1516.2
Sneezing or runny or blocked nose (when no cold) ever	5607 (32.6)	2510 (24.5)	3097 (44.4)	678.9	6392 (43.8)	2906 (28.1)	3486 (82.4)	2103.1
Sneezing or runny or blocked nose (when no cold) in the last 12 months	2474 (14.4)	750 (7.3)	1723 (24.7)	868.3	3400 (23.3)	785 (7.6)	2615 (61.8)	2354.0
Itchy watery eyes (when no cold) in the last 12 months	831 (4.8)	109 (1.1)	722 (10.4)	474.9	1845 (12.7)	149 (1.4)	1696 (40.1)	1022.1

Allergic rhinitis ever	648 (3.8)	97 (1.0)	551 (7.9)	296.4	2326 (15.9)	311 (3.0)	2015 (47.6)	1489.0
Rhinitis onset before 2 years of age	876 (5.1)	349 (3.4)	526 (7.5)	123.5	345 (2.4)	43 (0.4)	302 (7.1)	207.2
Itchy rash (coming and going for at least six months) ever	6290 (36.6)	252 (2.5)	6038 (86.6)	4373.7	6921 (47.5)	3755 (36.3)	3166 (74.8)	1311.6
Itchy rash (coming and going for at least six months) in the last 12 months	3353 (19.5)	33 (0.3)	3320 (47.6)	862.0	2126 (14.6)	1034 (10.0)	1092 (25.8)	455.9
Itchy rash affecting common areas	4820 (28.0)	664 (6.5)	4156 (59.6)	3643.0	1657 (11.4)	738 (7.1)	919 (21.7)	468.1
Itchy rash onset before 2 years of age	3734 (21.7)	121 (1.2)	3613 (51.8)	1264.4	3477 (23.8)	1413 (13.6)	2064 (48.8)	1492.9
Eczema ever	4614 (26.8)	792 (7.7)	3823 (54.8)	3258.7	5049 (34.6)	2281 (22.0)	2769 (65.4)	1943.6
Urticaria ever	3403 (19.8)	1611 (15.7)	1792 (25.7)	166.3	3043 (20.9)	1506 (14.5)	1538 (36.3)	542.7
Food allergy ever	1850 (10.7)	430 (4.2)	1420 (20.4)	834.3	2699 (18.5)	900 (8.7)	1800 (42.5)	1548.0
IgE sensitisation	3611 (21.0)	1629 (15.9)	1982 (28.4)	243.7	5680 (38.9)	2861 (27.6)	2819 (66.6)	958.1
Weight (kg), m (SD)	17.0 (2.7)	17.1 (2.6)	17.0 (3.0)	3.0	32.3 (7.7)	32.0 (7.1)	33.1 (8.9)	59.1
Height (cm), m (SD)	103.8 (6.0)	104.0 (6.0)	103.6 (6.4)	14.1	137.9 (9.4)	137.5 (8.6)	139.1 (11.1)	77.4

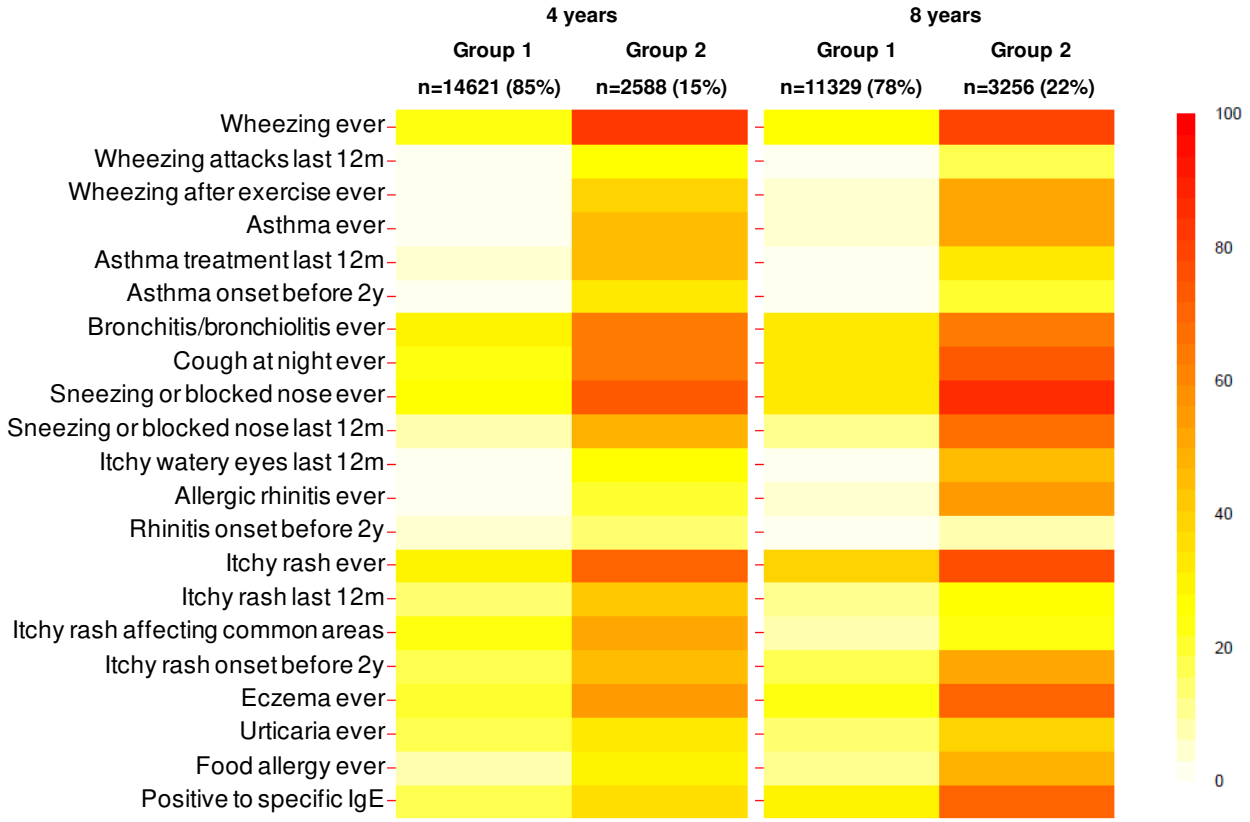
* F values correspond to the ratio of the variance of the group means (between-group variance) over the overall variance of the variable (higher values meaning higher relevance of the variable for separating cluster groups), and were obtained by means of linear regression models using each variable as the outcome, and the cluster group as the exposure.

Figure E9. Distribution of Calinsky-Harabasz and Average silhouette width stopping rules*, and graphical description† of the two groups identified by self-organising maps analysis at 4 and 8 years





* Higher values indicate higher separation between groups and similarity within groups.



† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

342 **Table E11. Description of the two groups identified by cluster analysis at 4 and 8 years, using self-organising maps as the clustering method**
343

	4 years				8 years			
	All	**Group 1**	**Group 2**		**All**	**Group 1**	**Group 2**	
	N = 17209	**14621 (85.0)**	**2588 (15.0)**	**F***	**N = 14585**	**11329 (77.7)**	**3256 (22.3)**	**F***
	n (%)	**n (%)**	**n (%)**		**n (%)**	**n (%)**	**n (%)**	
Wheezing ever	5641 (32.8)	3501 (23.9)	2141 (82.7)	1979.3	5767 (39.5)	3173 (28.0)	2595 (79.7)	1813.4
Wheezing attacks in the last 12 months								
None	15309 (89.0)	14026 (95.9)	1282 (49.5)		13112 (89.9)	11001 (97.1)	2111 (64.8)	
1 - 3 times	1289 (7.5)	532 (3.6)	757 (29.2)	612.6	1005 (6.9)	271 (2.4)	734 (22.6)	371.4
4 - 12 times	482 (2.8)	54 (0.4)	428 (16.5)		358 (2.5)	42 (0.4)	315 (9.7)	
> 12 times	129 (0.8)	8 (0.1)	121 (4.7)		110 (0.8)	15 (0.1)	96 (2.9)	
Wheezing after exercise ever	1346 (7.8)	322 (2.2)	1024 (39.6)	1886.2	2345 (16.1)	658 (5.8)	1688 (51.8)	1675.5
Asthma ever	1410 (8.2)	214 (1.5)	1196 (46.2)	1696.6	2243 (15.4)	576 (5.1)	1667 (51.2)	2116.8
Asthma treatment in the last 12 months	1936 (11.3)	738 (5.1)	1198 (46.3)	2111.9	1371 (9.4)	281 (2.5)	1090 (33.5)	1213.0
Asthma onset before 2 years of age	924 (5.4)	110 (0.8)	814 (31.5)	1067.6	879 (6.0)	247 (2.2)	632 (19.4)	622.1
Bronchitis or Bronchiolitis ever	5794 (33.7)	4130 (28.2)	1664 (64.3)	833.8	5760 (39.5)	3674 (32.4)	2086 (64.1)	872.9
Cough at night (when no cold) ever	4948 (28.8)	3316 (22.7)	1632 (63.1)	1304.3	6189 (42.4)	3778 (33.3)	2411 (74.1)	1249.9
Sneezing or runny or blocked nose (when no cold) ever	5607 (32.6)	3712 (25.4)	1895 (73.2)	1681.4	6392 (43.8)	3602 (31.8)	2790 (85.7)	1442.3
Sneezing or runny or blocked nose (when no cold) in the last 12 months	2474 (14.4)	1219 (8.3)	1255 (48.5)	1994.1	3400 (23.3)	1224 (10.8)	2176 (66.8)	1992.2
Itchy watery eyes (when no cold) in the last 12 months	831 (4.8)	152 (1.0)	679 (26.2)	1153.3	1845 (12.7)	346 (3.1)	1500 (46.1)	1431.2

Allergic rhinitis ever	648 (3.8)	142 (1.0)	506 (19.5)	853.8	2326 (15.9)	531 (4.7)	1795 (55.1)	1634.2
Rhinitis onset before 2 years of age	876 (5.1)	485 (3.3)	391 (15.1)	438.6	345 (2.4)	69 (0.6)	276 (8.5)	237.2
Itchy rash (coming and going for at least six months) ever	6290 (36.6)	4510 (30.8)	1780 (68.8)	1119.6	6921 (47.5)	4412 (38.9)	2509 (77.1)	1051.8
Itchy rash (coming and going for at least six months) in the last 12 months	3353 (19.5)	2260 (15.5)	1093 (42.3)	803.0	2126 (14.6)	1277 (11.3)	849 (26.1)	302.6
Itchy rash affecting common areas	4820 (28.0)	3446 (23.6)	1374 (53.1)	821.0	1657 (11.4)	931 (8.2)	726 (22.3)	344.0
Itchy rash onset before 2 years of age	3734 (21.7)	2582 (17.7)	1152 (44.5)	718.3	3477 (23.8)	1773 (15.6)	1704 (52.3)	1382.1
Eczema ever	4614 (26.8)	3160 (21.6)	1454 (56.2)	995.8	5049 (34.6)	2797 (24.7)	2252 (69.2)	1579.5
Urticaria ever	3403 (19.8)	2517 (17.2)	886 (34.2)	280.9	3043 (20.9)	1767 (15.6)	1277 (39.2)	572.1
Food allergy ever	1850 (10.7)	1080 (7.4)	770 (29.8)	852.1	2699 (18.5)	1147 (10.1)	1553 (47.7)	1518.8
IgE sensitisation	3611 (21.0)	2671 (18.3)	940 (36.3)	216.0	5680 (38.9)	3362 (29.7)	2318 (71.2)	951.0
Weight (kg), m (SD)	17.0 (2.7)	17.1 (2.6)	17.0 (3.1)	2.2	32.3 (7.7)	32.0 (7.3)	33.4 (9.0)	70.4
Height (cm), m (SD)	103.8 (6.0)	103.9 (6.0)	103.2 (6.7)	28.0	137.9 (9.4)	137.5 (8.8)	139.5 (11.1)	98.3

344 * F values correspond to the ratio of the variance of the group means (between-group variance) over the overall variance of the variable (higher values meaning higher relevance of the
345 variable for separating cluster groups), and were obtained by means of linear regression models using each variable as the outcome, and the cluster group as the exposure.

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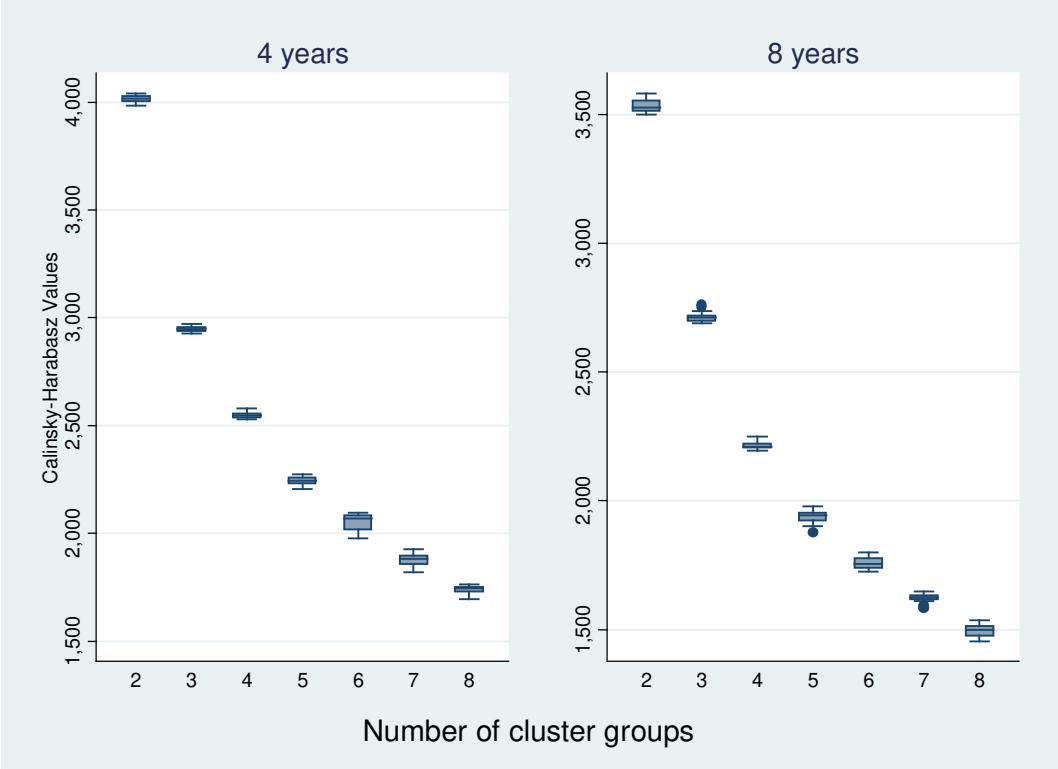
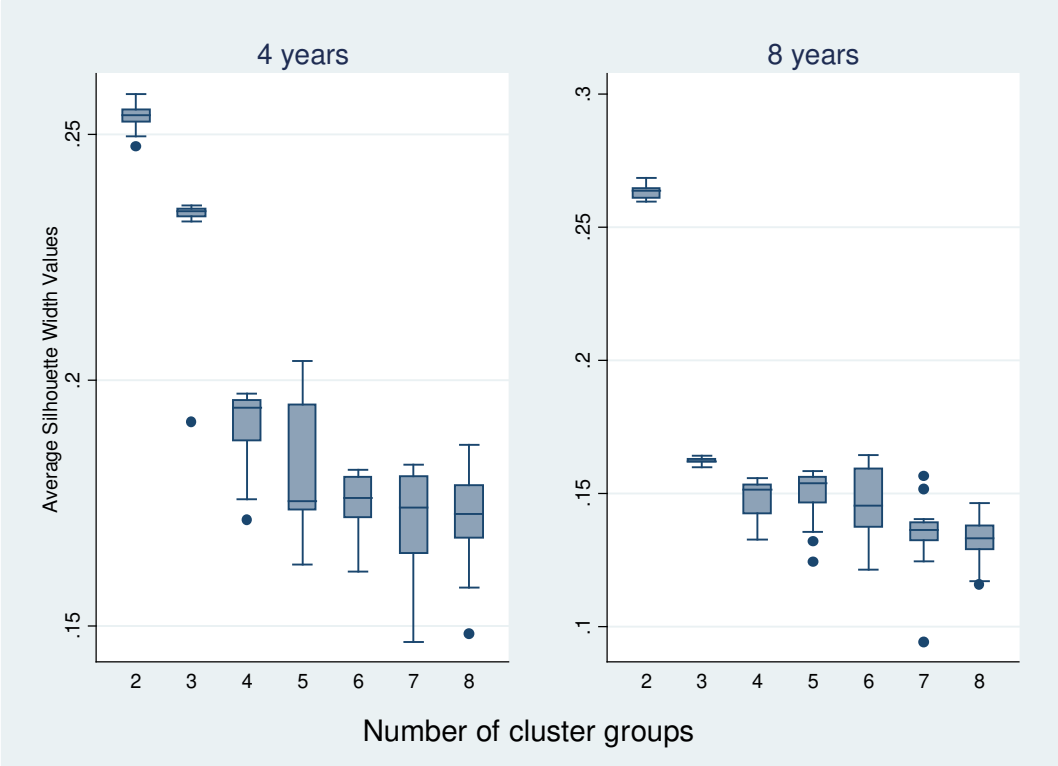
Figure E10. Distribution of average values over 20 imputed datasets of the Calinsky-Harabasz and Average silhouette width stopping rules* in several cluster strategies using variables scaled from 0 to 1, across 2 to 8 cluster groups at 4 and 8 years

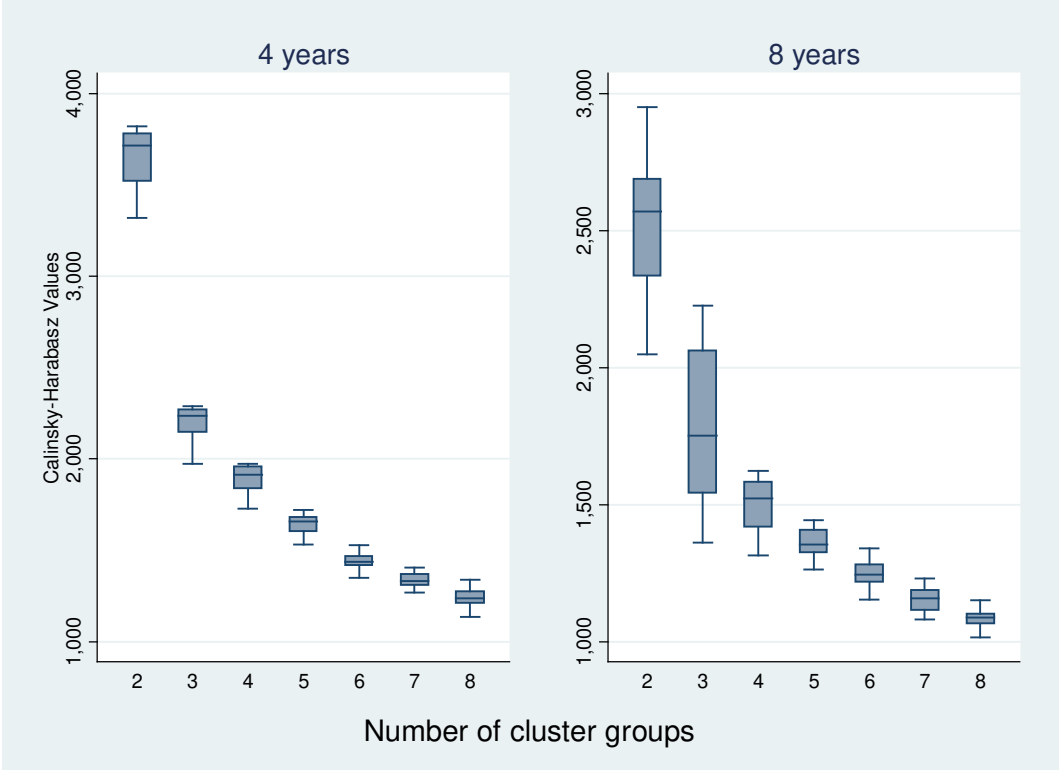
Cluster analysis with k–means

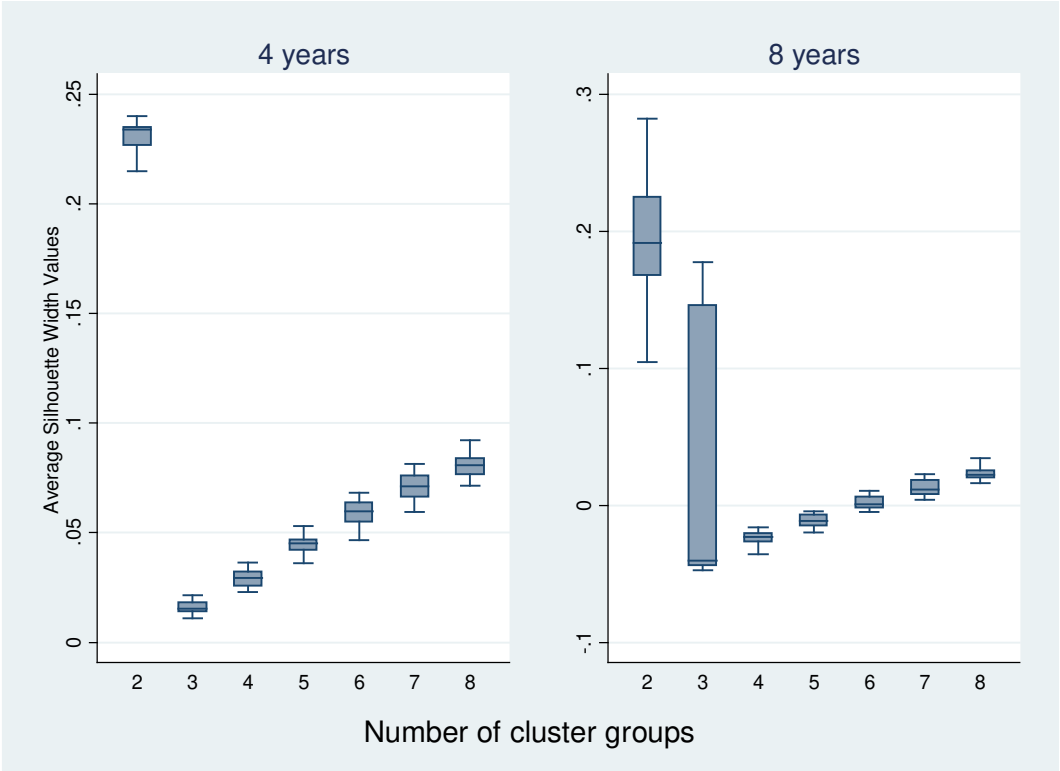




* Higher values indicate higher separation between groups and similarity within groups.

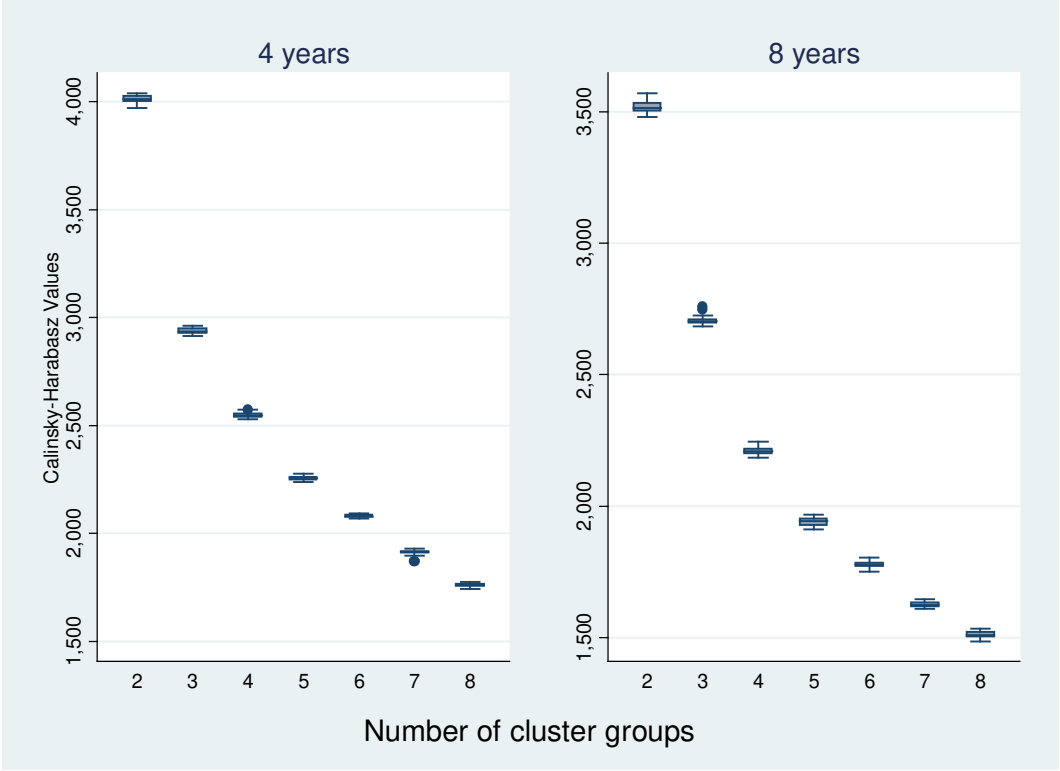
Hierarchical cluster analysis

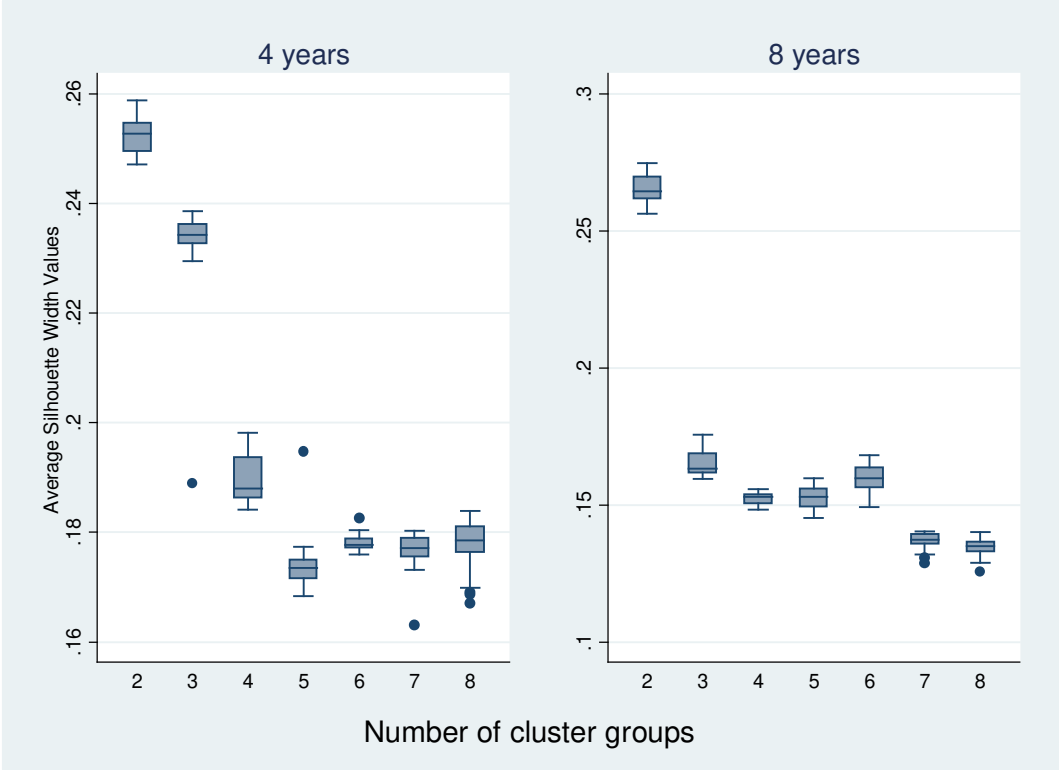




* Higher values indicate higher separation between groups and similarity within groups.

Self-organising maps



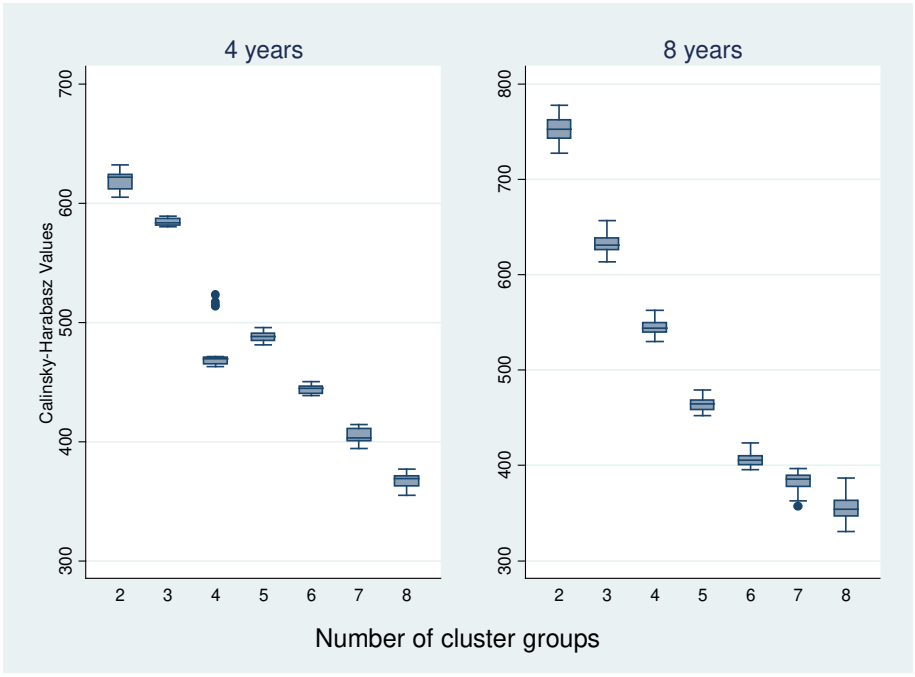


* Higher values indicate higher separation between groups and similarity within groups.

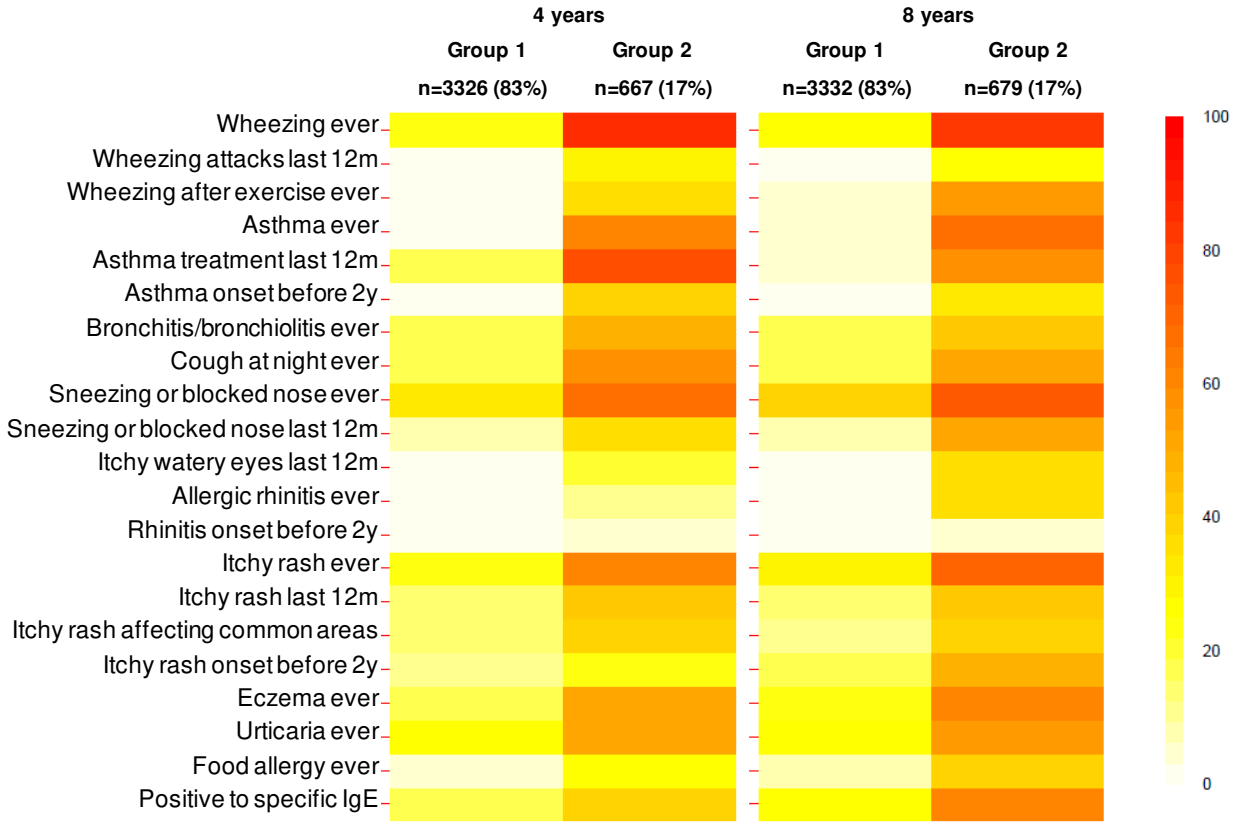
SENSITIVITY ANALYSIS II— deal with potential selection bias

Figure E11. Distribution of Calinsky-Harabasz stopping rule* and graphical description† of the two groups identified by cluster analysis at 4 and 8 years, after stratifying cluster analysis according to cohort

BAMSE

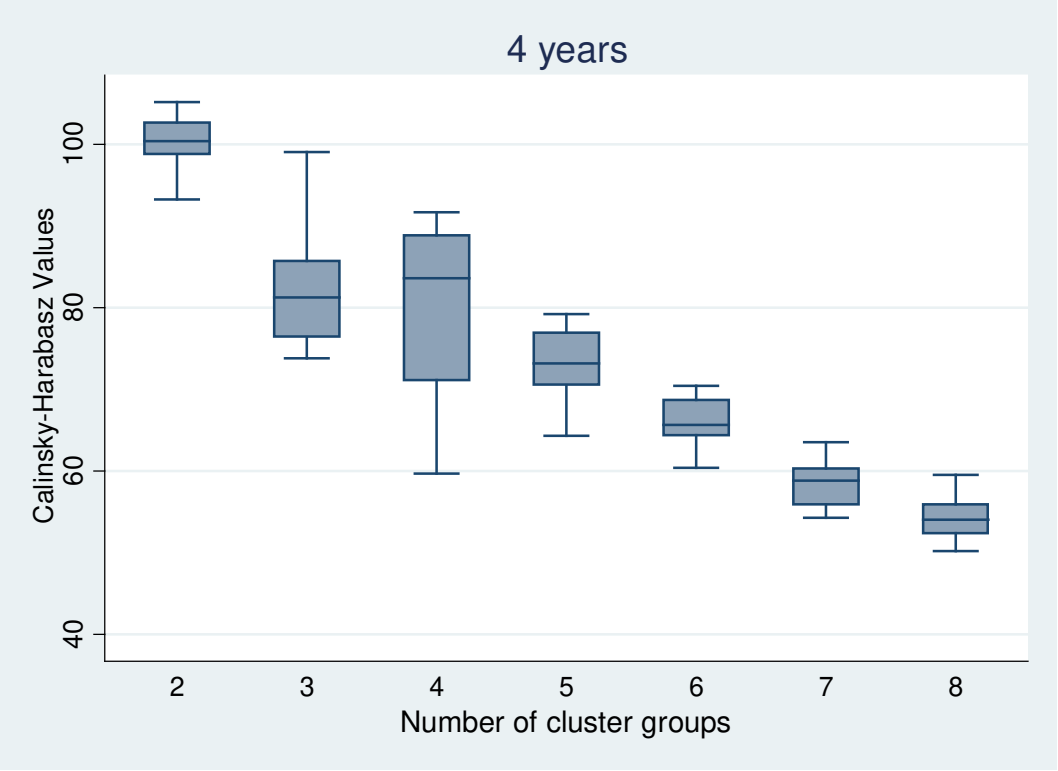


* Higher values indicate higher separation between groups and similarity within groups.

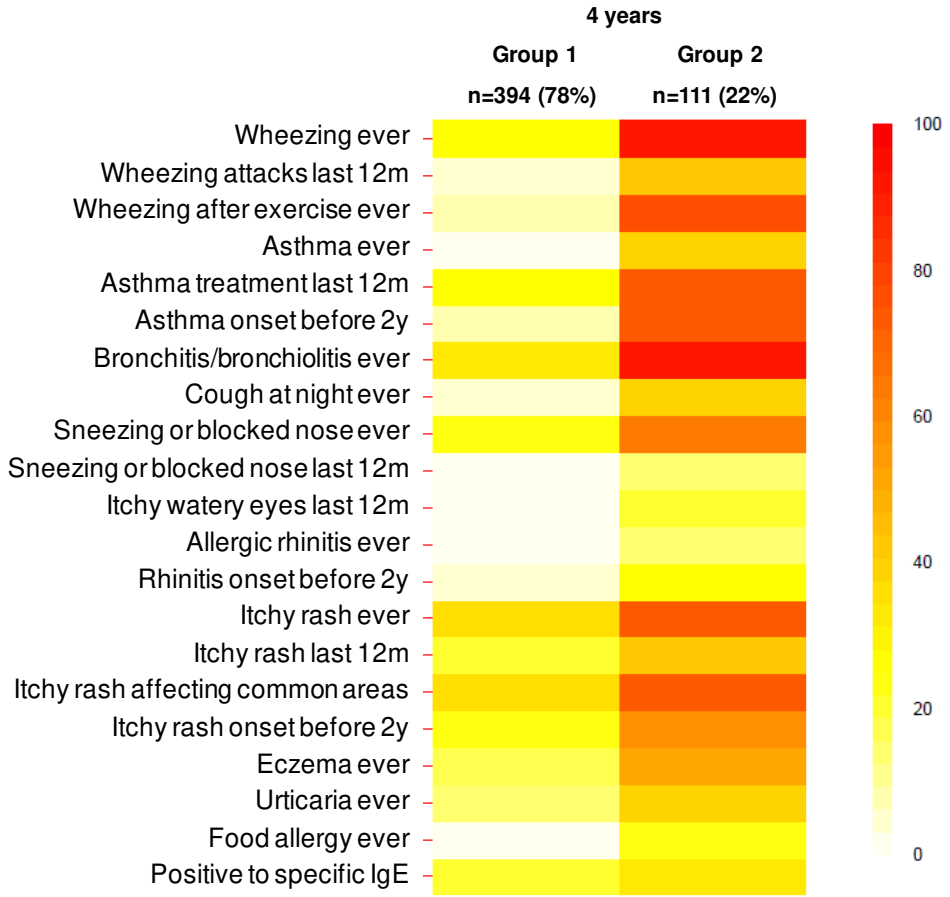


† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

DARC

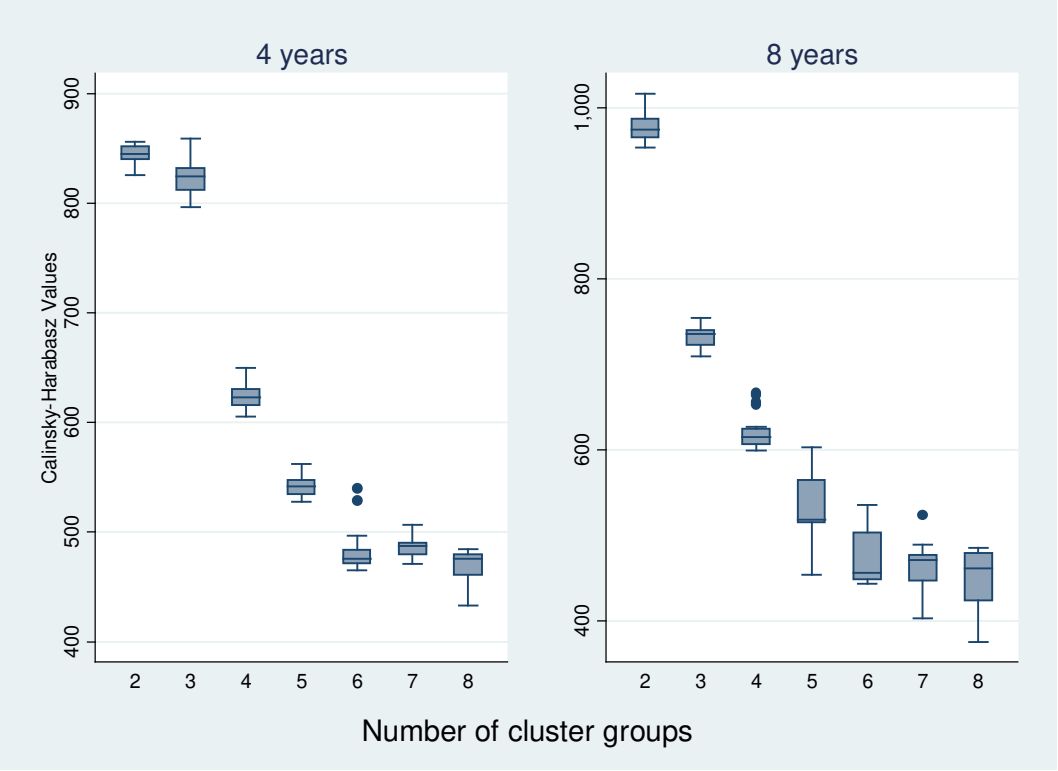


* Higher values indicate higher separation between groups and similarity within groups.

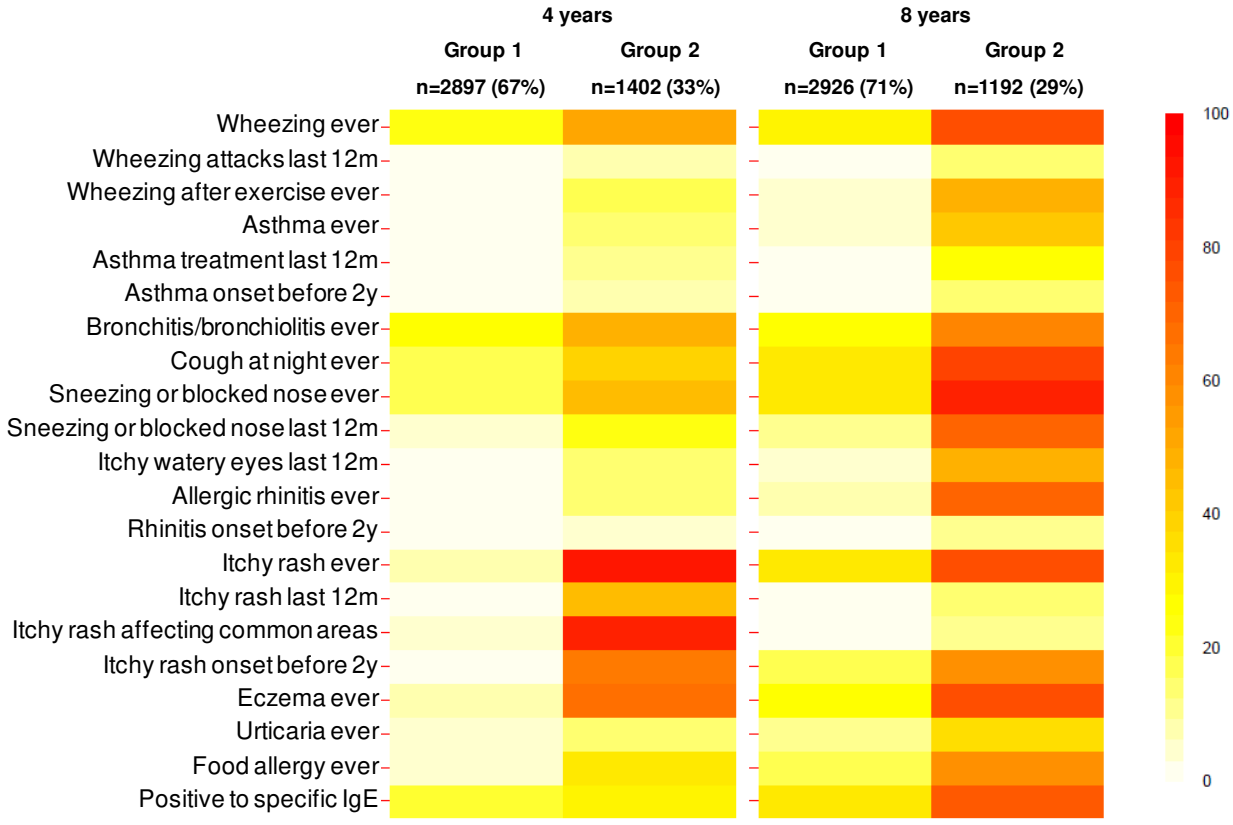


† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

GINIplus

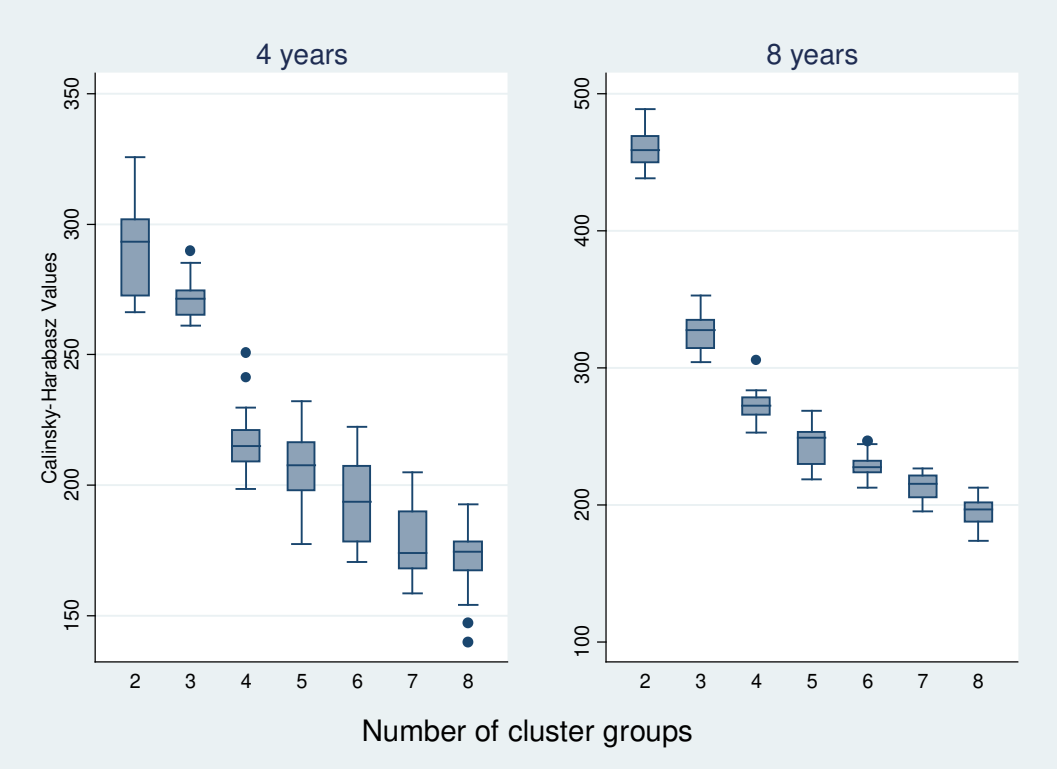


* Higher values indicate higher separation between groups and similarity within groups.

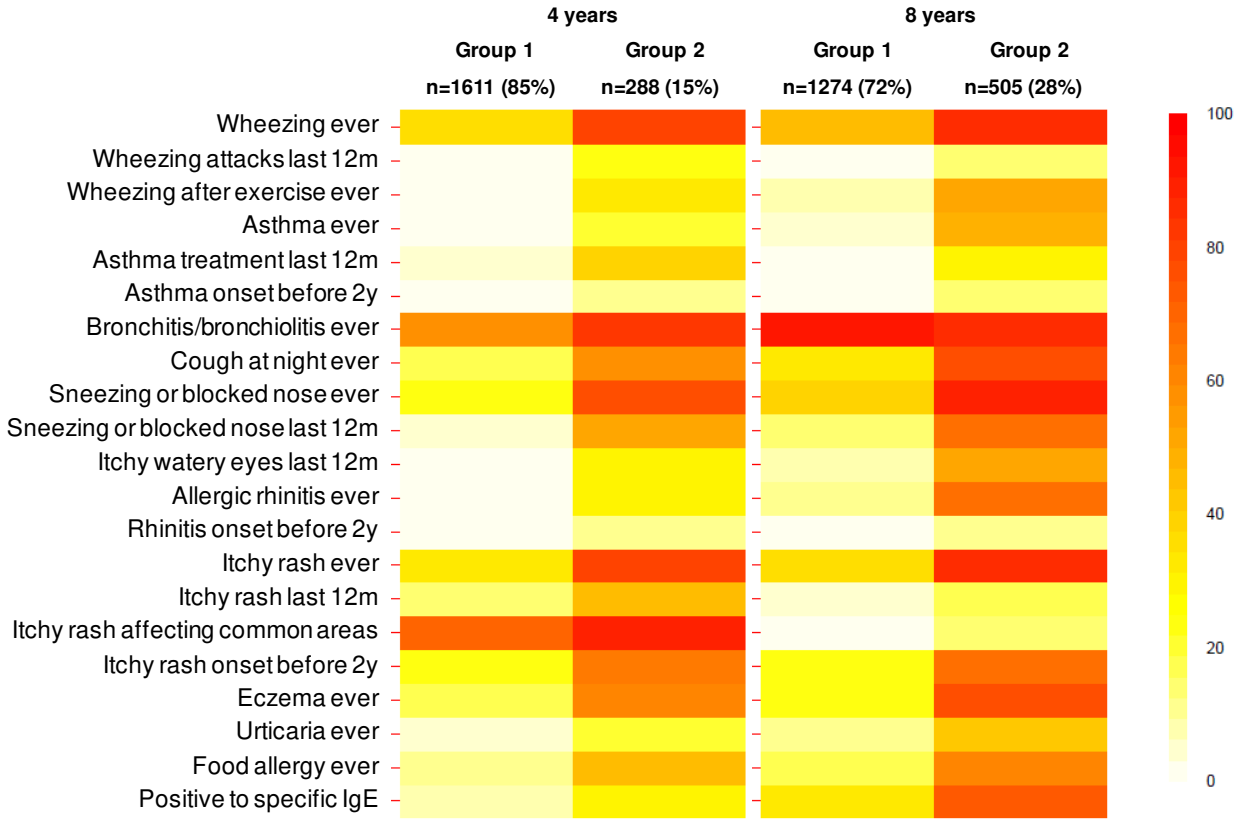


† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

LISAplus

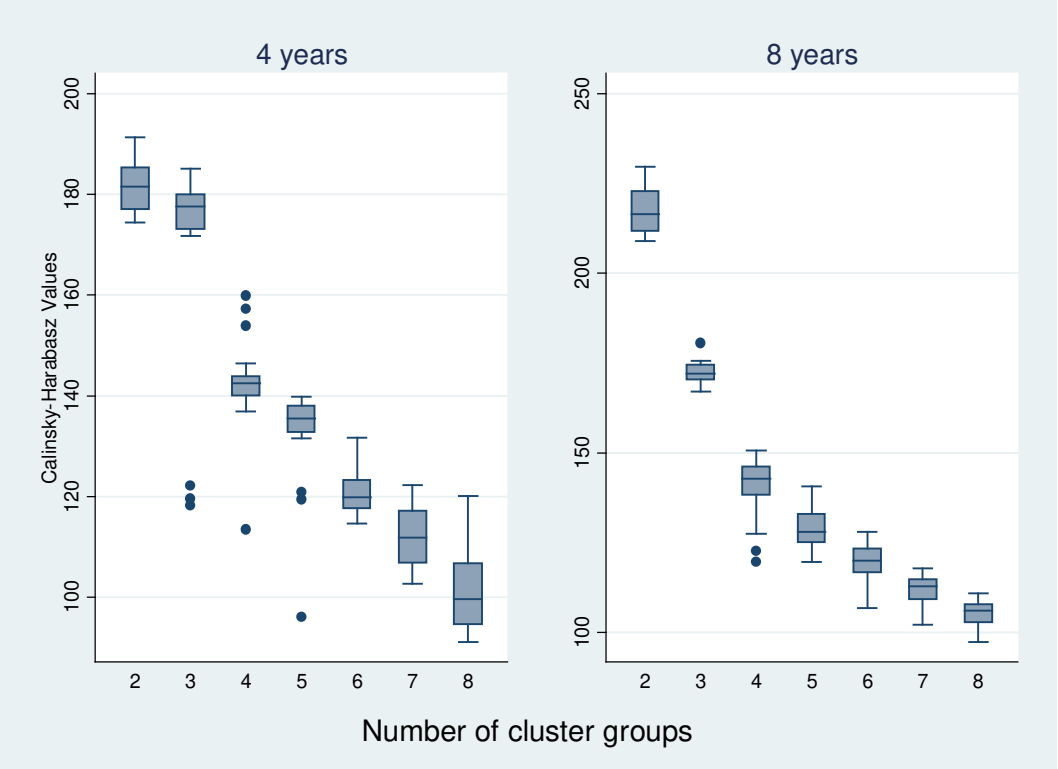


* Higher values indicate higher separation between groups and similarity within groups.

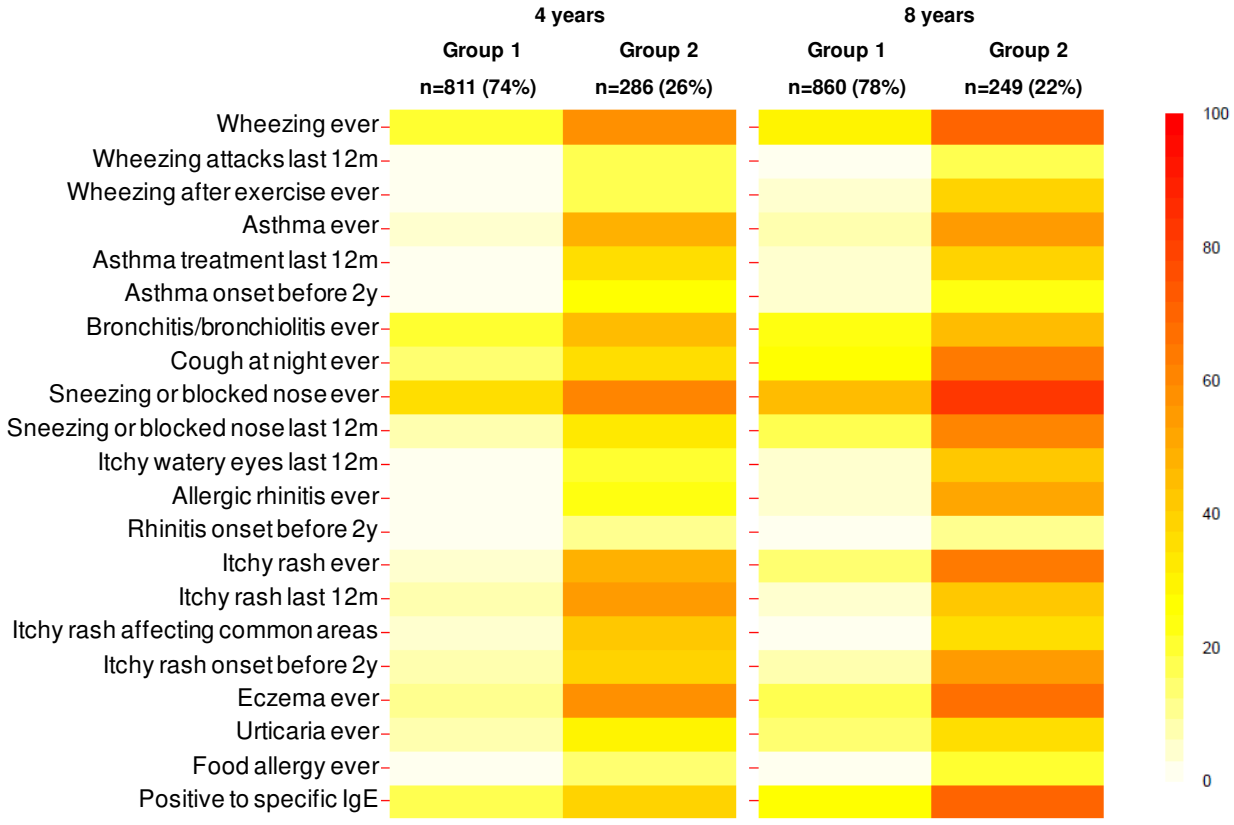


† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

MAS

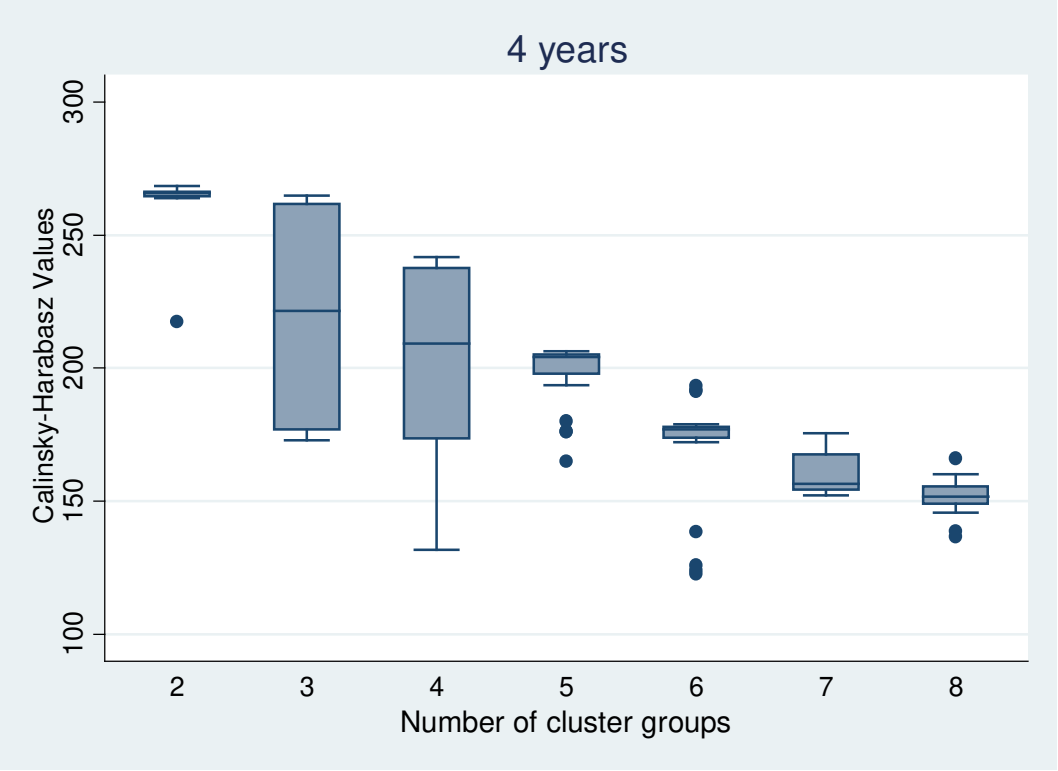


* Higher values indicate higher separation between groups and similarity within groups.

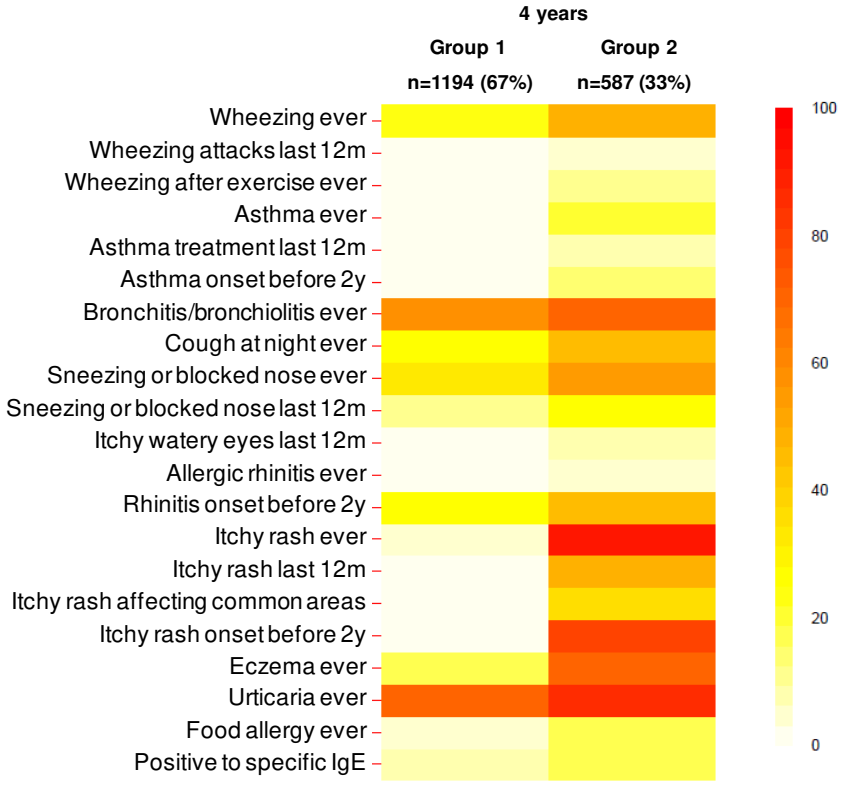


† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

PARIS

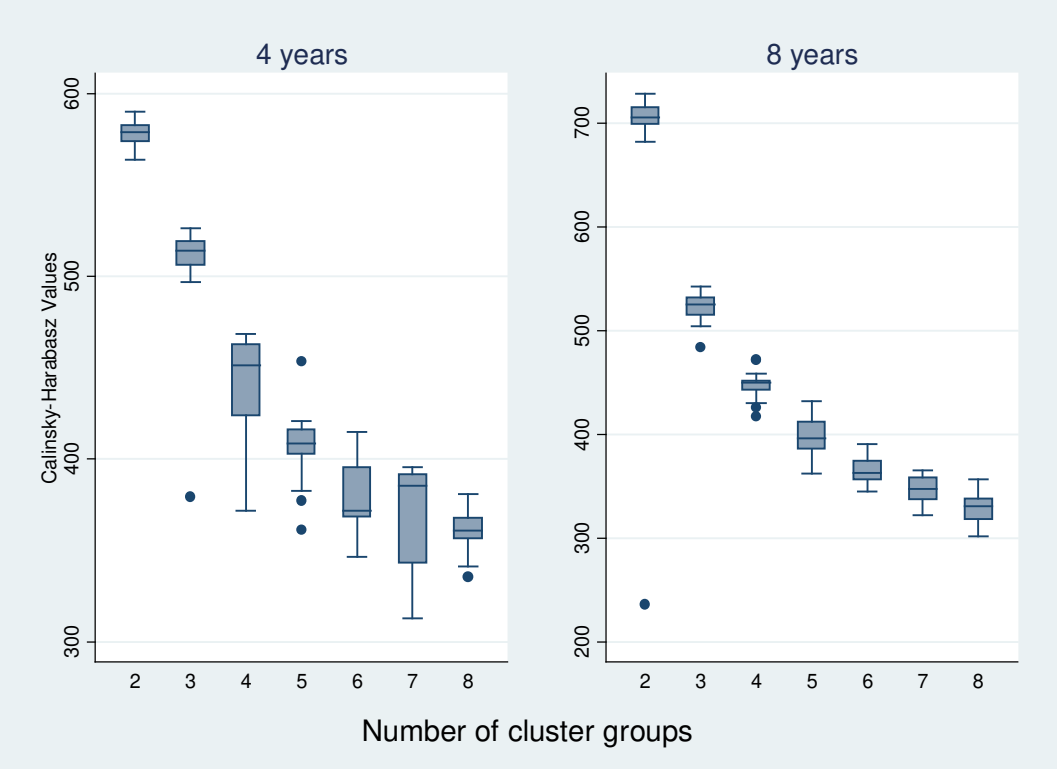


* Higher values indicate higher separation between groups and similarity within groups.

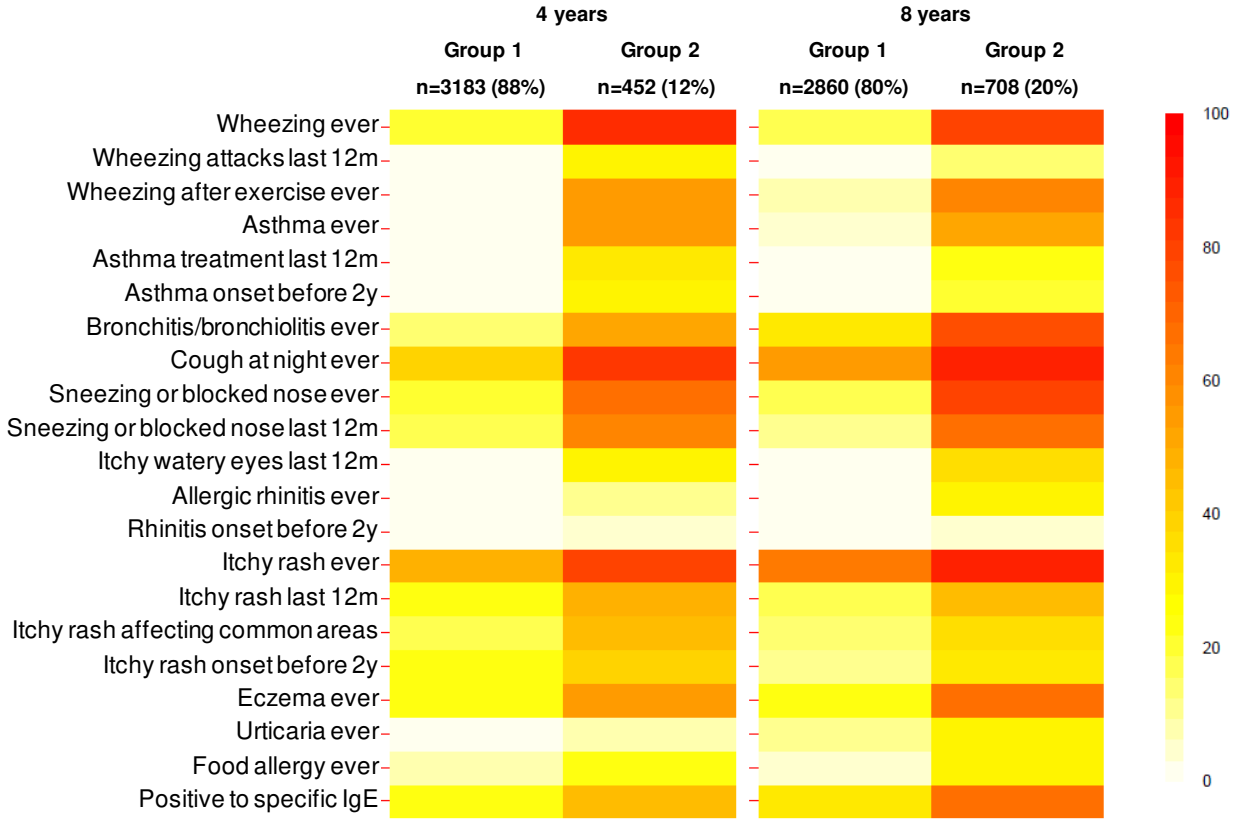


† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

PIAMA



* Higher values indicate higher separation between groups and similarity within groups.



† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

418 **Table E12. Description of the two groups identified by cluster analysis at 4 and 8 years after, after stratifying cluster analysis according to cohort**
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	4 years													
	BAMSE		**DARC**		**GINIplus**		**LISAplus**		**MAS**		**PARIS**		**PIAMA**	
	G1	**G2**	**G1**	**G2**	**G1**	**G2**	**G1**	**G2**	**G1**	**G2**	**G1**	**G2**	**G1**	**G2**
	N=3326 (83.3)	**N=667 (16.7)**	**N=394 (78.0)**	**N=111 (22.0)**	**N=2897 (67.4)**	**N=1402 (32.6)**	**N=1611 (84.8)**	**N=288 (15.2)**	**N=811 (73.9)**	**N=286 (26.1)**	**N=1194 (67.0)**	**N=587 (33.0)**	**N=3183 (87.6)**	**N=452 (12.4)**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Wheezing ever	735 (22.1)	569 (85.4)	105 (26.6)	102 (91.8)	718 (24.8)	701 (50.0)	577 (35.8)	229 (79.4)	152 (18.8)	169 (59.2)	285 (23.9)	283 (48.2)	626 (19.7)	390 (86.4)
Wheezing attacks in the last 12 months														
None	3113 (93.6)	266 (39.9)	351 (89.2)	30 (27.0)	2877 (99.3)	1213 (86.5)	1499 (93.0)	152 (52.9)	782 (96.4)	186 (65.0)	1150 (96.3)	495 (84.3)	3027 (95.1)	166 (36.7)
1 - 3 times	192 (5.8)	223 (33.4)	31 (7.8)	37 (33.6)	13 (0.4)	95 (6.8)	101 (6.3)	81 (28.1)	26 (3.2)	53 (18.5)	43 (3.6)	75 (12.8)	142 (4.5)	177 (39.2)
4 - 12 times	18 (0.5)	138 (20.7)	6 (1.4)	25 (22.5)	6 (0.2)	76 (5.4)	11 (0.7)	49 (17.0)	3 (0.4)	34 (11.9)	1 (0.1)	17 (2.9)	14 (0.4)	85 (18.8)
> 12 times	3 (0.1)	40 (6.0)	6 (1.6)	19 (17.0)	0 (0)	18 (1.3)	0 (0)	6 (2.0)	0 (0)	13 (4.5)	0 (0)	0 (0)	1 (0)	23 (5.1)
Wheezing after exercise ever	54 (1.6)	235 (35.2)	36 (9.1)	85 (76.4)	87 (3.0)	257 (18.3)	44 (2.7)	97 (33.7)	4 (0.5)	49 (17.0)	20 (1.7)	58 (9.9)	75 (2.4)	247 (54.6)
Asthma ever	72 (2.2)	400 (60.0)	4 (1.0)	44 (39.2)	38 (1.3)	180 (12.9)	5 (0.3)	62 (21.5)	27 (3.4)	136 (47.6)	35 (2.9)	124 (21.1)	38 (1.2)	244 (54.0)
Asthma treatment in the last 12 months	526 (15.8)	503 (75.4)	106 (26.9)	82 (74.1)	17 (0.6)	172 (12.3)	71 (4.4)	117 (40.5)	19 (2.4)	104 (36.3)	3 (0.3)	55 (9.4)	9 (0.3)	152 (33.6)

Asthma onset before 2 years of age	28 (0.8)	256 (38.3)	33 (8.3)	82 (73.6)	28 (1.0)	121 (8.6)	4 (0.2)	34 (11.7)	14 (1.8)	79 (27.6)	19 (1.6)	86 (14.7)	7 (0.2)	135 (29.8)
Bronchitis or Bronchiolitis ever	566 (17.0)	316 (47.4)	126 (32.0)	102 (91.9)	744 (25.7)	669 (47.7)	947 (58.8)	238 (82.7)	176 (21.6)	128 (44.8)	684 (57.3)	414 (70.5)	448 (14.1)	237 (52.3)
Cough at night (when no cold) ever	543 (16.3)	383 (57.4)	16 (4.0)	44 (39.7)	541 (18.7)	561 (40.0)	289 (17.9)	166 (57.7)	125 (15.5)	106 (37.2)	304 (25.5)	257 (43.8)	1241 (39.0)	372 (82.3)
Sneezing or runny or blocked nose (when no cold) ever	1133 (34.1)	457 (68.6)	97 (24.7)	70 (62.7)	504 (17.4)	631 (45.0)	398 (24.7)	219 (76.0)	288 (35.5)	171 (59.7)	379 (31.7)	316 (53.8)	639 (20.1)	305 (67.5)
Sneezing or runny or blocked nose (when no cold) in the last 12 months	254 (7.6)	235 (35.3)	4 (0.9)	14 (12.5)	154 (5.3)	346 (24.7)	77 (4.8)	152 (52.6)	57 (7.0)	92 (32.1)	142 (11.9)	156 (26.6)	511 (16.1)	280 (61.9)
Itchy watery eyes (when no cold) in the last 12 months	37 (1.1)	130 (19.4)	9 (2.3)	21 (19.1)	46 (1.6)	179 (12.8)	13 (0.8)	83 (28.9)	9 (1.1)	56 (19.7)	22 (1.8)	53 (9.0)	38 (1.2)	134 (29.6)
Allergic rhinitis ever	17 (0.5)	65 (9.8)	1 (0.4)	16 (14.1)	49 (1.7)	209 (14.9)	9 (0.6)	85 (29.3)	17 (2.1)	68 (23.8)	18 (1.5)	25 (4.3)	13 (0.4)	56 (12.3)
Rhinitis onset before 2 years of age	24 (0.7)	35 (5.3)	19 (4.9)	30 (26.8)	12 (0.4)	69 (5.0)	5 (0.3)	29 (10.1)	11 (1.4)	29 (10.0)	323 (27.1)	262 (44.6)	2 (0.1)	25 (5.6)
Itchy rash (coming and going for at least six months) ever	825 (24.8)	406 (60.9)	146 (36.9)	83 (74.9)	184 (6.4)	1274 (90.9)	521 (32.3)	226 (78.4)	37 (4.6)	141 (49.3)	50 (4.2)	537 (91.5)	1505 (47.3)	354 (78.4)
Itchy rash (coming and going for at least six months) in the last 12 months	495 (14.9)	272 (40.8)	85 (21.6)	45 (40.8)	3 (0.1)	621 (44.3)	234 (14.5)	135 (46.7)	62 (7.6)	153 (53.7)	7 (0.6)	285 (48.6)	731 (23.0)	225 (49.9)
Itchy rash affecting common areas	444 (13.4)	256 (38.3)	145 (36.9)	82 (73.8)	142 (4.9)	1241 (88.5)	1144 (71.0)	261 (90.5)	29 (3.5)	124 (43.5)	0 (0)	216 (36.8)	532 (16.7)	205 (45.3)
Itchy rash onset before 2 years of age	338 (10.2)	157 (23.5)	90 (22.8)	66 (59.3)	54 (1.9)	918 (65.5)	373 (23.1)	186 (64.4)	55 (6.8)	112 (39.3)	36 (3.0)	474 (80.7)	701 (22.0)	175 (38.7)
Eczema ever	606 (18.2)	337 (50.6)	73 (18.6)	57 (51.3)	234 (8.1)	931 (66.4)	289 (17.9)	176 (61.0)	90 (11.1)	165 (57.8)	202 (16.9)	407 (69.3)	793 (24.9)	254 (56.2)
Urticaria ever	848 (25.5)	354 (53.1)	55 (14.0)	44 (39.4)	136 (4.7)	206 (14.7)	86 (5.3)	63 (21.8)	70 (8.7)	87 (30.4)	849 (71.1)	498 (84.9)	77 (2.4)	30 (6.6)

Food allergy ever	183 (5.5)	187 (28.1)	5 (1.4)	27 (24.0)	171 (5.9)	450 (32.1)	168 (10.4)	127 (44.1)	19 (2.4)	42 (14.7)	44 (3.7)	107 (18.2)	220 (6.9)	99 (21.9)
IgE sensitisation	567 (17.0)	254 (38.1)	77 (19.6)	38 (33.8)	585 (20.2)	435 (31.0)	138 (8.5)	83 (28.8)	134 (16.5)	110 (38.5)	110 (9.2)	94 (16.0)	788 (24.8)	199 (44.1)
Weight (kg), m (SD)	18.2 (2.7)	18.1 (2.8)	14.7 (1.8)	14.8 (2.2)	17.1 (2.5)	16.9 (2.6)	17.1 (2.4)	17.0 (3.4)	17.1 (2.5)	16.9 (2.4)	14.5 (1.8)	14.3 (1.8)	17.4 (2.5)	17.5 (2.6)
Height (cm), m (SD)	106.0 (5.3)	105.3 (5.8)	95.8 (5.8)	95.3 (6.2)	104.9 (4.7)	104.1 (5.5)	104.5 (4.9)	104.2 (7.4)	104.6 (4.5)	104.0 (4.7)	95.8 (4.4)	95.3 (4.4)	105.2 (5.2)	105.2 (5.3)

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	8 years									
	BAMSE		**GINIplus**		**LISAplus**		**MAS**		**PIAMA**	
	G1	**G2**	**G1**	**G2**	**G1**	**G2**	**G1**	**G2**	**G1**	**G2**
	N=3332 (83.1)	**N=679 (16.9)**	**N=2926 (70.8)**	**N=1192 (28.9)**	**N=1274 (71.6)**	**N=505 (28.4)**	**N=860 (77.5)**	**N=249 (22.5)**	**N=2860 (80.2)**	**N=708 (19.8)**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Wheezing ever	869 (26.1)	573 (84.4)	906 (31.0)	928 (77.9)	569 (44.6)	431 (85.3)	245 (28.5)	177 (70.9)	518 (18.1)	553 (78.1)
Wheezing attacks in the last 12 months										
None	3223 (96.7)	337 (49.7)	2846 (97.3)	843 (70.7)	1232 (96.7)	339 (67.0)	846 (98.4)	173 (69.5)	2801 (97.9)	472 (66.7)
1 - 3 times	88 (2.6)	194 (28.6)	70 (2.4)	240 (20.1)	31 (2.4)	110 (21.7)	10 (1.2)	42 (16.9)	51 (1.8)	169 (23.9)
4 - 12 times	14 (0.4)	108 (15.8)	8 (0.3)	89 (7.4)	9 (0.7)	45 (8.9)	3 (0.3)	24 (9.6)	6 (0.2)	53 (7.5)
> 12 times	7 (0.2)	40 (5.9)	2 (0.1)	21 (1.8)	2 (0.2)	12 (2.3)	1 (0.1)	10 (4.0)	2 (0.1)	14 (2.0)
Wheezing after exercise ever	126 (3.8)	361 (53.2)	162 (5.5)	572 (48.0)	97 (7.6)	266 (52.7)	44 (5.1)	100 (40.3)	188 (6.6)	430 (60.7)
Asthma ever	181 (5.4)	455 (67.1)	117 (4.0)	521 (43.7)	53 (4.2)	245 (48.6)	75 (8.8)	139 (55.7)	101 (3.5)	355 (50.1)
Asthma treatment in the last 12 months	154 (4.6)	390 (57.4)	31 (1.1)	308 (25.8)	22 (1.7)	156 (30.9)	39 (4.6)	94 (37.9)	21 (0.7)	157 (22.2)
Asthma onset before 2 years of age	86	217	45	163	17	73	45	61	32	142

	(2.6)	(31.9)	(1.5)	(13.7)	(1.3)	(14.4)	(5.2)	(24.4)	(1.1)	(20.0)
Bronchitis or Bronchiolitis ever	576 (17.3)	291 (42.8)	764 (26.1)	733 (61.5)	1176 (92.3)	439 (86.9)	196 (22.8)	109 (43.8)	931 (32.6)	545 (76.9)
Cough at night (when no cold) ever	569 (17.1)	359 (52.9)	983 (33.6)	936 (78.5)	415 (32.6)	388 (76.8)	220 (25.6)	159 (63.7)	1522 (53.2)	638 (90.1)
Sneezing or runny or blocked nose (when no cold) ever	1332 (40.0)	504 (74.2)	922 (31.5)	1065 (89.3)	516 (40.5)	455 (90.1)	379 (44.1)	207 (83.2)	454 (15.9)	558 (78.8)
Sneezing or runny or blocked nose (when no cold) in the last 12 months	289 (8.7)	341 (50.2)	359 (12.3)	833 (69.9)	182 (14.3)	343 (68.0)	144 (16.8)	155 (62.2)	287 (10.1)	465 (65.6)
Itchy watery eyes (when no cold) in the last 12 months	102 (3.1)	238 (35.0)	156 (5.3)	589 (49.4)	80 (6.3)	253 (50.1)	41 (4.8)	104 (41.7)	32 (1.1)	251 (35.4)
Allergic rhinitis ever	100 (3.0)	234 (34.5)	274 (9.4)	820 (68.8)	123 (9.7)	336 (66.6)	51 (5.9)	132 (53.0)	45 (1.6)	210 (29.7)
Rhinitis onset before 2 years of age	17 (0.5)	35 (5.2)	20 (0.7)	117 (9.8)	16 (1.3)	52 (10.3)	12 (1.4)	28 (11.2)	7 (0.2)	40 (5.6)
Itchy rash (coming and going for at least six months) ever	1010 (30.3)	476 (70.2)	938 (32.1)	929 (78.0)	443 (34.8)	429 (84.9)	110 (12.8)	160 (64.4)	1789 (62.5)	635 (89.8)
Itchy rash (coming and going for at least six months) in the last 12 months	490 (14.7)	294 (43.3)	88 (3.0)	154 (12.9)	40 (3.2)	88 (17.5)	34 (4.0)	106 (42.7)	522 (18.2)	310 (43.8)
Itchy rash affecting common areas	363 (10.9)	256 (37.7)	60 (2.1)	132 (11.1)	29 (2.2)	73 (14.4)	22 (2.6)	93 (37.2)	370 (12.9)	258 (36.5)
Itchy rash onset before 2 years of age	557 (16.7)	335 (49.4)	475 (16.2)	698 (58.6)	284 (22.3)	341 (67.6)	68 (7.9)	134 (54.0)	345 (12.1)	238 (33.6)
Eczema ever	755 (22.7)	410 (60.3)	803 (27.4)	902 (75.7)	298 (23.4)	392 (77.7)	145 (16.8)	167 (66.9)	710 (24.8)	467 (66.0)
Urticaria ever	842 (25.3)	363 (53.4)	352 (12.0)	439 (36.8)	149 (11.7)	209 (41.5)	118 (13.8)	90 (36.3)	274 (9.6)	207 (29.2)
Food allergy ever	261	271	478	695	211	315	25	54	168	221

	(7.8)	(40.0)	(16.3)	(58.3)	(16.6)	(62.3)	(2.9)	(21.7)	(5.9)	(31.2)
IgE sensitisation	842 (25.3)	413 (60.8)	925 (31.6)	882 (74.0)	430 (33.8)	371 (73.5)	234 (27.2)	175 (70.5)	941 (32.9)	466 (65.9)
Weight (kg), m (SD)	30.7 (6.8)	30.9 (7.4)	34.9 (7.0)	35.2 (9.5)	34.5 (7.4)	34.9 (9.4)	35.0 (8.7)	35.4 (8.9)	28.8 (5.3)	30.0 (6.7)
Height (cm), m (SD)	133.2 (7.2)	132.9 (8.7)	143.6 (7.4)	143.7 (10.5)	142.9 (8.1)	142.7 (10.8)	139.9 (8.6)	139.9 (9.0)	133.5 (6.5)	134.6 (8.3)

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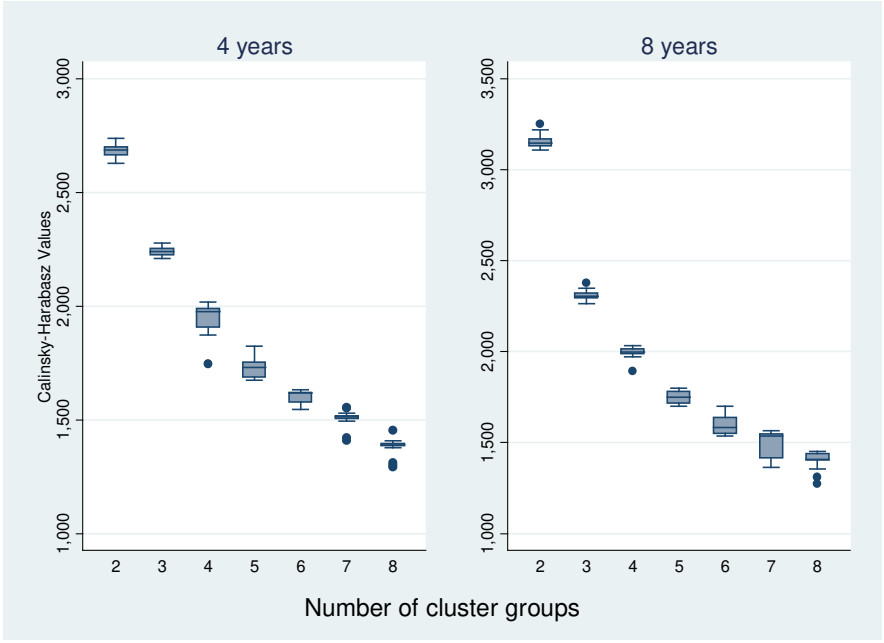
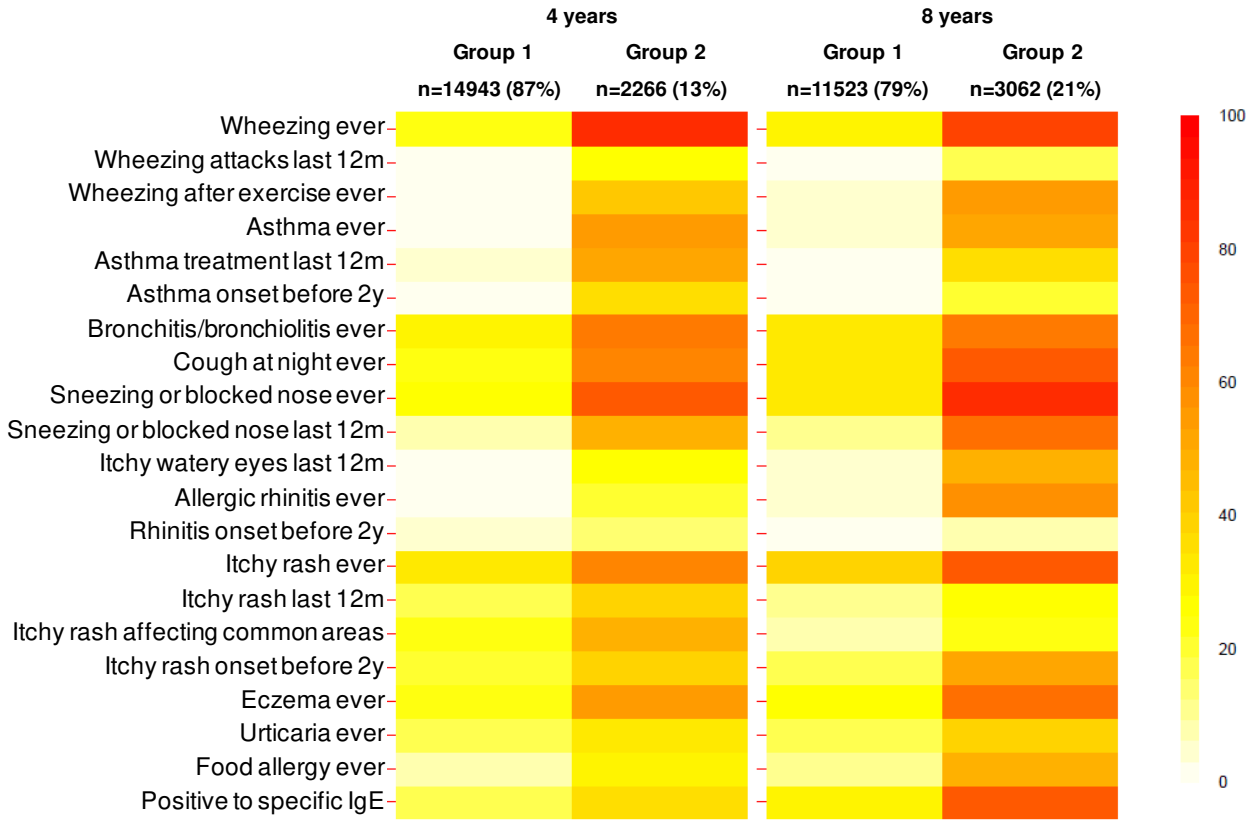
SENSITIVITY ANALYSIS III—deal with potential information bias

Figure E12. Distribution of Calinsky-Harabasz stopping rule* and graphical description† of the two groups identified by cluster analysis at 4 and 8 years, without including "itchy rash ever" as a variable in the cluster analysis



* Higher values indicate higher separation between groups and similarity within groups.



† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

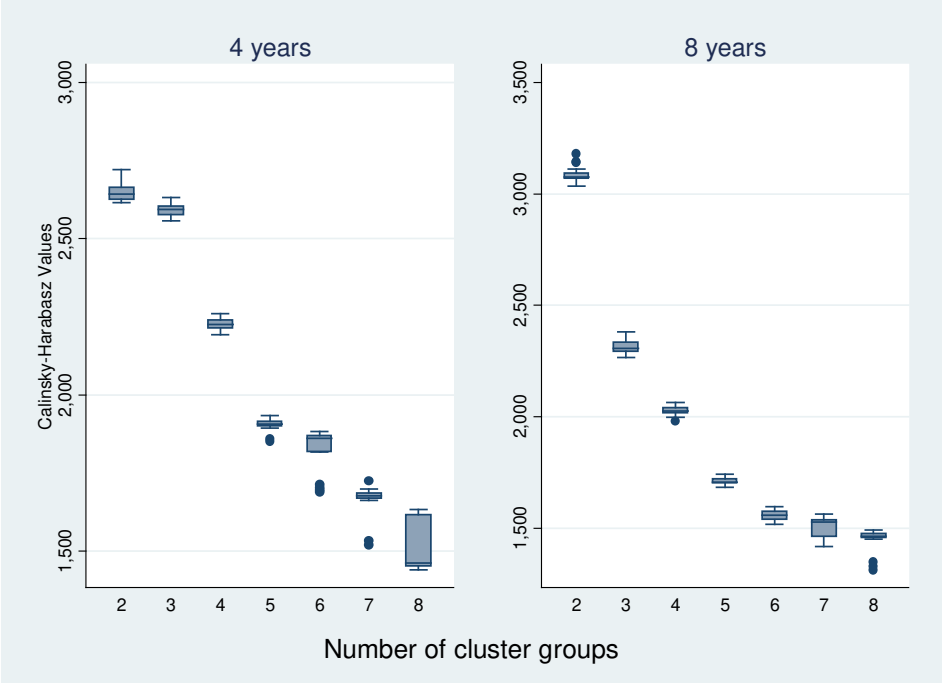
435 **Table E13. Description of the two groups identified by cluster analysis at 4 and 8 years after, <u>without including "itchy rash ever"</u> as a variable in the cluster analysis**
436

	4 years				8 years			
	All	**Group 1**	**Group 2**		**All**	**Group 1**	**Group 2**	
	N = 17209	**14943 (86.8)**	**2266 (13.2)**	**F***	**N = 14585**	**11523 (79.0)**	**3062 (21.0)**	**F***
	n (%)	**n (%)**	**n (%)**		**n (%)**	**n (%)**	**n (%)**	
Wheezing ever	5641 (32.8)	3722 (24.9)	1919 (84.7)	1937.7	5767 (39.5)	3308 (28.7)	2459 (80.3)	1509.5
Wheezing attacks in the last 12 months								
None	15309 (89.0)	14279 (95.6)	1030 (45.5)	603.7	13112 (89.9)	11170 (96.9)	1941 (63.4)	384.4
1 - 3 times	1289 (7.5)	594 (4.0)	695 (30.7)		1005 (6.9)	287 (2.5)	718 (23.5)	
4 - 12 times	482 (2.8)	61 (0.4)	421 (18.6)		358 (2.5)	48 (0.4)	309 (10.1)	
> 12 times	129 (0.8)	10 (0.1)	119 (5.3)		110 (0.8)	17 (0.2)	93 (3.0)	
Wheezing after exercise ever	1346 (7.8)	392 (2.6)	954 (42.1)	2075.4	2345 (16.1)	712 (6.2)	1633 (53.3)	1906.0
Asthma ever	1410 (8.2)	202 (1.4)	1208 (53.3)	1995.2	2243 (15.4)	623 (5.4)	1620 (52.9)	1965.5
Asthma treatment in the last 12 months	1936 (11.3)	768 (5.1)	1168 (51.5)	2345.7	1371 (9.4)	297 (2.6)	1074 (35.1)	1181.8
Asthma onset before 2 years of age	924 (5.4)	94 (0.6)	830 (36.6)	1103.4	879 (6.0)	266 (2.3)	613 (20.0)	591.4
Bronchitis or Bronchiolitis ever	5794 (33.7)	4329 (29.0)	1465 (64.6)	780.8	5760 (39.5)	3780 (32.8)	1980 (64.7)	828.8
Cough at night (when no cold) ever	4948 (28.8)	3538 (23.7)	1410 (62.2)	1135.8	6189 (42.4)	3921 (34.0)	2268 (74.1)	1172.9
Sneezing or runny or blocked nose (when no cold) ever	5607 (32.6)	3960 (26.5)	1647 (72.7)	1425.0	6392 (43.8)	3738 (32.4)	2654 (86.7)	1409.8
Sneezing or runny or blocked nose (when no cold) in the last 12 months	2474 (14.4)	1370 (9.2)	1103 (48.7)	1716.2	3400 (23.3)	1301 (11.3)	2099 (68.6)	1973.5
Itchy watery eyes (when no cold) in the last 12 months	831 (4.8)	194 (1.3)	637 (28.1)	1288.0	1845 (12.7)	377 (3.3)	1469 (48.0)	1449.5

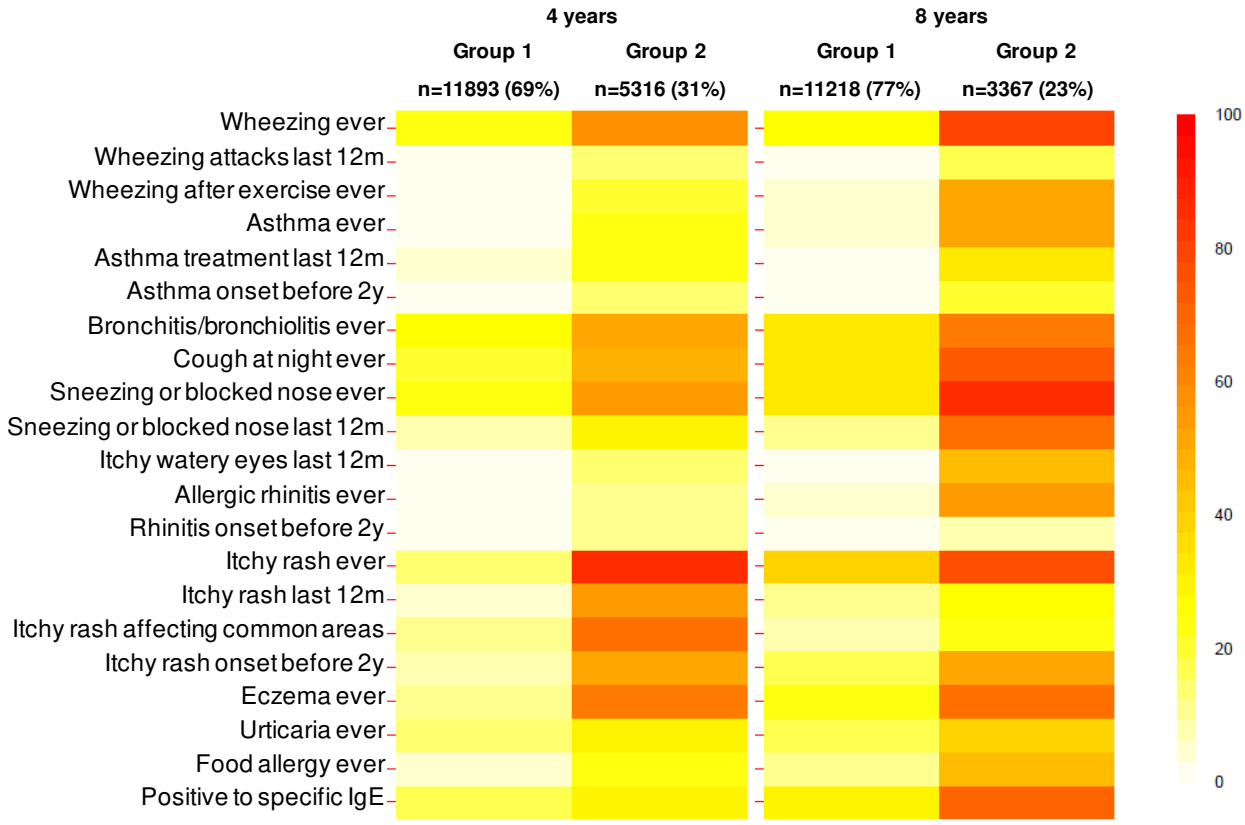
Allergic rhinitis ever	648 (3.8)	169 (1.1)	479 (21.1)	842.3	2326 (15.9)	582 (5.0)	1744 (57.0)	1736.1
Rhinitis onset before 2 years of age	876 (5.1)	531 (3.6)	344 (15.2)	386.9	345 (2.4)	79 (0.7)	266 (8.7)	270.3
Itchy rash (coming and going for at least six months) in the last 12 months	3353 (19.5)	2479 (16.6)	875 (38.6)	506.8	2126 (14.6)	1339 (11.6)	787 (25.7)	252.7
Itchy rash affecting common areas	4820 (28.0)	3733 (25.0)	1087 (48.0)	471.1	1657 (11.4)	978 (8.5)	678 (22.2)	296.5
Itchy rash onset before 2 years of age	3734 (21.7)	2820 (18.9)	914 (40.3)	415.5	3477 (23.8)	1920 (16.7)	1558 (50.9)	1199.6
Eczema ever	4614 (26.8)	3410 (22.8)	1205 (53.2)	719.0	5049 (34.6)	2965 (25.7)	2085 (68.1)	1406.2
Urticaria ever	3403 (19.8)	2648 (17.7)	755 (33.3)	227.6	3043 (20.9)	1842 (16.0)	1202 (39.2)	505.3
Food allergy ever	1850 (10.7)	1211 (8.1)	639 (28.2)	613.2	2699 (18.5)	1234 (10.7)	1466 (47.9)	1421.1
IgE sensitisation	3611 (21.0)	2776 (18.6)	835 (36.8)	177.4	5680 (38.9)	3467 (30.1)	2213 (72.3)	969.7
Weight (kg), m (SD)	17.0 (2.7)	17.1 (2.7)	17.0 (3.1)	0.7	32.3 (7.7)	32.0 (7.3)	33.4 (8.9)	67.5
Height (cm), m (SD)	103.8 (6.0)	103.9 (6.0)	103.2 (6.9)	19.9	137.9 (9.4)	137.5 (8.8)	139.5 (10.7)	96.2
Variable not included in the cluster analysis:								
Itchy rash (coming and going for at least six months) ever	6290 (36.6)	4875 (32.6)	1415 (62.5)	—	6921 (47.5)	4630 (40.2)	2291 (74.8)	—

* F values correspond to the ratio of the variance of the group means (between-group variance) over the overall variance of the variable (higher values meaning higher relevance of the variable for separating cluster groups), and were obtained by means of linear regression models using each variable as the outcome, and the cluster group as the exposure.

Figure E13. Distribution of Calinsky-Harabasz stopping rule* and graphical description† of the two groups identified by cluster analysis at 4 and 8 years, <u>without including "food allergy ever"</u> as a variable in the cluster analysis



* Higher values indicate higher separation between groups and similarity within groups.



† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

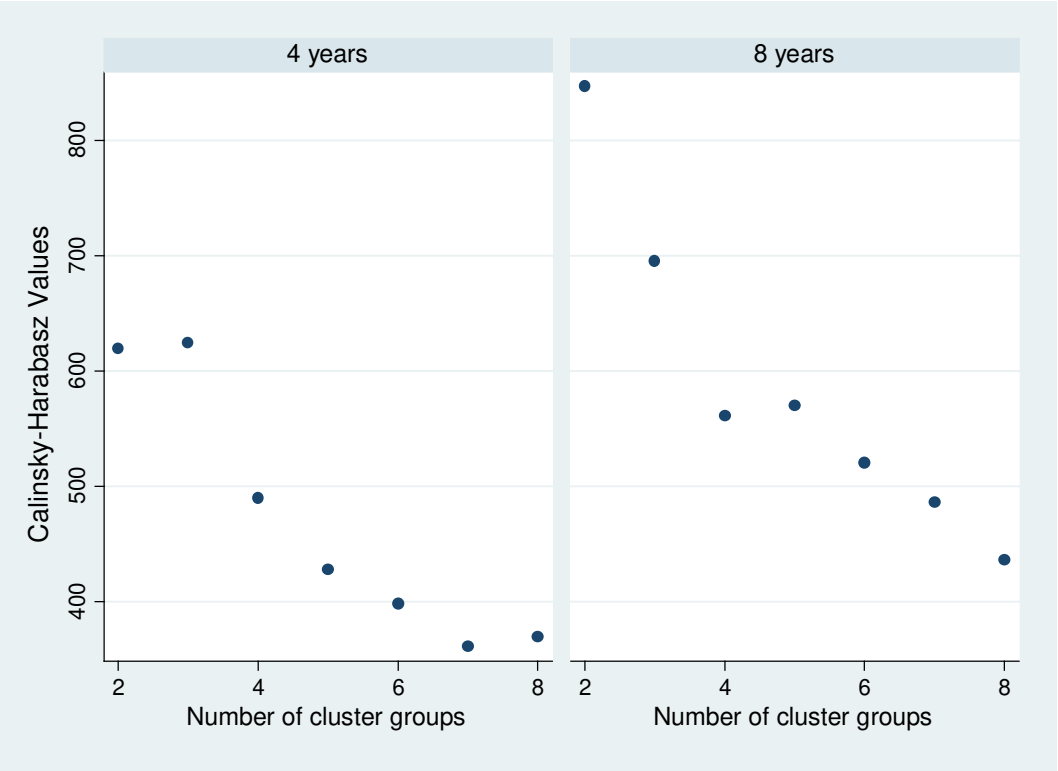
448 **Table E14. Description of the two groups identified by cluster analysis at 4 and 8 years after, without including "food allergy ever" as a variable in the cluster analysis**

	4 years				8 years			
	All	**Group 1**	**Group 2**		**All**	**Group 1**	**Group 2**	
	N = 17209	**11893 (69.1)**	**5316 (30.9)**	**F***	**N = 14585**	**11218 (76.9)**	**3367 (23.1)**	**F***
	n (%)	**n (%)**	**n (%)**		**n (%)**	**n (%)**	**n (%)**	
Wheezing ever	5641 (32.8)	2649 (22.3)	2992 (56.3)	1643.4	5767 (39.5)	3097 (27.6)	2671 (79.3)	1770.8
Wheezing attacks in the last 12 months								
None	15309 (89.0)	11403 (95.9)	3905 (73.5)	346.3	13112 (89.9)	10918 (97.3)	2194 (65.2)	382.0
1 - 3 times	1289 (7.5)	435 (3.7)	853 (16.1)		1005 (6.9)	248 (2.2)	758 (22.5)	
4 - 12 times	482 (2.8)	46 (0.4)	436 (8.2)		358 (2.5)	39 (0.3)	319 (9.5)	
> 12 times	129 (0.8)	8 (0.1)	121 (2.3)		110 (0.8)	14 (0.1)	97 (2.9)	
Wheezing after exercise ever	1346 (7.8)	254 (2.1)	1092 (20.5)	1026.8	2345 (16.1)	612 (5.5)	1733 (51.5)	1693.3
Asthma ever	1410 (8.2)	218 (1.8)	1192 (22.4)	966.8	2243 (15.4)	545 (4.9)	1698 (50.4)	1961.6
Asthma treatment in the last 12 months	1936 (11.3)	616 (5.2)	1320 (24.8)	1065.2	1371 (9.4)	257 (2.3)	1114 (33.1)	1208.5
Asthma onset before 2 years of age	924 (5.4)	123 (1.0)	801 (15.1)	666.4	879 (6.0)	234 (2.1)	645 (19.2)	570.8
Bronchitis or Bronchiolitis ever	5794 (33.7)	3118 (26.2)	2676 (50.3)	768.9	5760 (39.5)	3600 (32.1)	2160 (64.1)	908.2
Cough at night (when no cold) ever	4948 (28.8)	2419 (20.3)	2530 (47.6)	1119.1	6189 (42.4)	3705 (33.0)	2484 (73.8)	1270.7
Sneezing or runny or blocked nose (when no cold) ever	5607 (32.6)	2759 (23.2)	2848 (53.6)	1353.7	6392 (43.8)	3517 (31.3)	2875 (85.4)	1479.7
Sneezing or runny or blocked nose (when no cold) in the last 12 months	2474 (14.4)	844 (7.1)	1629 (30.6)	1326.9	3400 (23.3)	1155 (10.3)	2245 (66.7)	2077.0
Itchy watery eyes (when no cold) in the last 12 months	831 (4.8)	119 (1.0)	712 (13.4)	647.1	1845 (12.7)	305 (2.7)	1541 (45.8)	1350.8

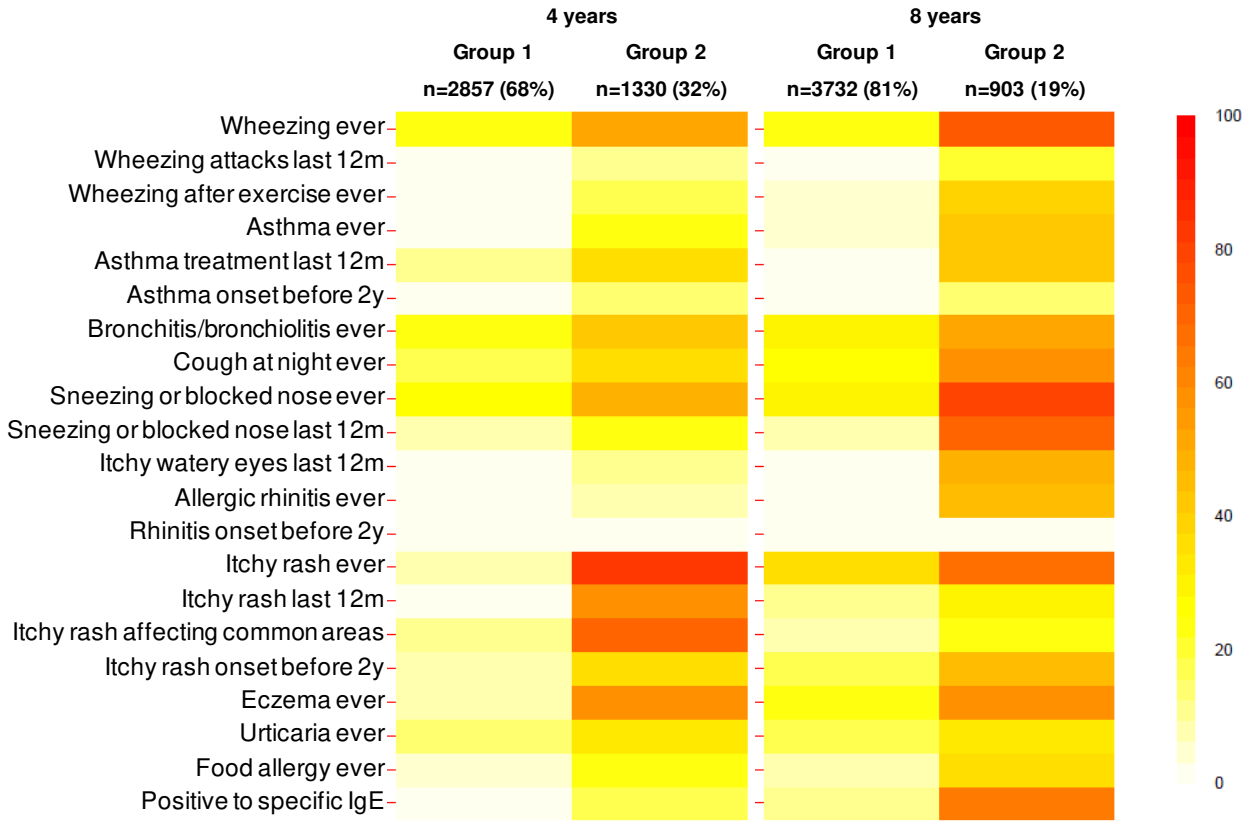
Allergic rhinitis ever	648 (3.8)	108 (0.9)	540 (10.2)	424.3	2326 (15.9)	510 (4.5)	1816 (53.9)	1553.6
Rhinitis onset before 2 years of age	876 (5.1)	351 (3.0)	524 (9.9)	286.2	345 (2.4)	69 (0.6)	276 (8.2)	231.1
Itchy rash (coming and going for at least six months) ever	6290 (36.6)	1779 (15.0)	4511 (84.9)	5001.3	6921 (47.5)	4349 (38.8)	2572 (76.4)	1061.6
Itchy rash (coming and going for at least six months) in the last 12 months	3353 (19.5)	428 (3.6)	2926 (55.0)	3554.8	2126 (14.6)	1237 (11.0)	889 (26.4)	356.6
Itchy rash affecting common areas	4820 (28.0)	1198 (10.1)	3622 (68.1)	4204.7	1657 (11.4)	893 (8.0)	764 (22.7)	388.5
Itchy rash onset before 2 years of age	3734 (21.7)	1021 (8.6)	2713 (51.0)	2559.2	3477 (23.8)	1767 (15.8)	1710 (50.8)	1312.4
Eczema ever	4614 (26.8)	1291 (10.9)	3323 (62.5)	3763.4	5049 (34.6)	2765 (24.6)	2285 (67.9)	1558.6
Urticaria ever	3403 (19.8)	1816 (15.3)	1587 (29.8)	326.9	3043 (20.9)	1759 (15.7)	1284 (38.1)	546.2
IgE sensitisation	3611 (21.0)	1985 (16.7)	1626 (30.6)	265.7	5680 (38.9)	3300 (29.4)	2380 (70.7)	942.8
Weight (kg), m (SD)	17.0 (2.7)	17.1 (2.6)	16.9 (3.1)	13.4	32.3 (7.7)	32.0 (7.4)	33.3 (9.1)	60.2
Height (cm), m (SD)	103.8 (6.0)	104.1 (6.0)	103.3 (6.6)	50.8	137.9 (9.4)	137.5 (8.9)	139.4 (11.0)	84.4
Variable not included in the cluster analysis:								
Food allergy ever	1850 (10.7)	617 (5.2)	1233 (23.2)	–	2699 (18.5)	1205 (10.7)	1494 (44.4)	–

* F values correspond to the ratio of the variance of the group means (between-group variance) over the overall variance of the variable (higher values meaning higher relevance of the variable for separating cluster groups), and were obtained by means of linear regression models using each variable as the outcome, and the cluster group as the exposure.

Figure E14. Values of Calinsky-Harabasz stopping rule* and graphical description† of the two groups identified by cluster analysis at 4 and 8 years, using a ≥ 3.5 kUA/l cut-off for IgE-sensitisation in the cluster analysis



* Higher values indicate higher separation between groups and similarity within groups. Calinsky-Harabasz at each cluster group is a single value (instead of a distribution) because this analysis was done using the complete case database instead of the multiple imputations.



† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

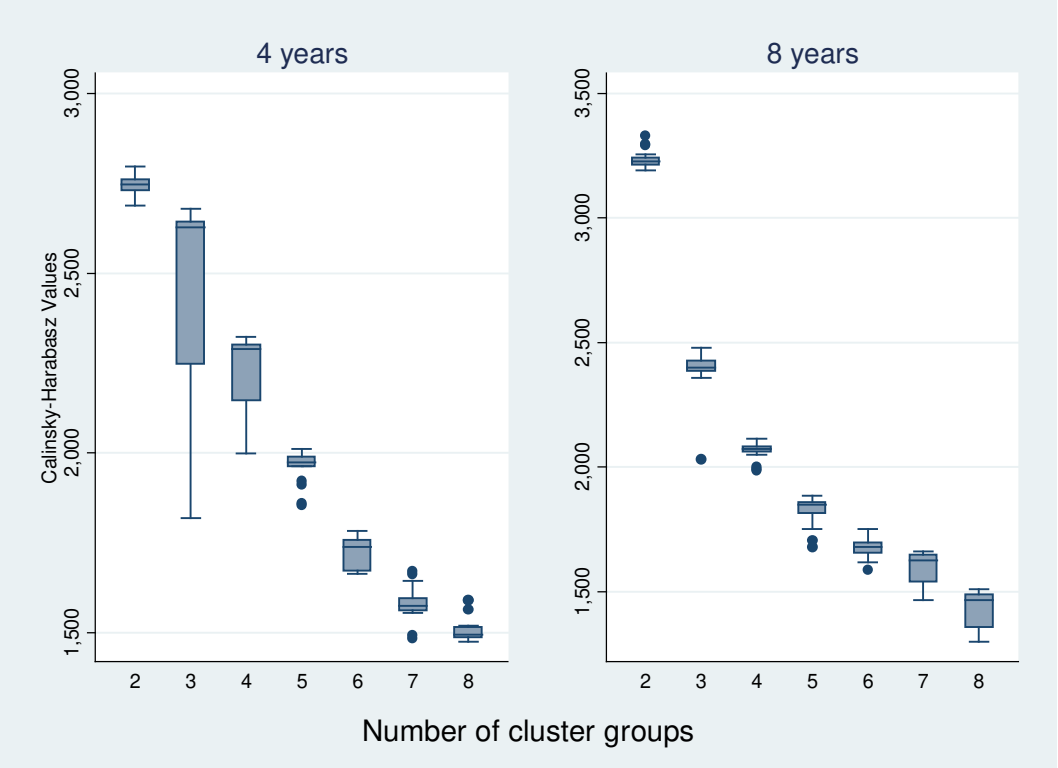
462 **Table E15. Description of the two groups identified by cluster analysis at 4 and 8 years after, using a ≥ 3.5 kUA/l cut-off for IgE-sensitisation in the cluster analysis**

	4 years				8 years			
	All	**Group 1**	**Group 2**		**All**	**Group 1**	**Group 2**	
	N = 4187	**2857 (68.2)**	**1330 (31.8)**	**F***	**N= 4635**	**3732 (80.5)**	**903 (19.5)**	**F***
	n (%)	**n (%)**	**n (%)**		**n (%)**	**n (%)**	**n (%)**	
Wheezing ever	1343 (32.1)	649 (22.7)	694 (52.2)	343.6	1537 (33.2)	883 (23.7)	654 (72.4)	649.8
Wheezing attacks in the last 12 months								
None	3626 (86.6)	2715 (95.0)	911 (68.5)		4216 (91.0)	3678 (98.5)	538 (59.6)	
1 - 3 times	381 (9.1)	135 (4.7)	246 (18.5)		292 (6.3)	53 (1.4)	239 (26.5)	
3 - 12 times	141 (3.4)	7 (0.3)	134 (10.1)	184.4	95 (2.1)	1 (0.1)	94 (10.4)	496.9
> 12 times	39 (0.9)	0 (0)	39 (2.9)		32 (0.7)	0 (0)	32 (3.5)	
Wheezing after exercise ever	304 (7.3)	63 (2.2)	241 (18.1)	244.9	486 (10.5)	125 (3.3)	361 (40.0)	677.7
Asthma ever	336 (8.0)	36 (1.3)	300 (22.6)	301.6	525 (11.3)	135 (3.6)	390 (43.2)	741.9
Asthma treatment in the last 12 months	806 (19.3)	310 (10.9)	496 (37.3)	368.3	426 (9.2)	46 (1.2)	380 (42.1)	622.1
Asthma onset before 2 years of age	228 (5.4)	23 (0.8)	205 (15.4)	195.2	183 (3.9)	56 (1.5)	127 (14.1)	206.6
Bronchitis or Bronchiolitis ever	1238 (29.6)	691 (24.2)	547 (41.1)	122.5	1550 (33.4)	1085 (29.1)	465 (51.5)	158.0
Cough at night (when no cold) ever	965 (23.0)	475 (16.6)	490 (36.8)	200.2	1508 (32.5)	995 (26.7)	513 (56.8)	281.1
Sneezing or runny or blocked nose (when no cold) ever	1432 (34.2)	784 (27.4)	648 (48.7)	178.0	1773 (38.3)	1064 (28.5)	709 (78.5)	622.8
Sneezing or runny or blocked nose (when no cold) in the last 12 months	516 (12.3)	200 (7.0)	316 (23.8)	211.9	897 (19.4)	274 (7.3)	623 (69.0)	1220.2

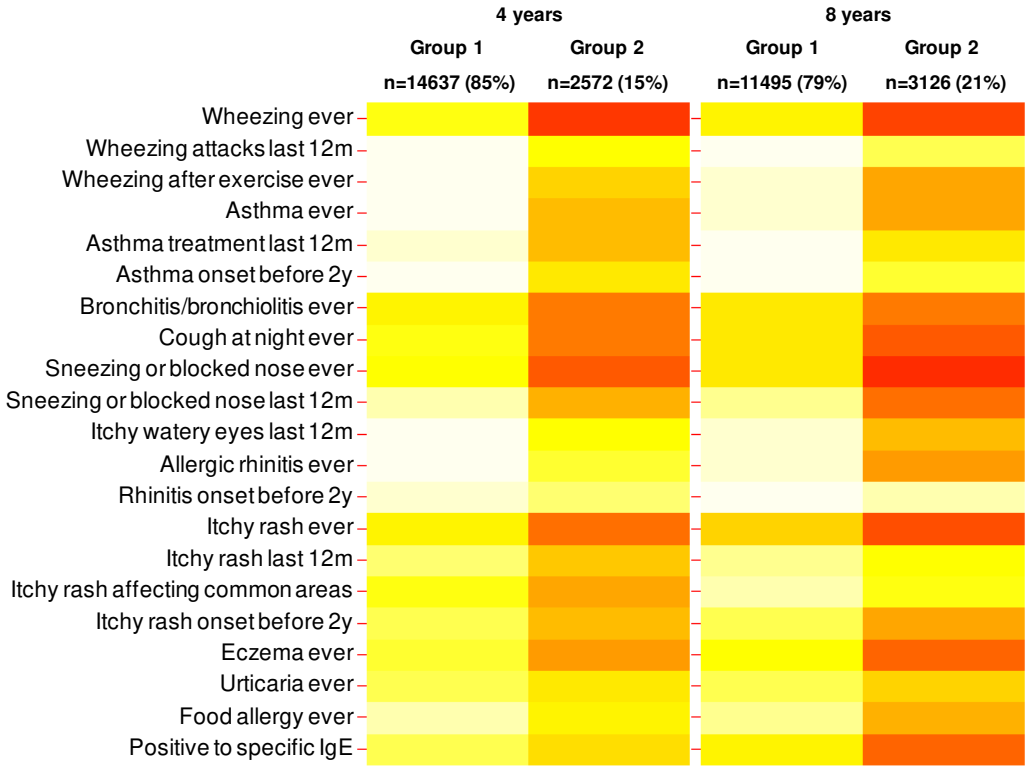
Itchy watery eyes (when no cold) in the last 12 months	203 (4.8)	41 (1.4)	162 (12.2)	159.9	474 (10.2)	27 (0.7)	447 (49.5)	575.7
Allergic rhinitis ever	111 (2.7)	21 (0.7)	90 (6.8)	87.0	492 (10.6)	85 (2.3)	407 (45.1)	768.1
Rhinitis onset before 2 years of age	54 (1.3)	16 (0.6)	38 (2.9)	30.4	36 (0.8)	13 (0.3)	23 (2.5)	33.2
Itchy rash (coming and going for at least six months) ever	1358 (32.4)	260 (9.1)	1098 (82.6)	1573.0	1939 (41.8)	1329 (35.6)	610 (67.6)	282.5
Itchy rash (coming and going for at least six months) in the last 12 months	801 (19.1)	23 (0.8)	778 (58.5)	566.7	652 (14.1)	390 (10.5)	262 (29.0)	190.7
Itchy rash affecting common areas	1271 (30.4)	349 (12.2)	922 (69.3)	1142.7	515 (11.1)	290 (7.8)	225 (24.9)	194.6
Itchy rash onset before 2 years of age	681 (16.3)	199 (7.0)	482 (36.2)	474.8	991 (21.4)	591 (15.8)	400 (44.3)	319.7
Eczema ever	1043 (24.9)	259 (9.1)	784 (58.9)	967.7	1391 (30.0)	874 (23.4)	517 (57.3)	362.4
Urticaria ever	846 (20.2)	408 (14.3)	438 (32.9)	186.5	907 (19.6)	607 (16.3)	300 (33.2)	127.1
Food allergy ever	402 (9.6)	104 (3.6)	298 (22.4)	289.2	640 (13.8)	319 (8.5)	321 (35.5)	381.4
IgE sensitisation	879 (21.0)	77 (2.7)	216 (16.2)	200.6	1634 (35.3)	399 (10.7)	576 (63.8)	951.2
Weight (kg), m (SD)	17.6 (2.4)	17.6 (2.3)	17.7 (2.4)	2.2	31.3 (6.1)	31.2 (6.0)	31.6 (6.2)	3.6
Height (cm), m (SD)	105.0 (4.8)	105.0 (4.8)	104.9 (4.9)	0.5	135.9 (7.9)	135.8 (7.8)	136.5 (8.2)	6.3

* F values correspond to the ratio of the variance of the group means (between-group variance) over the overall variance of the variable (higher values meaning higher relevance of the variable for separating cluster groups), and were obtained by means of linear regression models using each variable as the outcome, and the cluster group as the exposure.

Figure E15. Distribution of Calinsky-Harabasz stopping rule* and graphical description† of the two groups identified by cluster analysis at 4 and 8 years, including BMI (instead of weight and height separately) as a variable in the cluster analysis.



* Higher values indicate higher separation between groups and similarity within groups.



† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour)

Table E16. Description of the two groups identified by cluster analysis at 4 and 8 years, including BMI (instead of weight and height separately) as a variable in the cluster analysis

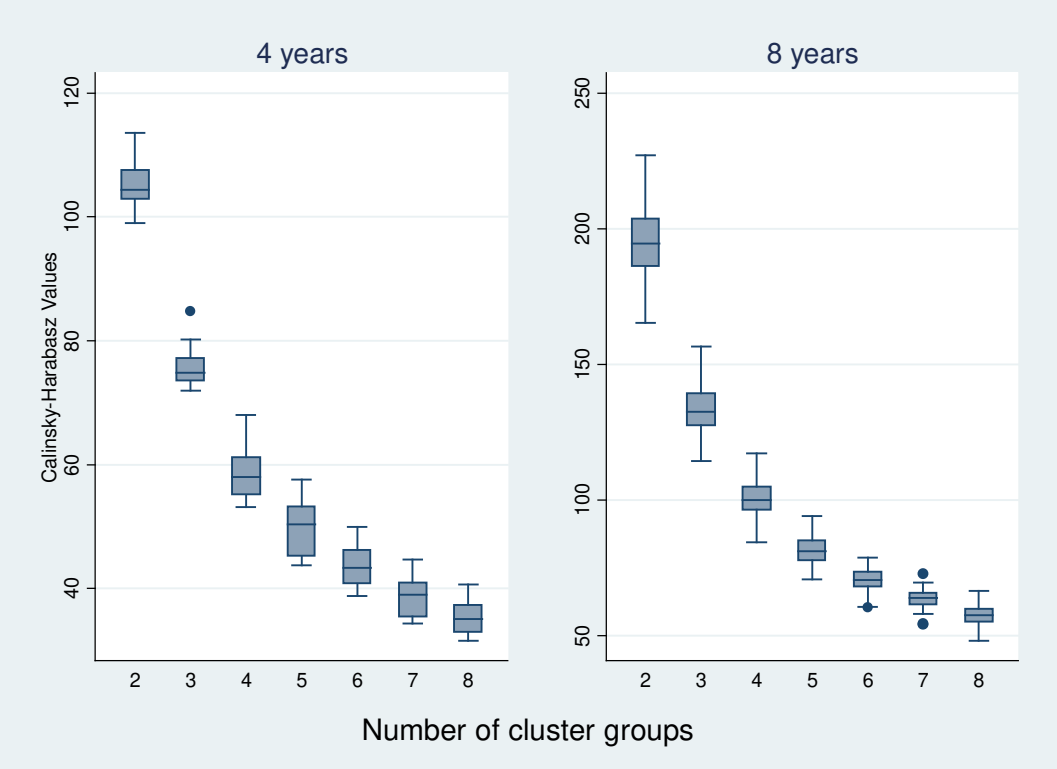
	4 years				8 years			
	All	**Group 1**	**Group 2**		**All**	**Group 1**	**Group 2**	
	N = 17209	**14637 (85.0)**	**2572 (15.0)**	**F***	**N = 14585**	**11495 (78.6)**	**3126 (21.4)**	**F***
	n (%)	**n (%)**	**n (%)**		**n (%)**	**n (%)**	**n (%)**	
Wheezing ever	5641 (32.8)	3523 (24.1)	2118 (82.4)	2153.0	5767 (39.5)	3268 (28.5)	2499 (79.9)	1681.3
Wheezing attacks in the last 12 months								
None	15309 (89.0)	14028 (95.8)	1280 (49.8)		13112 (89.9)	11108 (96.9)	2004 (64.1)	605.6
1 - 3 times	1289 (7.5)	541 (3.7)	748 (29.1)	1461.3	1005 (6.9)	286 (2.5)	719 (23.0)	
4 - 12 times	482 (2.8)	59 (0.4)	423 (16.5)		358 (2.5)	47 (0.4)	310 (9.9)	
> 12 times	129 (0.8)	9 (0.1)	120 (4.7)		110 (0.8)	18 (0.2)	93 (3.0)	
Wheezing after exercise ever	1346 (7.8)	331 (2.3)	1015 (39.5)	1991.7	2345 (16.1)	698 (6.1)	1647 (52.7)	1789.0
Asthma ever	1410 (8.2)	206 (1.4)	1205 (46.8)	1818.6	2243 (15.4)	614 (5.4)	1629 (52.1)	1958.8
Asthma treatment in the last 12 months	1936 (11.3)	739 (5.0)	1197 (46.5)	2113.5	1371 (9.4)	299 (2.6)	1072 (34.3)	1256.6
Asthma onset before 2 years of age	924 (5.4)	105 (0.7)	819 (31.8)	1095.2	879 (6.0)	264 (2.3)	616 (19.7)	599.3
Bronchitis or Bronchiolitis ever	5794 (33.7)	4153 (28.4)	1642 (63.8)	812.6	5760 (39.5)	3742 (32.7)	2018 (64.6)	838.6
Cough at night (when no cold) ever	4948 (28.8)	3333 (22.8)	1615 (62.8)	1282.0	6189 (42.4)	3870 (33.8)	2318 (74.2)	1185.3
Sneezing or runny or blocked nose (when no cold) ever	5607 (32.6)	3714 (25.4)	1893 (73.6)	1652.6	6392 (43.8)	3705 (32.3)	2687 (85.9)	1353.8
Sneezing or runny or blocked nose (when no cold) in the last 12 months	2474 (14.4)	1221 (8.3)	1252 (48.7)	1984.9	3400 (23.3)	1290 (11.3)	2111 (67.5)	1972.7

Itchy watery eyes (when no cold) in the last 12 months	831 (4.8)	148 (1.0)	683 (26.6)	1135.2	1845 (12.7)	386 (3.4)	1.460 (46.7)	1579.1
Allergic rhinitis ever	648 (3.8)	132 (0.9)	516 (20.0)	832.5	2326 (15.9)	586 (5.1)	1740 (55.6)	1695.1
Rhinitis onset before 2 years of age	876 (5.1)	476 (3.2)	400 (15.6)	473.4	345 (2.4)	76 (0.7)	269 (8.6)	256.2
Itchy rash (coming and going for at least six months) ever	6290 (36.6)	4543 (31.0)	1747 (67.9)	1065.5	6921 (47.5)	4497 (39.2)	2424 (77.5)	1046.7
Itchy rash (coming and going for at least six months) in the last 12 months	3353 (19.5)	2283 (15.6)	1071 (41.6)	781.1	2126 (14.6)	1275 (11.1)	852 (27.2)	364.6
Itchy rash affecting common areas	4820 (28.0)	3485 (23.8)	1336 (51.9)	742.8	1657 (11.4)	924 (8.1)	733 (23.5)	421.2
Itchy rash onset before 2 years of age	3734 (21.7)	2604 (17.8)	1131 (44.0)	654.7	3477 (23.8)	1834 (16.0)	1643 (52.6)	1335.8
Eczema ever	4614 (26.8)	3183 (21.7)	1431 (55.7)	960.7	5049 (34.6)	2868 (25.0)	2182 (69.8)	1519.5
Urticaria ever	3403 (19.8)	2521 (17.2)	882 (34.3)	286.9	3043 (20.9)	1803 (15.7)	1240 (39.7)	534.7
Food allergy ever	1850 (10.7)	1095 (7.5)	755 (29.4)	787.1	2699 (18.5)	1195 (10.4)	1504 (48.1)	1466.2
IgE sensitisation	3611 (21.0)	2678 (18.3)	933 (36.3)	207.3	5680 (38.9)	3442 (30.0)	2238 (71.6)	1017.0
BMI (kg/m^2), m (SD)	15.8 (1.9)	15.7 (1.8)	15.9 (2.1)	10.1	16.9 (2.8)	16.8 (2.6)	17.0 (3.1)	10.3

* F values correspond to the ratio of the variance of the group means (between-group variance) over the overall variance of the variable (higher values meaning higher relevance of the variable for separating cluster groups), and were obtained by means of linear regression models using each variable as the outcome, and the cluster group as the exposure.

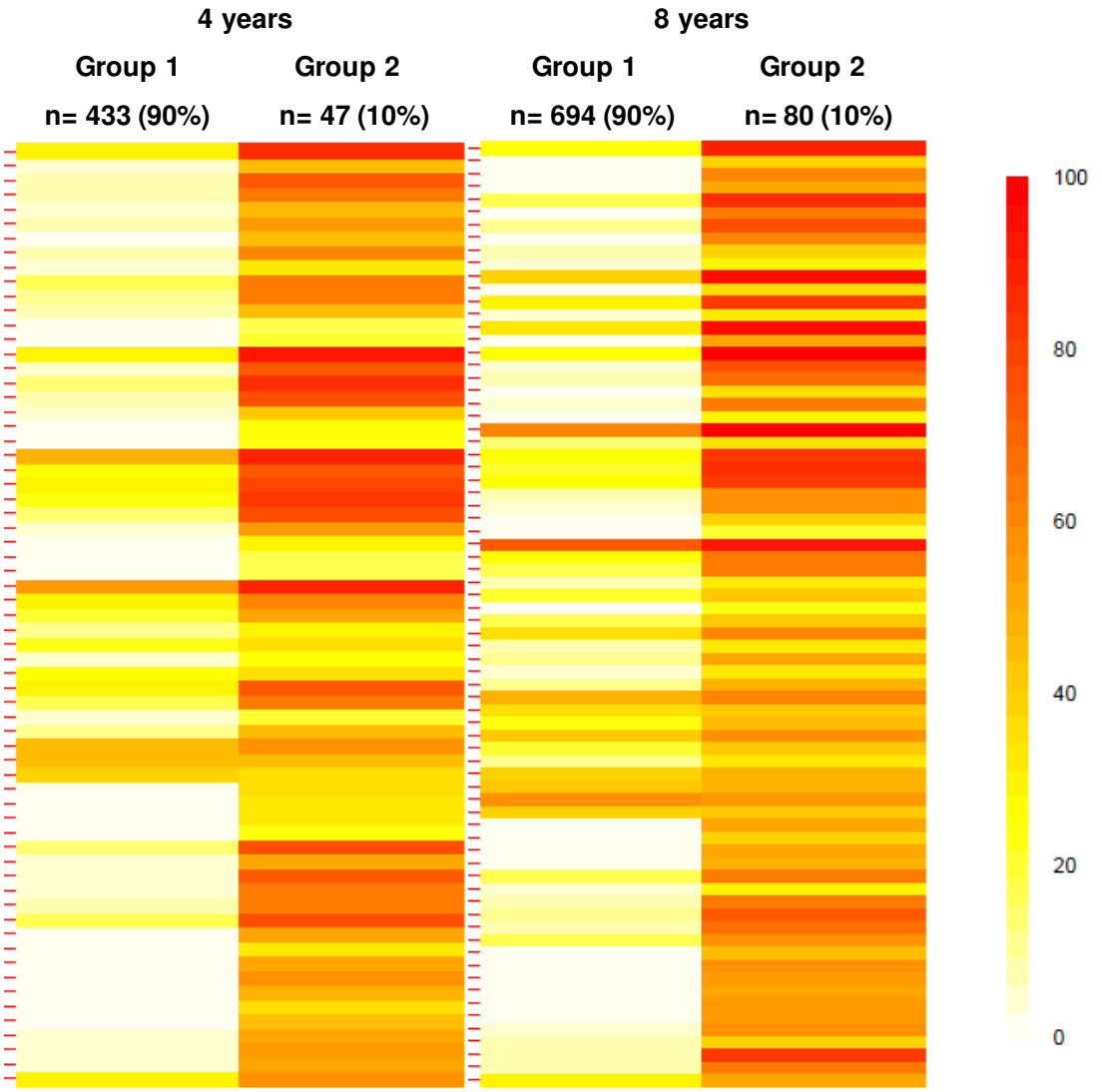
SENSITIVITY ANALYSIS IV—including additional variables and biological measurements

Figure E16. Distribution of values over 20 imputed datasets of the Calinski-Harabasz stopping rule* across 2 to 8 cluster groups at 4 and 8 years, restricting analysis to a subset of the PIAMA cohort (including 67 variables in 480 children at 4 y and 76 variables in 774 children at 8 y).



* Higher values indicate higher separation between groups and similarity within groups.

Figure E17. Prevalence* of symptoms of asthma, rhinitis, and eczema according to the two groups identified in cluster analysis, at 4 and 8 years, restricting analysis to a subset of the PIAMA cohort (including 67 variables† in 480 children at 4 y and 76 variables† in 774 children at 8 y).



* Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

† The names of the variables are not presented in the figure because the small font size would not allow to read them with clarity. The complete list of variables (in the same order) is presented in the following table.

Table E17. Description of the two groups identified by cluster analysis at 4 and 8 years, restricting analysis to a subset of the PIAMA cohort (including 67 variables in 480 children at 4 y and 76 variables in 774 children at 8 y).

	4 years				8 years			
	All	**Group 1**	**Group 2**	**F***	**All**	**Group 1**	**Group 2**	**F***
	n = 480	**433 (90.2%)**	**47 (9.8%)**		**n = 774**	**694 (89.7)**	**80 (10.3)**	
	n (%)	**n (%)**	**n (%)**		**n (%)**	**n (%)**	**n (%)**	
Wheezing ever	164 (34.2)	124 (28.7)	40 (84.5)	15.3	251 (32.5)	181 (26.1)	70 (88.1)	24.7
Number of wheezing attacks in the last 12 months								
None	392 (81.6)	380 (87.8)	11 (24.4)	55.8	677 (87.5)	661 (95.2)	16 (20.0)	104.0
1 - 3 times	57 (11.9)	44 (10.3)	13 (27.1)		64 (8.3)	31 (4.5)	34 (42.5)	
3 - 12 times	24 (5.0)	7 (1.7)	17 (36.0)		32 (4.1)	2 (0.3)	30 (37.5)	
> 12 times	7 (1.4)	1 (0.2)	6 (12.6)		1 (0.1)	0 (0.0)	1 (1.3)	
Wheezing or whistling in the chest accompanied by an attack of breathlessness in the last 12 months	62 (12.9)	28 (6.5)	34 (72.7)	78.6	62 (8.0)	13 (1.8)	49 (61.6)	98.0
Number of attacks of breathlessness in the last 12 months	NA	NA	NA	NA				
None					663 (85.7)	644 (92.8)	19 (23.8)	75.0

1 - 3 times					60 (7.8)	41 (5.9)	19 (24.0)	
3 - 12 times					27 (3.5)	8 (1.2)	19 (23.6)	
> 12 times					23 (3.0)	0 (0.0)	23 (28.6)	
Wheezing after exercise	65 (13.6)	35 (8.0)	30 (64.6)	61.9	179 (23.1)	109 (15.7)	70 (87.3)	25.4
Wheezing after exercise in the last 12 months	42 (8.8)	20 (4.7)	22 (46.5)	43.3	61 (7.9)	11 (1.6)	50 (62.9)	63.9
Asthma ever	53 (11.1)	28 (6.5)	25 (53.6)	51.0	132 (17.0)	70 (10.1)	62 (77.1)	54.2
Any asthma treatment in the last 12 months	33 (6.9)	13 (2.9)	21 (43.8)	47.1	65 (8.4)	16 (2.4)	48 (60.4)	67.2
Any corticosteroid treatment in the last 12 months	57 (11.9)	28 (6.5)	29 (62.1)	51.6	77 (10.0)	47 (6.7)	31 (38.8)	56.2
Asthma onset before 2 years of age	30 (6.3)	15 (3.4)	16 (33.4)	34.2	48 (6.2)	24 (3.4)	25 (30.8)	15.3
Bronchitis or Bronchiolitis ever	111 (23.1)	81 (18.7)	30 (63.4)	28.0	340 (43.9)	265 (38.2)	75 (94.0)	26.1
Bronchitis or Bronchiolitis in the last 12 months	NA	NA	NA	NA	39 (5.0)	11 (1.6)	28 (34.8)	26.4
Congested in the chest or coughed up phlegm (when no cold) ever	78 (16.2)	48 (11.2)	30 (63.1)	38.1	260 (33.7)	195 (28.2)	65 (81.3)	29.5
Congested in the chest or coughed up phlegm (when no cold) in the last 12 months	52 (10.8)	31 (7.1)	21 (45.2)	31.9	64 (8.3)	37 (5.3)	27 (34.3)	20.3
Number of hospital admissions due to wheezing, breathlessness or asthma in the	0 (0-0)	0 (0-0)	0 (0-0.25)	5.0	NA	NA	NA	NA

last 12 months, median (P25-P75)								
Number of hospital admissions due to asthma in the last 12 months, median (P25-P75)	0 (0-0)	0 (0-0)	0 (0-0.35)	13.2	NA	NA	NA	NA
Wheezing at night (when no cold) ever	170 (35.3)	127 (29.3)	43 (91.1)	23.9	300 (38.7)	223 (32.2)	76 (95.3)	29.4
Wheezing at night (when no cold) in the last 12 months	62 (12.8)	26 (6.1)	35 (74.7)	76.2	54 (7.0)	12 (1.7)	42 (52.6)	46.9
Breathlessness at night (when no cold) ever	108 (22.5)	67 (15.5)	41 (86.8)	46.5	256 (33.1)	177 (25.5)	79 (98.8)	NC
Breathlessness at night (when no cold) in the last 12 months	76 (15.9)	40 (9.3)	36 (76.3)	66.0	85 (11.0)	24 (3.4)	61 (76.4)	116.6
Breathless speech ever	35 (7.4)	16 (3.6)	20 (42.2)	49.1	104 (13.4)	51 (7.3)	53 (66.4)	44.7
Breathless speech in the last 12 months	19 (4.0)	6 (1.5)	13 (27.6)	33.5	30 (3.9)	1 (0.2)	29 (36.4)	25.5
Speech limited by wheeze ever	NA	NA	NA	NA	90 (11.6)	40 (5.7)	50 (62.9)	55.0
Speech limited by wheeze in the last 12 months	14 (2.8)	2 (0.5)	12 (24.5)	26.6	26 (3.3)	1 (0.1)	25 (30.6)	23.9
Cough at night (when no cold) ever	249 (51.9)	207 (47.7)	42 (90.2)	15.8	499 (64.4)	421 (60.6)	78 (97.3)	NC
Cough at night (when no cold) in the last 12 months	145 (30.2)	111 (25.5)	34 (72.9)	26.6	133 (17.1)	103 (14.8)	30 (37.4)	7.7
Sneezing or runny or blocked nose ever (when no cold)	162 (33.8)	125 (28.8)	37 (79.6)	18.2	256 (33.1)	191 (27.6)	65 (81.5)	10.5
Sneezing or runny or blocked nose in the	140 (29.1)	101 (23.4)	39 (82.4)	35.9	213 (27.5)	145 (20.9)	68 (84.9)	31.9

last 12 months (when no cold)								
Itchy watery eyes (when no cold) ever	100 (20.9)	65 (15.0)	35 (75.5)	54.7	244 (31.5)	178 (25.7)	66 (81.9)	33.6
Itchy watery eyes in the last 12 months (when no cold)	47 (9.7)	20 (4.7)	26 (56.0)	57.3	109 (14.1)	63 (9.0)	46 (57.9)	21.3
Allergic rhinitis ever	19 (4.0)	5 (1.3)	14 (29.6)	30.9	78 (10.1)	33 (4.7)	46 (57.1)	44.0
Any rhinitis treatment in the last 12 months	9 (1.9)	1 (0.3)	8 (16.3)	14.5	46 (5.9)	16 (2.3)	30 (37.7)	41.3
Rhinitis onset before 2 years of age	9 (1.9)	1 (0.3)	8 (17.1)	12.8	19 (2.4)	3 (0.5)	15 (19.0)	13.8
Itchy rash (coming and going for at least six months) ever	279 (58.1)	237 (54.8)	41 (87.8)	12.8	583 (75.4)	508 (73.3)	75 (93.7)	6.9
Itchy rash (coming and going for at least six months) in the last 12 months	155 (32.3)	127 (29.2)	28 (60.2)	10.7	238 (30.7)	187 (27.0)	50 (63.0)	8.1
Itchy rash affecting common areas in the last 12 months	115 (24.0)	91 (21.1)	24 (50.5)	13.8	177 (22.9)	127 (18.3)	50 (62.6)	14.8
Itchy rash affecting nappy area and hairy parts of head in the last 12 months	61 (12.8)	48 (11.1)	13 (28.4)	6.0	71 (9.2)	44 (6.3)	27 (34.0)	15.0
Itchy rash cleared completely at any time during the last 12 months	113 (23.4)	96 (22.2)	17 (35.2)	2.7	180 (23.2)	145 (21.0)	34 (42.8)	3.2
Frequency of child's sleep disturbed by itchy rash in the last 12 months								
Never	431 (89.8)	400 (92.4)	31 (66.1)	16.2	711 (91.9)	656 (94.5)	55 (69.1)	23.0
< 1 night per week	31 (6.5)	23 (5.4)	8 (16.8)		47 (6.1)	36 (5.2)	11 (13.9)	

One or more nights per week	17 (3.6)	9 (2.2)	8 (17.1)		16 (2.0)	2 (0.3)	14 (16.9)	
Itchy rash onset before 2 years of age	128 (26.7)	111 (25.7)	17 (35.3)	1.4	157 (20.2)	123 (17.7)	34 (41.9)	5.4
Eczema ever	162 (33.7)	128 (29.5)	34 (72.7)	18.1	288 (37.2)	239 (34.5)	49 (61.0)	3.9
Eczema or atopic dermatitis treatment in the last 12 months	110 (23.0)	80 (18.5)	30 (64.5)	24.1	86 (11.1)	58 (8.4)	28 (34.4)	11.8
Urticaria ever	24 (5.0)	15 (3.4)	9 (19.8)	8.6	128 (16.6)	86 (12.4)	42 (52.9)	16.9
Urticaria in the last 12 months	NA	NA	NA	NA	48 (6.3)	22 (3.1)	27 (33.4)	22.2
Allergy to food ever	62 (12.9)	41 (9.4)	21 (45.2)	28.5	109 (14.1)	70 (10.1)	39 (48.8)	23.9
Positive to one specific IgE	222 (46.3)	196 (45.2)	27 (56.7)	1.9	385 (49.8)	336 (48.5)	49 (61.1)	3.6
FeNO (ppb), median (P25-P75)	9.1 (6.6-12.8)	8.9 (6.6-12.6)	10.6 (7.6-14.3)	3.4	9.3 (6.5-13.9)	9.1 (6.4-13.5)	11.6 (7.6-21.8)	10.8
Rint (kPa/l), m(SD)	1.0 (0.2)	1.0 (0.2)	1.1 (0.3)	12.7	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	3.1
Bronchial hiperresponsiveness	NA	NA	NA	NA	337 (43.5)	290 (41.8)	47 (58.3)	6.3
Positive to skin prick test to any allergen	NA	NA	NA	NA	177 (22.8)	142 (20.5)	35 (43.4)	16.0
Positive to skin prick test only to house dust mite	NA	NA	NA	NA	110 (14.3)	85 (12.3)	25 (31.3)	15.5
Prebronchodilator FEV_1 (%), m (SD)	NA	NA	NA	NA	106.8 (12.2)	106.9 (12.2)	105.9 (12.6)	0.5
Prebronchodilator FEV_1 (litres), m (SD)	NA	NA	NA	NA	1.8 (0.2)	1.8 (0.2)	1.8 (0.3)	0.3
Prebronchodilator FVC (%), m (SD)	NA	NA	NA	NA	101.1 (11.3)	101.0 (11.3)	102.4 (11.0)	1.1
Prebronchodilator FVC (litres), m (SD)	NA	NA	NA	NA	2.0 (0.3)	2.0 (0.3)	2.0 (0.3)	0.7

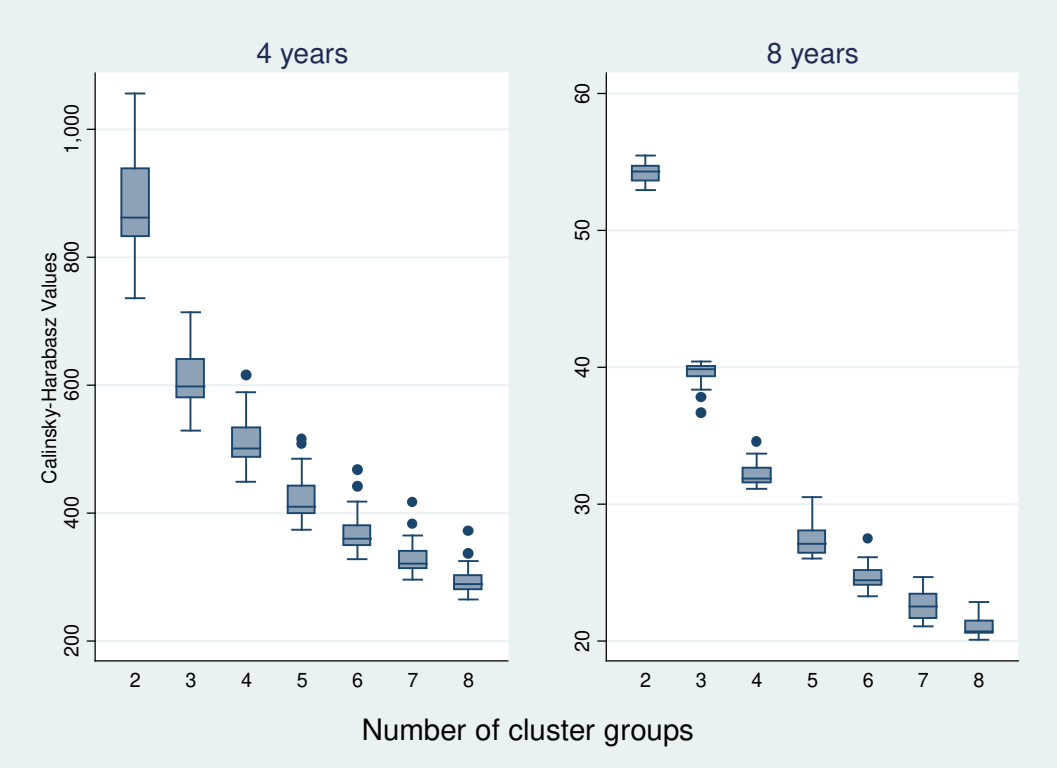
Triggers of wheezing: dust	21 (4.3)	3 (0.8)	17 (36.3)	35.0	49 (6.3)	7 (1.0)	42 (51.9)	67.5
Triggers of wheezing: tobacco	24 (5.1)	8 (2.0)	16 (33.6)	27.9	37 (4.8)	6 (0.9)	31 (38.8)	38.2
Triggers of wheezing: animals	18 (3.7)	3 (0.7)	15 (31.6)	25.9	46 (6.0)	6 (0.9)	40 (50.2)	60.5
Triggers of wheezing: trees/grass	11 (2.2)	0 (0.0)	10 (22.3)	NC	40 (5.2)	1 (0.2)	39 (48.3)	NC
Triggers of shortness of breath: dust	94 (19.6)	58 (13.4)	36 (76.4)	47.8	180 (23.2)	129 (18.5)	51 (63.8)	10.2
Triggers of shortness of breath: tobacco	43 (9.0)	20 (4.5)	24 (50.9)	39.6	50 (6.4)	26 (3.7)	24 (30.3)	15.7
Triggers of shortness of breath: animals	57 (11.9)	22 (5.1)	35 (74.1)	70.5	107 (13.8)	54 (7.8)	53 (65.6)	34.8
Triggers of shortness of breath: trees/grass	56 (11.8)	26 (6.1)	30 (63.9)	68.6	133 (17.2)	75 (10.8)	58 (72.9)	48.7
Triggers of cough: dust	59 (12.2)	29 (6.7)	30 (63.6)	56.5	117 (15.1)	64 (9.2)	54 (66.9)	35.5
Triggers of cough: tobacco	113 (23.5)	77 (17.8)	36 (75.9)	32.8	157 (20.3)	111 (16.0)	46 (57.6)	14.8
Triggers of cough: animals	33 (6.9)	9 (2.2)	24 (50.5)	65.5	48 (6.2)	12 (1.7)	36 (45.4)	35.6
Triggers of cough: trees/grass	20 (4.1)	4 (0.8)	16 (33.9)	37.2	60 (7.7)	14 (2.0)	46 (57.2)	69.9
Triggers of sneezing: dust	27 (5.6)	3 (0.6)	24 (51.8)	49.3	63 (8.1)	18 (2.6)	45 (56.1)	74.0
Triggers of sneezing: tobacco	34 (7.0)	7 (1.6)	27 (56.4)	44.1	62 (8.0)	22 (3.1)	40 (50.5)	36.9
Triggers of sneezing: animals	28 (5.8)	5 (1.1)	24 (50.0)	54.2	55 (7.0)	10 (1.5)	44 (55.6)	46.9
Triggers of sneezing: trees/grass	20 (4.1)	2 (0.5)	17 (36.9)	24.1	49 (6.3)	5 (0.7)	44 (55.0)	60.4
Triggers of itchy watery eyes: dust	33 (7.0)	13 (2.9)	21 (44.3)	48.7	73 (9.4)	26 (3.8)	47 (58.7)	40.9
Triggers of itchy watery eyes: tobacco	40 (8.4)	16 (3.7)	24 (51.4)	52.8	79 (10.2)	48 (7.0)	30 (37.8)	19.6

Triggers of itchy watery eyes: animals	42 (8.8)	17 (4.0)	25 (53.7)	62.3	115 (14.9)	50 (7.2)	65 (81.5)	57.0
Triggers of itchy watery eyes: trees/grass	39 (8.1)	15 (3.4)	24 (51.6)	64.3	103 (13.3)	51 (7.4)	52 (64.8)	52.9
Missing school in the last 2 months due to wheezing, breathlessness, asthma, rhinitis, itchy rash, eczema or food allergy	161 (33.6)	135 (31.1)	26 (56.3)	6.8	247 (31.9)	204 (29.5)	42 (52.9)	4.1
Weight (kg), m (SD)	17.5 (2.7)	17.5 (2.5)	17.4 (3.7)	0.1	29.0 (6.2)	28.8 (4.7)	30.7 (12.6)	2.3
Height (cm), m (SD)	105.0 (5.2)	105.0 (5.0)	104.8 (7.9)	0.0	133.7 (6.7)	133.6 (5.7)	134.9 (12.3)	1.0

NA: Not available. NC: Not computable.

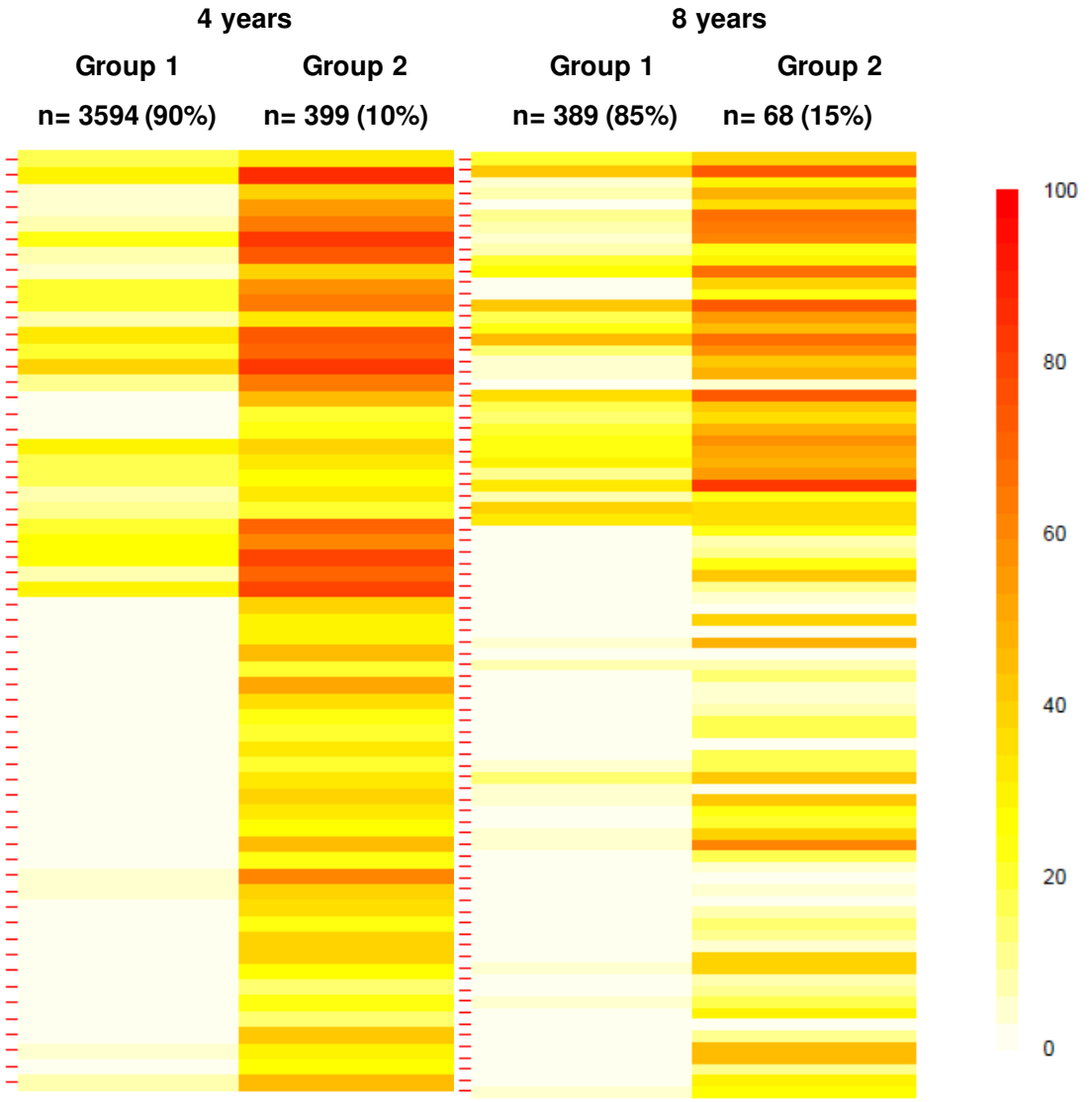
* F values correspond to the ratio of the variance of the group means (between-group variance) over the overall variance of the variable (higher values meaning higher relevance of the variable for separating cluster groups), and were obtained by means of linear regression models using each variable as the outcome, and the cluster group as the exposure.

Figure E18. Distribution of values over 20 imputed datasets of the Calinski-Harabasz stopping rule* across 2 to 8 cluster groups at 4 and 8 years, restricting analysis to a subset of the BAMSE cohort (including 61 variables in 3993 children at 4 y and 86 variables in 457 children at 8 y).



* Higher values indicate higher separation between groups and similarity within groups.

Figure E19. Prevalence* of symptoms of asthma, rhinitis, and eczema according to the two groups identified in cluster analysis, at 4 and 8 years, restricting analysis to a subset of the BAMSE cohort (including 61 variables† in 3993 children at 4 y and 86 variables† in 457 children at 8 y).



* Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

† The names of the variables are not presented in the figure because the small font size would not allow to read them with clarity. The complete list of variables (in the same order) is presented in the following table.

Table E18. Description of the two groups identified by cluster analysis at 4 and 8 years, restricting analysis to a subset of the BAMSE cohort (including 61 variables in 3993 children at 4 y and 86 variables in 457 children at 8 y).

	4 years				8 years			
	All	**Group 1**	**Group 2**	**F***	**All**	**Group 1**	**Group 2**	**F***
	n = 3993	**3594 (90.0%)**	**399 (10.0%)**		**n = 457**	**389 (85.1%)**	**68 (14.9%)**	
	n (%)	**n (%)**	**n (%)**		**n (%)**	**n (%)**	**n (%)**	
Any hospital admission or emergency room visit for respiratory symptoms in the first 2 years of life	711 (17.8)	577 (16.0)	134 (33.7)	59.8	107 (23.4)	80 (20.5)	27 (39.7)	11.3
Wheezing ever	1411 (35.3)	1072 (29.8)	339 (85.1)	157.1	218 (47.7)	169 (43.4)	49 (72.5)	17.5
Number of wheezing attacks in the last 12 months				96.9				53.6
None	3276 (82.1)	3131 (87.1)	146 (36.5)		388 (85.0)	357 (91.8)	31 (46.0)	
1 - 3 times	448 (11.2)	346 (9.6)	102 (25.6)		48 (10.5)	28 (7.2)	20 (29.6)	
3 - 12 times	188 (4.7)	90 (2.5)	98 (24.6)		11 (2.4)	3 (0.8)	8 (12.0)	
> 12 times	81 (2.0)	28 (0.8)	53 (13.4)		9 (2.1)	1 (0.3)	8 (12.4)	
Wheezing after exercise	393 (9.9)	179 (5.0)	215 (53.8)	84.5	68 (14.8)	36 (9.2)	32 (47.1)	50.3
Wheezing after exercise in the last 12m	NA	NA	NA		34 (7.4)	10 (2.6)	24 (34.7)	53.5
Asthma ever	592 (14.8)	333 (9.3)	259 (64.9)	155.9	90 (19.7)	45 (11.5)	45 (66.2)	79.8

Any asthma treatment in the last 12 months	1190 (29.8)	860 (23.9)	330 (82.6)	104.6	77 (16.8)	34 (8.7)	43 (63.2)	87.0
Any corticosteroid treatment in the last 12 months	NA	NA	NA	NA	57 (12.5)	16 (4.1)	41 (60.5)	83.0
Any corticosteroid treatment in the last 24 months	621 (15.6)	327 (9.1)	294 (73.6)	160.5	NA	NA	NA	NA
Asthma onset before 2 years of age	359 (9.0)	207 (5.8)	152 (38.1)	34.7	46 (10.1)	30 (7.8)	16 (23.4)	12.9
Bronchitis or Bronchiolitis ever	929 (23.3)	701 (19.5)	229 (57.3)	63.5	105 (23.0)	85 (21.7)	20 (30.1)	2.2
Emergency visit or hospital admission due to wheezing, breathlessness or asthma ever	991 (24.8)	731 (20.3)	260 (65.2)	33.7	148 (32.4)	101 (26.1)	47 (68.7)	35.6
Emergency visit or hospital admission due to wheezing, breathlessness or asthma in the last 12m	NA	NA	NA	NA	35 (7.7)	9 (2.3)	26 (38.8)	46.8
Number of hospital admissions due to wheezing, breathlessness or asthma in the last 12 months, median (P25-P75)	0 (0-0)	0 (0-0)	0.9 (0-1.5)	47.4	0 (0-0)	0 (0-0)	0 (0-0)	19.6
Breathlessness at night (when no cold) ever	NA	NA	NA	NA	216 (47.2)	166 (42.6)	50 (73.5)	20.2
Breathlessness at night (when no cold) in the last 12 months	1507 (37.7)	1218 (33.9)	289 (72.4)	16.7	107 (23.4)	70 (18.0)	37 (54.4)	37.4
Cough at night (when no cold) ever	1006 (25.2)	725 (20.2)	281 (70.4)	86.5	121 (26.6)	91 (23.5)	30 (44.0)	11.7
Sneezing or runny or blocked nose (when no cold) ever	1686 (42.2)	1355 (37.7)	331 (82.8)	93.8	222 (48.5)	176 (45.2)	46 (67.6)	11.1
Sneezing or runny or blocked nose (when	589 (14.8)	337 (9.4)	252 (63.2)	74.0	88 (19.3)	49 (12.6)	39 (57.4)	59.8

no cold) in the last 12 months								
Itchy watery eyes (when no cold) in the last 12 months	260 (6.5)	85 (2.4)	176 (44.1)	157.4	48 (10.5)	19 (4.9)	29 (42.5)	60.2
Allergic rhinitis ever	120 (3.0)	33 (0.9)	87 (21.7)	61.4	53 (11.7)	20 (5.2)	33 (48.8)	72.0
Rhinitis onset before 2 years of age	106 (2.6)	17 (0.5)	89 (22.2)	53.8	7 (1.4)	3 (0.8)	4 (5.1)	4.7
Itchy rash (coming and going for at least six months) ever	1231 (30.8)	1076 (29.9)	155 (38.9)	13.5	188 (41.0)	138 (35.4)	50 (73.5)	30.4
Itchy rash (coming and going for at least six months) in the last 12 months	798 (20.0)	662 (18.4)	136 (34.2)	6.4	96 (21.0)	67 (17.2)	29 (42.6)	20.8
Itchy rash affecting common areas in the last 12 months	697 (17.5)	594 (16.5)	103 (25.9)	4.9	74 (16.2)	49 (12.6)	25 (36.8)	22.5
Frequency of child's sleep disturbed by itchy rash in the last 12 months					NA	NA	NA	NA
No itchy rash in the last 12m	3122 (78.2)	2938 (81.7)	185 (46.3)	95.2				
Never	526 (13.2)	436 (12.1)	91 (22.7)					
< 1 night per week	192 (4.8)	133 (3.7)	59 (14.7)					
One or more nights per week	152 (3.8)	87 (2.4)	65 (16.3)					
Itchy rash onset before 2 years of age	495 (12.4)	414 (11.5)	81 (20.4)	25.1	114 (25.0)	81 (20.9)	33 (48.5)	21.7
Eczema ever	1048 (26.3)	764 (21.3)	284 (71.2)	112.3	132 (28.9)	94 (24.1)	38 (56.4)	26.4
Eczema or atopic dermatitis treatment in the	1172 (29.3)	925 (25.7)	247 (61.8)	28.1	125 (27.3)	89 (22.9)	36 (52.5)	20.2

last 12 months								
Urticaria ever	1318 (33.0)	998 (27.8)	321 (80.4)	165.4	148 (32.4)	116 (29.7)	32 (47.6)	8.1
Food allergy ever	521 (13.1)	242 (6.7)	279 (69.9)	233.1	80 (17.5)	44 (11.3)	36 (53.2)	55.3
Positive to one specific IgE	1438 (36.0)	1119 (31.1)	319 (79.8)	17.0	188 (41.1)	131 (33.7)	56 (83.1)	42.8
FeNO (ppb), median (P25-P75)	NA	NA	NA	NA	7.6 (5.5-11.4)	7.3 (5.2-10.3)	11.6 (7.6-30.1)	34.4
Prebronchodilator FEV_1 (litres), m (SD)	NA	NA	NA	NA	1.7 (0.3)	1.8 (0.3)	1.7 (0.3)	0.3
Prebronchodilator FVC (litres), m (SD)	NA	NA	NA	NA	2.0 (0.3)	2.0 (0.3)	2.1 (0.3)	0.2
Triggers of wheezing: cat	195 (4.9)	39 (1.1)	156 (39.1)	133.1	22 (4.7)	7 (1.7)	15 (22.1)	31.7
Triggers of wheezing: dog	137 (3.4)	17 (0.5)	119 (29.9)	104.2	6 (1.4)	1 (0.4)	5 (7.4)	8.6
Triggers of wheezing: horse	127 (3.2)	13 (0.4)	113 (28.4)	70.3	9 (1.9)	2 (0.4)	7 (10.3)	11.7
Triggers of wheezing: grass	231 (5.8)	48 (1.3)	183 (45.9)	79.7	21 (4.5)	4 (0.9)	17 (25.0)	33.1
Triggers of wheezing: rodent	90 (2.3)	7 (0.2)	83 (20.9)	63.1	NA	NA	NA	NA
Triggers of wheezing: leafing	283 (7.1)	82 (2.3)	201 (50.4)	82.4	NA	NA	NA	NA
Triggers of wheezing: birch	NA	NA	NA	NA	33 (7.3)	5 (1.4)	28 (41.2)	59.1
Triggers of wheezing: food	NA	NA	NA	NA	9 (2.0)	1 (0.3)	8 (11.8)	12.6
Triggers of wheezing: tobacco	NA	NA	NA	NA	6 (1.3)	2 (0.5)	4 (5.9)	7.3
Triggers of wheezing: aromes	NA	NA	NA	NA	2 (0.5)	1 (0.3)	1 (1.5)	1.3
Triggers of wheezing: cold air	NA	NA	NA	NA	36 (7.8)	9 (2.2)	27 (39.7)	61.6

Triggers of wheezing: air pollution	NA	NA	NA	NA	4 (0.8)	2 (0.4)	2 (2.9)	3.2
Triggers of wheezing: exercise	NA	NA	NA	NA	51 (11.1)	17 (4.3)	34 (50.0)	78.8
Triggers of wheezing: psychological strain	NA	NA	NA	NA	2 (0.5)	1 (0.3)	1 (1.5)	1.2
Triggers of wheezing: others	NA	NA	NA	NA	29 (6.4)	24 (6.3)	5 (7.4)	0.1
Triggers of rash: cat	177 (4.4)	36 (1.0)	141 (35.2)	63.0	12 (2.6)	3 (0.7)	9 (13.2)	17.6
Triggers of rash: dog	107 (2.7)	19 (0.5)	88 (22.1)	67.1	5 (1.0)	0 (0.1)	4 (5.9)	NC
Triggers of rash: horse	102 (2.6)	18 (0.5)	84 (21.1)	51.7	4 (0.9)	1 (0.3)	3 (4.4)	5.5
Triggers of rash: grass	185 (4.6)	57 (1.6)	128 (32.1)	85.0	7 (1.4)	1 (0.1)	6 (8.8)	NC
Triggers of rash: rodent	87 (2.2)	5 (0.1)	82 (20.4)	61.1	NA	NA	NA	NA
Triggers of rash: leafing	176 (4.4)	45 (1.3)	130 (32.6)	84.5	NA	NA	NA	NA
Triggers of rash: birch	NA	NA	NA	NA	13 (2.8)	1 (0.2)	12 (17.6)	NC
Triggers of rash: food	NA	NA	NA	NA	18 (4.0)	6 (1.6)	12 (17.6)	24.5
Triggers of rash: psychological strain	NA	NA	NA	NA	5 (1.1)	4 (1.1)	1 (1.5)	0.1
Triggers of rash: respiratory infections	NA	NA	NA	NA	17 (3.8)	5 (1.4)	12 (17.6)	24.9
Triggers of rash: heat	NA	NA	NA	NA	32 (6.9)	21 (5.3)	11 (16.2)	9.6
Triggers of rash: cold temperature	NA	NA	NA	NA	82 (17.9)	54 (13.8)	28 (41.2)	26.4
Triggers of rash: other	NA	NA	NA	NA	17 (3.8)	16 (4.2)	1 (1.5)	1.1
Triggers of rhinitis: cat	225 (5.6)	65 (1.8)	160 (40.2)	108.2	45 (9.8)	15 (3.9)	30 (43.6)	67.3

Triggers of rhinitis: dog	164 (4.1)	30 (0.8)	134 (33.7)	86.0	19 (4.1)	3 (0.8)	16 (23.0)	31.7
Triggers of rhinitis: horse	135 (3.4)	25 (0.7)	110 (27.5)	57.5	16 (3.4)	2 (0.5)	14 (20.1)	25.3
Triggers of rhinitis: grass	284 (7.1)	98 (2.7)	186 (46.6)	101.9	46 (10.0)	20 (5.1)	26 (38.0)	50.9
Triggers of rhinitis: rodent	98 (2.5)	6 (0.2)	92 (23.1)	62.3	NA	NA	NA	NA
Triggers of rhinitis: leafing	406 (10.2)	163 (4.5)	243 (60.8)	149.7	NA	NA	NA	NA
Triggers of rhinitis: birch	NA	NA	NA	NA	66 (14.4)	24 (6.2)	42 (61.3)	94.2
Triggers of rhinitis: food	NA	NA	NA	NA	16 (3.4)	4 (1.0)	12 (17.2)	25.0
Triggers of rhinitis: tobacco	NA	NA	NA	NA	3 (0.6)	0 (0.0)	3 (4.0)	NC
Triggers of rhinitis: aromes	NA	NA	NA	NA	3 (0.6)	1 (0.3)	2 (2.5)	NC
Triggers of rhinitis: cold air	NA	NA	NA	NA	3 (0.7)	0 (0.0)	3 (4.9)	NC
Triggers of rhinitis: air pollution	NA	NA	NA	NA	1 (0.3)	0 (0.0)	2 (2.2)	NC
Triggers of rhinitis: other	NA	NA	NA	NA	17 (3.6)	11 (2.8)	6 (8.2)	4.1
Triggers of food allergy: milk	264 (6.6)	113 (3.1)	151 (37.9)	72.3	21 (4.6)	11 (2.8)	10 (15.1)	14.6
Triggers of food allergy: egg	209 (5.2)	59 (1.6)	149 (37.4)	90.0	10 (2.1)	2 (0.5)	8 (11.5)	15.0
Triggers of food allergy: fish	129 (3.2)	39 (1.1)	90 (22.7)	36.4	4 (0.8)	0 (0.0)	4 (5.4)	NC
Triggers of food allergy: nuts	227 (5.7)	68 (1.9)	159 (39.9)	66.4	35 (7.7)	8 (2.1)	27 (40.1)	62.5
Triggers of food allergy: peanut	229 (5.7)	71 (2.0)	158 (39.6)	86.8	44 (9.7)	17 (4.4)	27 (40.0)	56.0
Triggers of food allergy: soy	117 (2.9)	17 (0.5)	100 (25.2)	63.1	6 (1.4)	2 (0.5)	4 (6.5)	7.6

Triggers of food allergy: banana	59 (1.5)	8 (0.2)	51 (12.8)	26.4	8 (1.8)	1 (0.3)	7 (10.4)	12.0
Triggers of food allergy: pea	117 (2.9)	22 (0.6)	95 (23.7)	60.0	NA	NA	NA	NA
Triggers of food allergy: flour, wheat	67 (1.7)	14 (0.4)	53 (13.4)	46.4	3 (0.6)	1 (0.3)	2 (2.9)	2.6
Triggers of food allergy: stonefruits	230 (5.8)	62 (1.7)	168 (42.2)	136.7	NA	NA	NA	NA
Triggers of food allergy: citrus	255 (6.4)	141 (3.9)	114 (28.6)	24.6	NA	NA	NA	NA
Triggers of food allergy: chocolate	174 (4.4)	64 (1.8)	110 (27.6)	28.5	NA	NA	NA	NA
Triggers of food allergy: peach	NA	NA	NA	NA	22 (4.9)	1 (0.3)	21 (31.3)	24.9
Triggers of food allergy: shellfish	NA	NA	NA	NA	7 (1.6)	1 (0.3)	6 (9.4)	11.0
Triggers of food allergy: apple	NA	NA	NA	NA	34 (7.3)	2 (0.5)	32 (46.4)	46.5
Triggers of food allergy: kiwi	NA	NA	NA	NA	36 (7.9)	6 (1.5)	30 (44.6)	66.8
Triggers of food allergy: avocado	NA	NA	NA	NA	8 (1.7)	0 (0.0)	8 (11.6)	NC
Triggers of food allergy: carrot	NA	NA	NA	NA	24 (5.3)	3 (0.8)	21 (31.0)	40.3
Triggers of food allergy: other	493 (12.4)	317 (8.8)	176 (44.2)	50.0	26 (5.7)	15 (3.9)	11 (16.5)	12.5
Missing school in the last 12 months due to wheezing, breathlessness, asthma, rhinitis, itchy rash, eczema or food allergy	NA	NA	NA	NA	32 (7.0)	13 (3.3)	19 (27.9)	38.3
Weight (kg), m (SD)	18.3 (3.4)	18.4 (2.7)	17.7 (8.7)	2.6	29.7 (5.3)	29.7 (5.3)	29.6 (4.9)	0.0
Height (cm), m (SD)	106.1 (5.5)	106.3 (4.9)	104.7 (14.0)	4.7	131.1 (6.0)	131.3 (6.1)	130.2 (5.5)	1.9

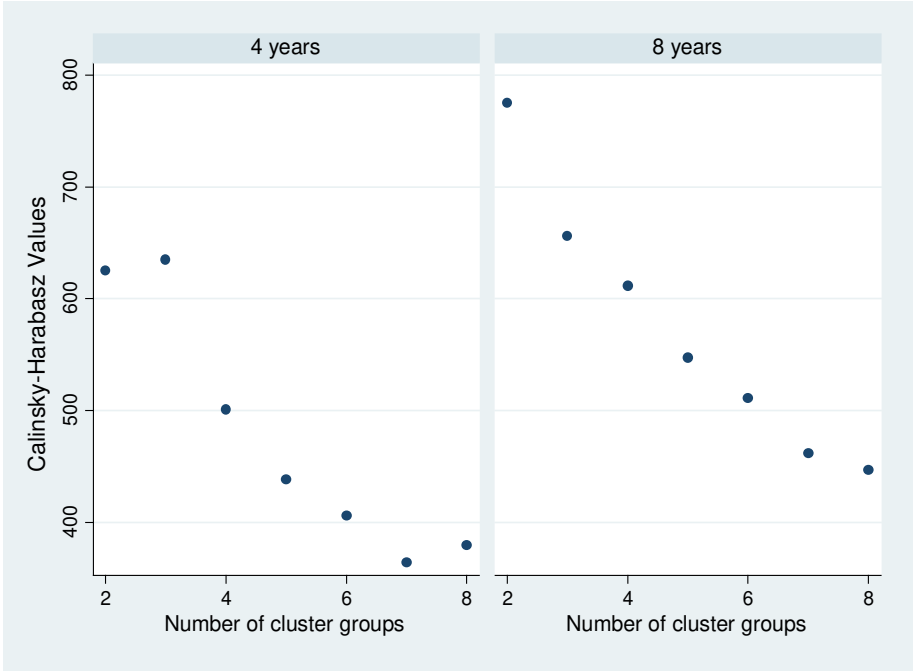
NA: Not available. NC: Not computable.

* F values correspond to the ratio of the variance of the group means (between-group variance) over the overall variance of the variable (higher values meaning higher relevance of the variable for separating cluster groups), and were obtained by means of linear regression models using each variable as the outcome, and the cluster group as the exposure.

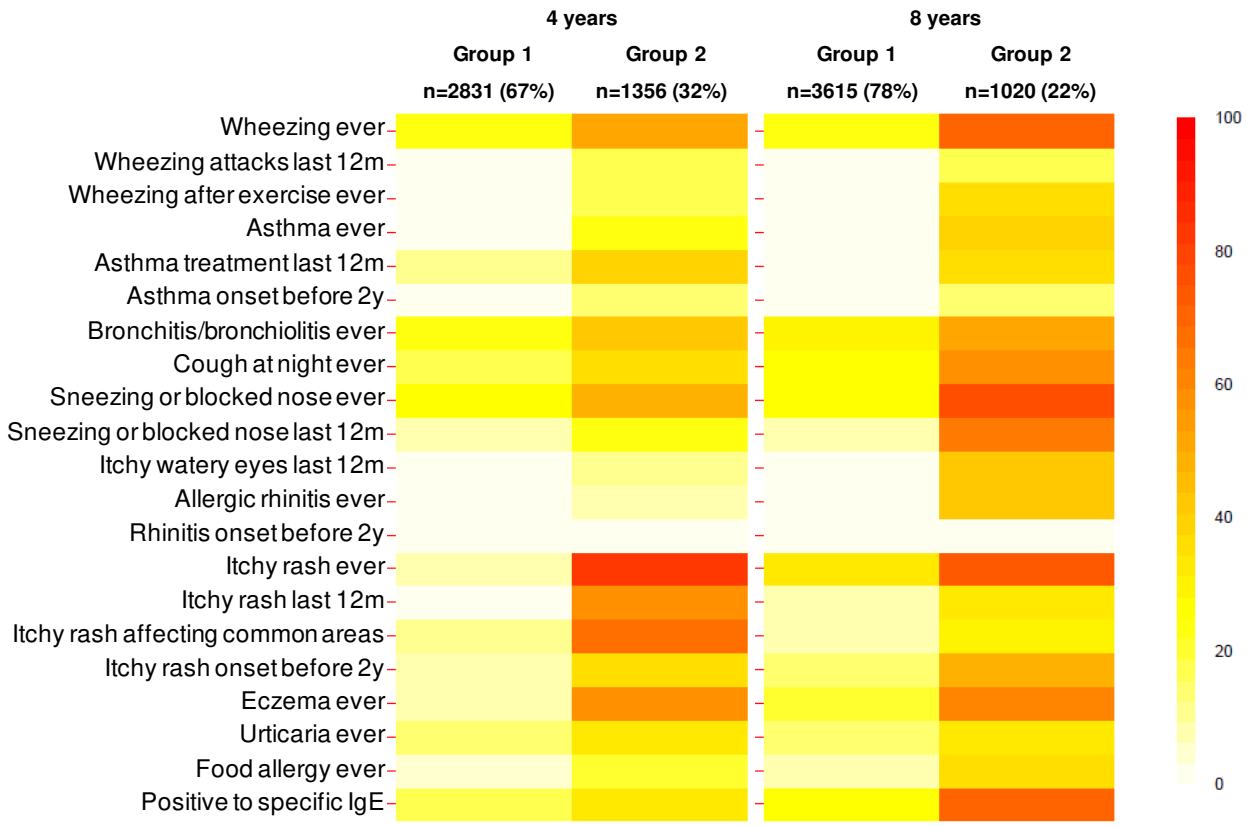
SENSITIVITY ANALYSIS V—evaluate multiple imputation

Figure E20. Distribution of Calinsky-Harabasz stopping rule* and graphical description† of the two groups identified by cluster analysis at 4 and 8 years, after stratifying according to the number of missings

No missing values

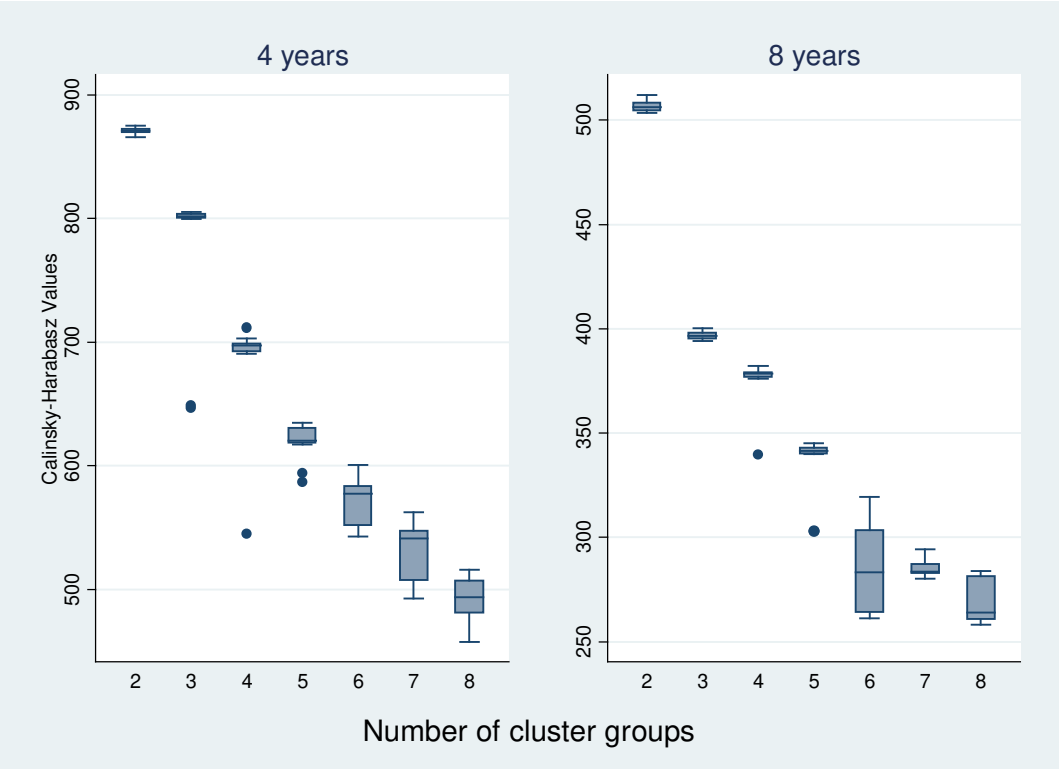


* Higher values indicate higher separation between groups and similarity within groups.

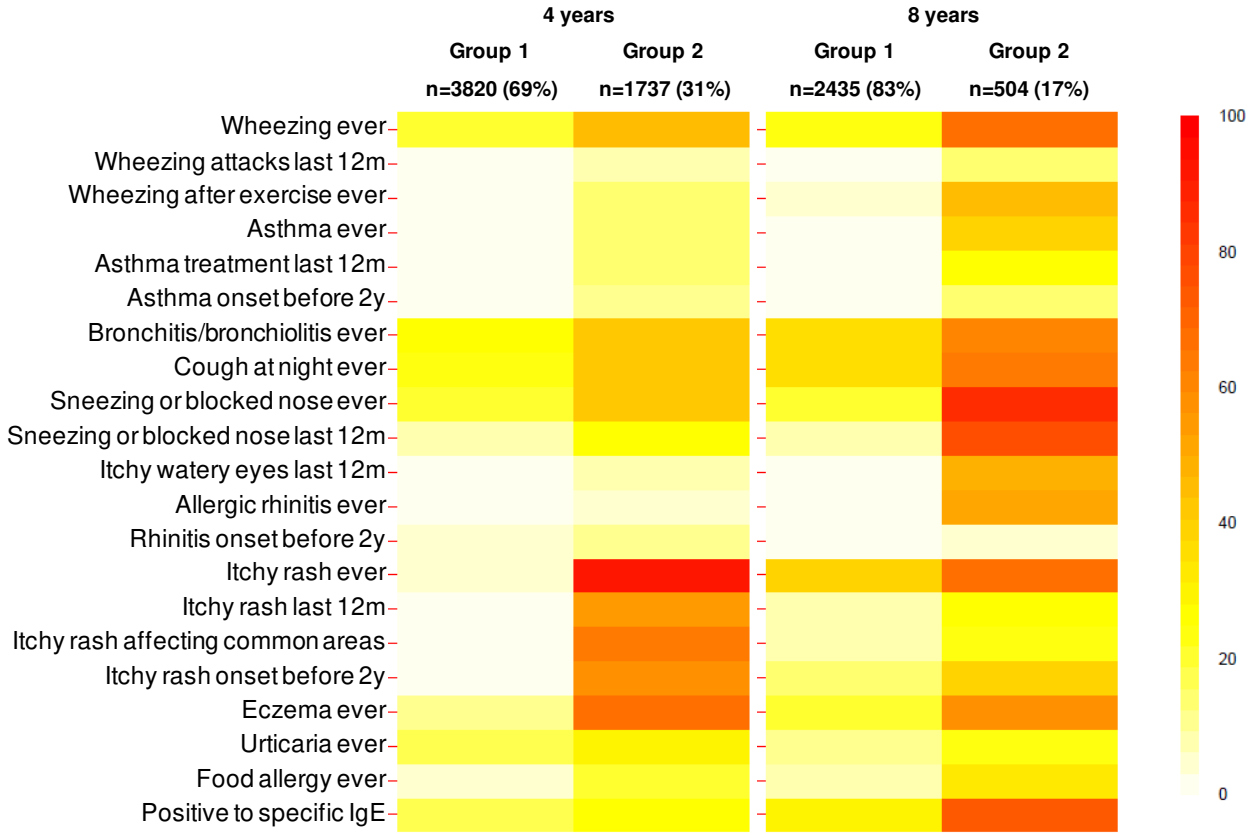


† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

One missing value

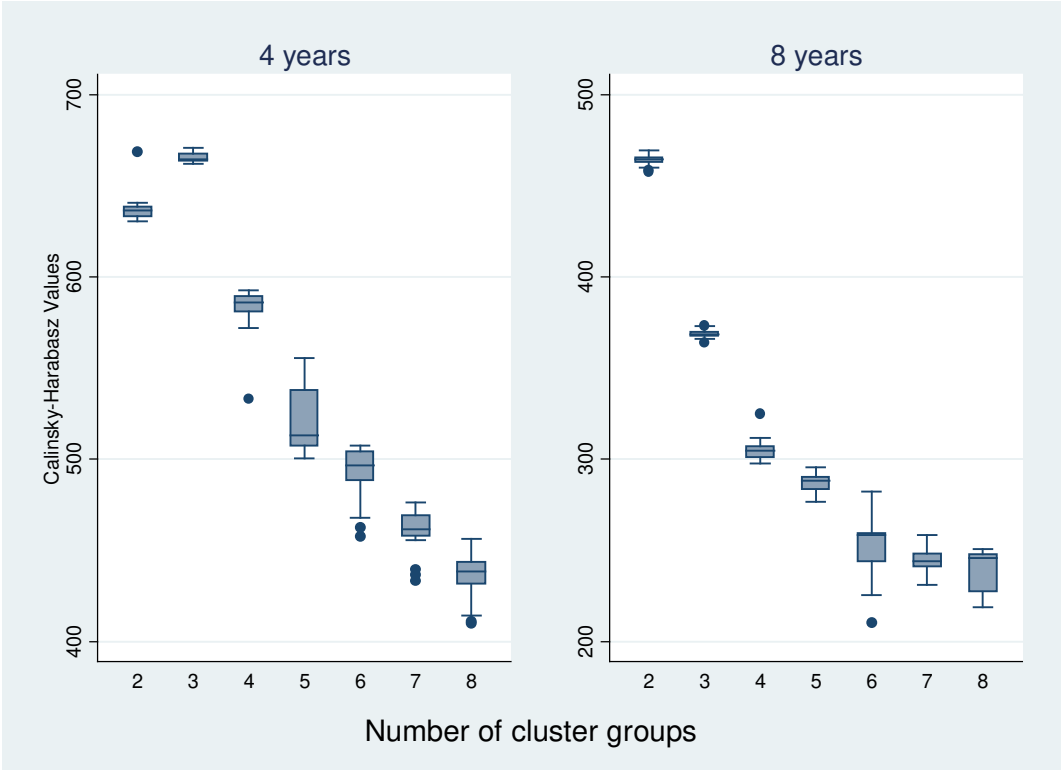


* Higher values indicate higher separation between groups and similarity within groups.

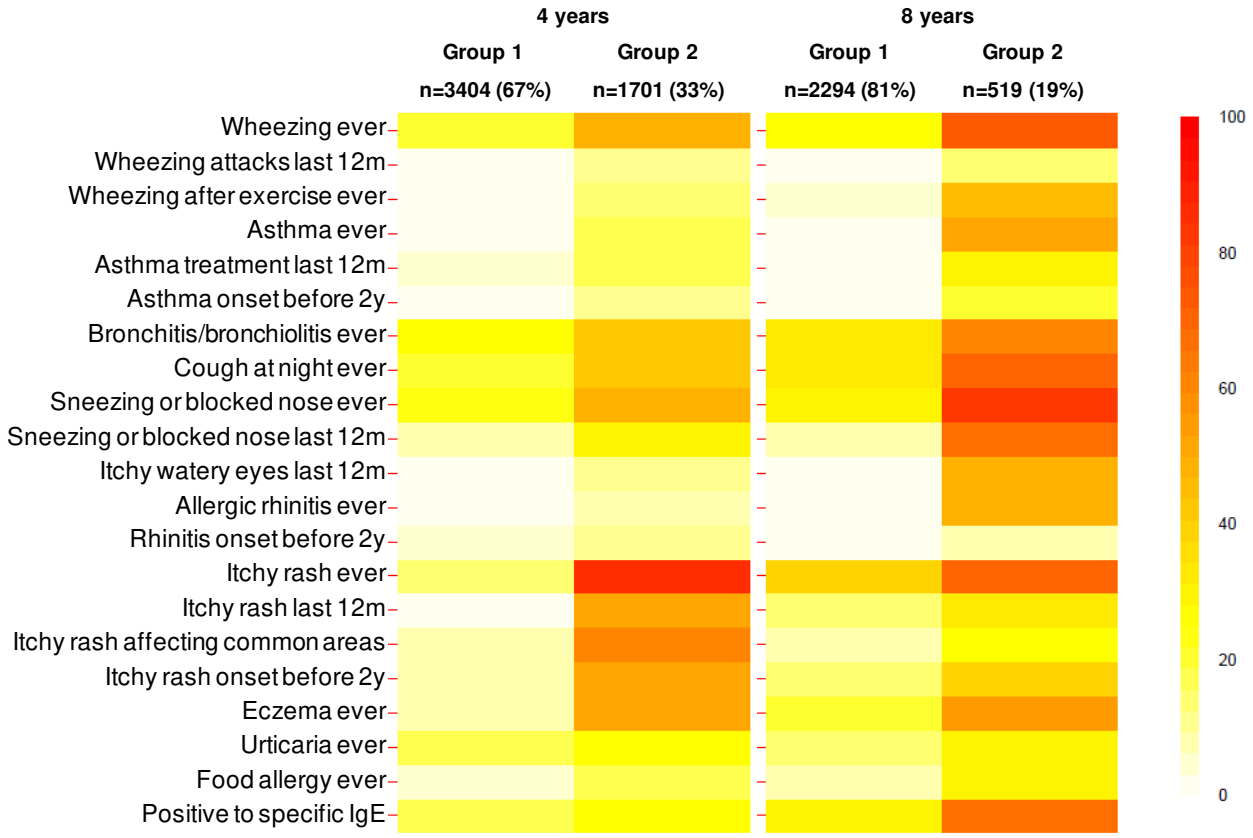


† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

Two or three missing values



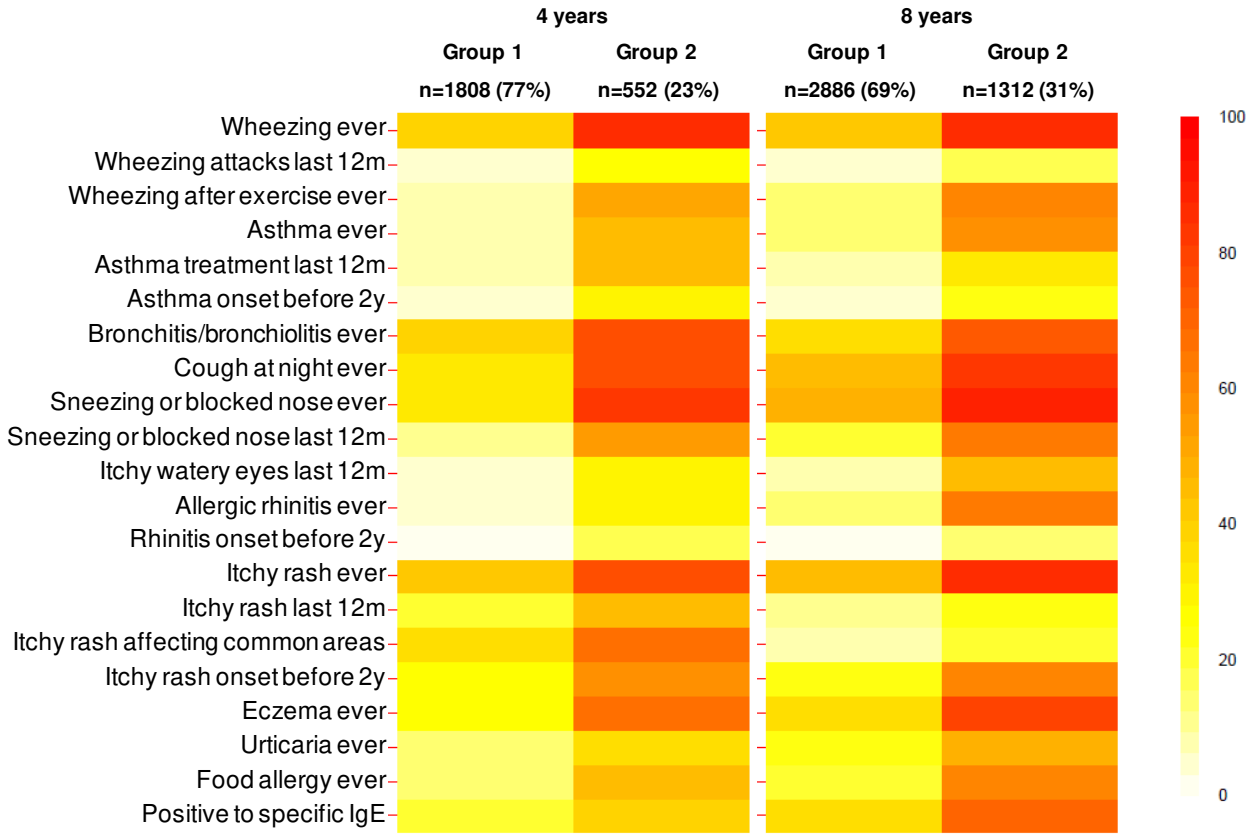
* Higher values indicate higher separation between groups and similarity within groups.



† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

Four or more missing values

* Higher values indicate higher separation between groups and similarity within groups.



† Each coloured line represents a variable, whose prevalence ranges from 0% (white colour) to 100% (red colour).

33 **Table E19. Description of the two groups identified by cluster analysis at 4 and 8 years after stratifying according to the number of missings**

4 years	No missing values		1 missing value		2–3 missing values		≥4 missing values	
	Group 1	**Group 2**	**Group 1**	**Group 2**	**Group 1**	**Group 2**	**Group 1**	**Group 2**
	N=2831 (67.6)	**N=1356 (32.4)**	**N=3820 (68.7)**	**N=1737 (31.3)**	**N=3404 (66.7)**	**N=1701 (33.3)**	**N=1808 (76.6)**	**N=552 (23.4)**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Wheezing ever	636 (22.5)	707 (52.1)	802 (21.0)	789 (45.4)	724 (21.3)	803 (47.2)	701 (38.8)	479 (86.8)
Wheezing attacks in the last 12 months								
None	2696 (95.2)	930 (68.6)	3715 (97.3)	1417 (81.6)	3274 (96.2)	1354 (79.6)	1646 (91.1)	275 (49.8)
1 - 3 times	128 (4.5)	253 (18.7)	92 (2.4)	201 (11.6)	119 (3.5)	231 (13.6)	123 (6.8)	143 (25.9)
4 - 12 times	7 (0.3)	134 (9.9)	11 (0.3)	98 (5.7)	10 (0.3)	90 (5.3)	31 (1.7)	100 (18.2)
> 12 times	0 (0)	39 (2.9)	2 (0.1)	20 (1.2)	1 (0.0)	26 (1.5)	7 (0.4)	33 (6.1)
Wheezing after exercise ever	67 (2.4)	237 (17.5)	79 (2.1)	251 (14.4)	56 (1.7)	257 (15.1)	121 (6.7)	277 (50.3)
Asthma ever	31 (1.1)	305 (22.5)	65 (1.7)	269 (15.5)	74 (2.2)	295 (17.3)	115 (6.4)	256 (46.4)
Asthma treatment in the last 12 months	293 (10.3)	513 (37.8)	80 (2.1)	251 (14.5)	132 (3.9)	283 (16.6)	140 (7.8)	244 (44.2)
Asthma onset before 2 years of age	19 (0.7)	209 (15.4)	37 (1.0)	181 (10.4)	42 (1.2)	195 (11.5)	70 (3.9)	170 (30.9)
Bronchitis or Bronchiolitis ever	680 (24.0)	558 (41.2)	1037 (27.1)	734 (42.2)	912 (26.8)	733 (43.1)	713 (39.4)	428 (77.5)
Cough at night (when no cold) ever	464 (16.4)	501 (36.9)	839 (22.0)	709 (40.8)	692 (20.3)	724 (42.5)	602 (33.3)	417 (75.6)
Sneezing or runny or blocked nose (when no cold) ever	778 (27.5)	654 (48.2)	748 (19.6)	750 (43.2)	806 (23.7)	821 (48.2)	593 (32.8)	457 (82.7)
Sneezing or runny or blocked nose (when no cold) in the last 12 months	201 (7.1)	315 (23.2)	272 (7.1)	439 (25.3)	228 (6.7)	505 (29.7)	218 (12.1)	295 (53.4)
Itchy watery eyes (when no cold) in the	45 (1.6)	158 (11.7)	28 (0.7)	153 (8.8)	29 (0.8)	187 (11.0)	62 (3.4)	169 (30.6)

last 12 months								
Allergic rhinitis ever	24 (0.8)	87 (6.4)	39 (1.0)	106 (6.1)	23 (0.7)	150 (8.8)	62 (3.4)	157 (28.4)
Rhinitis onset before 2 years of age	17 (0.6)	37 (2.7)	170 (4.5)	204 (11.8)	139 (4.1)	160 (9.4)	49 (2.7)	99 (18.0)
Itchy rash (coming and going for at least six months) ever	238 (8.4)	1120 (82.6)	230 (6.0)	1579 (90.9)	477 (14.0)	1455 (85.5)	766 (42.4)	426 (77.1)
Itchy rash (coming and going for at least six months) in the last 12 months	16 (0.6)	785 (57.9)	28 (0.7)	944 (54.4)	95 (2.8)	874 (51.4)	369 (20.4)	243 (44.0)
Itchy rash affecting common areas	343 (12.1)	928 (68.4)	118 (3.1)	1129 (65.0)	227 (6.7)	1061 (62.4)	641 (35.5)	373 (67.5)
Itchy rash onset before 2 years of age	184 (6.5)	497 (36.7)	107 (2.8)	1005 (57.8)	258 (7.6)	888 (52.2)	474 (26.2)	322 (58.3)
Eczema ever	247 (8.7)	796 (58.7)	377 (9.9)	1151 (66.3)	306 (9.0)	870 (51.1)	495 (27.4)	373 (67.5)
Urticaria ever	412 (14.6)	434 (32.0)	611 (16.0)	513 (29.5)	537 (15.8)	430 (25.3)	274 (15.2)	192 (34.8)
Food allergy ever	110 (3.9)	292 (21.5)	170 (4.5)	329 (19.0)	133 (3.9)	318 (18.7)	242 (13.4)	255 (46.3)
IgE sensitisation	443 (15.6)	436 (32.2)	646 (16.9)	483 (27.8)	569 (16.7)	468 (27.5)	349 (19.3)	218 (39.4)
Weight (kg), m (SD)	17.6 (2.3)	17.7 (2.4)	16.8 (2.4)	16.5 (2.5)	17.0 (2.9)	16.8 (3.1)	17.2 (3.0)	16.8 (4.0)
Height (cm), m (SD)	105.0 (4.8)	104.9 (4.9)	103.3 (5.7)	102.3 (6.3)	103.9 (6.6)	103.2 (6.9)	104.5 (6.2)	103.0 (8.9)

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8 years	No missing values		1 missing value		2–3 missing values		≥4 missing values	
	Group 1	**Group 2**	**Group 1**	**Group 2**	**Group 1**	**Group 2**	**Group 1**	**Group 2**
	N=3615 (78.0)	**N=1020 (22.0)**	**N=2435 (82.8)**	**N=504 (17.2)**	**N=2294 (81.5)**	**N=519 (18.5)**	**N=2886 (68.7)**	**N=1312 (31.3)**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Wheezing ever	826 (22.8)	711 (69.7)	546 (22.4)	346 (68.6)	594 (25.9)	388 (74.8)	1221 (42.3)	1135 (86.5)
Wheezing attacks in the last 12 months								
None	3552 (98.3)	664 (65.1)	2403 (98.7)	340 (67.4)	2256(98.3)	360 (69.3)	2682 (92.9)	855 (65.2)
1 - 3 times	59 (1.6)	233 (22.8)	30 (1.2)	113 (22.4)	38(1.7)	108 (20.7)	143 (5.0)	282 (21.5)
4 - 12 times	2 (0.1)	93 (9.1)	1 (0.0)	42 (8.4)	0 (0)	41 (7.8)	45 (1.6)	133 (10.2)
> 12 times	2 (0.1)	30 (2.9)	1 (0.0)	9 (1.8)	0 (0)	11 (2.1)	16 (0.6)	42 (3.2)
Wheezing after exercise ever	105 (2.9)	381 (37.4)	107 (4.4)	236 (46.8)	95 (4.1)	241 (46.4)	394 (13.6)	788 (60.0)
Asthma ever	112 (3.1)	413 (40.5)	46 (1.9)	203 (40.3)	67 (2.9)	266 (51.2)	394 (13.6)	743 (56.6)
Asthma treatment in the last 12 months	56 (1.5)	370 (36.3)	8 (0.3)	130 (25.9)	29 (1.3)	158 (30.4)	190 (6.6)	429 (32.7)
Asthma onset before 2 years of age	44 (1.2)	139 (13.6)	13 (0.5)	75 (14.9)	35 (1.5)	110 (21.3)	171 (5.9)	292 (22.2)
Bronchitis or Bronchiolitis ever	1038 (28.7)	512 (50.2)	838 (34.4)	311 (61.7)	731 (31.9)	323 (62.3)	1060 (36.7)	947 (72.2)
Cough at night (when no cold) ever	930 (25.7)	578 (56.7)	838 (34.4)	329 (65.4)	749 (32.7)	363 (70.0)	1300 (45.0)	1101 (83.9)
Sneezing or runny or blocked nose (when no cold) ever	980 (27.1)	793 (77.7)	475 (19.5)	439 (87.0)	699 (30.5)	432 (83.2)	1399 (48.5)	1175 (89.6)
Sneezing or runny or blocked nose (when no cold) in the last 12 months	241 (6.7)	656 (64.3)	158 (6.5)	385 (76.4)	189 (8.2)	347 (66.9)	564 (19.5)	860 (65.6)

Itchy watery eyes (when no cold) in the last 12 months	30 (0.8)	444 (43.5)	16 (0.7)	246 (48.9)	19 (0.8)	244 (47.0)	252 (8.7)	593 (45.2)
Allergic rhinitis ever	77 (2.1)	415 (40.7)	42 (1.7)	259 (51.4)	46 (2.0)	245 (47.3)	399 (13.8)	842 (64.2)
Rhinitis onset before 2 years of age	12 (0.3)	24 (2.4)	2 (0.1)	18 (3.5)	7 (0.3)	46 (8.9)	60 (2.1)	176 (13.4)
Itchy rash (coming and going for at least six months) ever	1205 (33.3)	734 (72.0)	958 (39.3)	344 (68.3)	874 (38.1)	364 (70.2)	1334 (46.2)	1108 (84.4)
Itchy rash (coming and going for at least six months) in the last 12 months	316 (8.7)	336 (32.9)	227 (9.3)	136 (27.0)	302 (13.2)	171 (33.0)	348 (12.1)	289 (22.1)
Itchy rash affecting common areas	227 (6.3)	288 (28.2)	162 (6.6)	119 (23.7)	206 (9.0)	143 (27.6)	265 (9.2)	246 (18.8)
Itchy rash onset before 2 years of age	506 (14.0)	485 (47.5)	312 (12.8)	200 (39.7)	314 (13.7)	209 (40.2)	632 (21.9)	819 (62.5)
Eczema ever	765 (21.2)	626 (61.4)	513 (21.1)	289 (57.4)	450 (19.6)	289 (55.8)	1062 (36.8)	1055 (80.4)
Urticaria ever	559 (15.5)	348 (34.1)	250 (10.3)	117 (23.2)	321 (14.0)	159 (30.6)	653 (22.6)	637 (48.5)
Food allergy ever	274 (7.6)	366 (35.9)	187 (7.7)	158 (31.3)	162 (7.1)	153 (29.5)	582 (20.2)	818 (62.4)
IgE sensitisation	912 (25.2)	722 (70.8)	719 (29.5)	372 (73.8)	650 (28.3)	347 (66.8)	1025 (35.5)	933 (71.1)
Weight (kg), m (SD)	31.2 (6.0)	31.6 (6.3)	31.9 (6.8)	32.7 (7.1)	32.5 (8.1)	33.1 (7.6)	33.0 (8.7)	34.4 (9.8)
Height (cm), m (SD)	135.8 (7.8)	136.3 (8.3)	138.4 (8.5)	138.9 (8.4)	138.0 (9.0)	138.9 (9.4)	138.8 (10.5)	141.3 (11.6)

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