Comorbidity of eczema, rhinitis, and asthma in IgE-sensitised and non-IgE-sensitised children in MeDALL: a population-based cohort study

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Summary

Background Eczema, rhinitis, and asthma often coexist (comorbidity) in children, but the proportion of comorbidity not attributable to either chance or the role of IgE sensitisation is unknown. We assessed these factors in children aged 4–8 years.

Methods In this prospective cohort study, we assessed children from 12 ongoing European birth cohort studies participating in MeDALL (Mechanisms of the Development of ALLergy). We recorded current eczema, rhinitis, and asthma from questionnaires and serum-specific IgE to six allergens. Comorbidity of eczema, rhinitis, and asthma was defined as coexistence of two or three diseases in the same child. We estimated relative and absolute excess comorbidity by comparing observed and expected occurrence of diseases at 4 years and 8 years. We did a longitudinal analysis using log-linear models of the relation between disease at age 4 years and comorbidity at age 8 years.

Findings We assessed 16 147 children aged 4 years and 11 080 aged 8 years in cross-sectional analyses. The absolute excess of any comorbidity was 1·6% for children aged 4 years and 2·2% for children aged 8 years; 44% of the observed comorbidity at age 4 years and 50·0% at age 8 years was not a result of chance. Children with comorbidities at 4 years had an increased risk of having comorbidity at 8 years. The relative risk of any cormorbidity at age 8 years ranged from 36·2 (95% CI 26·8–48·8) for children with rhinitis and eczema at age 4 years to 63·5 (95% CI 51·7–78·1) for children with asthma, rhinitis, and eczema at age 4 years. We did longitudinal assessment of 10 107 children with data at both ages. Children with comorbidities at 4 years without IgE sensitisation had higher relative risks of comorbidity at 8 years than did children who were sensitised to IgE. For children without comorbidity at age 4 years, 38% of the comorbidity at age 8 years was attributable to the presence of IgE sensitisation at age 4 years.

Interpretation Coexistence of eczema, rhinitis, and asthma in the same child is more common than expected by chance alone—both in the presence and absence of IgE sensitisation—suggesting that these diseases share causal mechanisms. Although IgE sensitisation is independently associated with excess comorbidity of eczema, rhinitis, and asthma, its presence accounted only for 38% of comorbidity, suggesting that IgE sensitisation can no longer be considered the dominant causal mechanism of comorbidity for these diseases.

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Introduction

Although widely acknowledged, coexisting disorders in patients with chronic diseases (comorbidity) are still underexplored.[1] The coexistence of several diseases in the same person could be a result of chance, selection bias, or causation.[2] If chance and bias can be excluded, the remaining excess comorbidity can be ascribed to causal relationships between the coexisting diseases. A network topology-based approach assessing the connections between pairs of diseases (comorbidity) and enzyme-encoding genes has been proposed to gain insight into the shared pathophysiology of coexisting diseases.[3] Better understanding of how common risk factors interact with shared pathophysiological pathways affecting comorbidity could inform prevention and treatment of common chronic diseases.[1] The prevalence of allergy-related diseases such as eczema, rhinitis, and asthma has reached epidemic proportions in high-income countries.[4] An important feature of this rise is that these diseases coexist in many children[5]—termed allergic or atopic comorbidity. For example, in the ISAAC study,[6] almost 15% of asthmatic children aged 6–7 years and 40% of those aged 13–14 years also had allergic rhinitis.[6] A study of 3778 pairs of 7-year-old children matched to their siblings suggests that eczema in infancy might cause hay fever in patients with asthma.[7] A unifying hypothesis—the atopic march—states that atopic disorders progress sequentially, from eczema in infants to rhinitis and asthma in children, suggesting that atopy could be a common link[8] although the evidence

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that allergic comorbidity is more common in IgE-sensitised children[9,10] has not been confirmed by other studies.[11] However, no previous studies have assessed how much of the comorbidity of eczema, rhinitis, and asthma is attributable to chance or to causal determinants,[2] which could have led to erroneous assumptions about allergic comorbidity. A better understanding of comorbidity of eczema, rhinitis, and asthma could help to improve prediction and care of such diseases during childhood. Several predictive indices have been proposed for childhood asthma, but none have been developed for comorbidity of asthma, eczema, and rhinitis. Yet, early treatment is paramount to minimise symptoms and increase quality of life.

As part of the Mechanisms of the Development of ALLergy (MeDALL) project,[12,13] we used data from a large network of birth cohorts in Europe to assess the excess comorbidity of eczema, rhinitis, and asthma in children aged 4 years and 8 years, and the role of IgE-mediated sensitisation. We postulated that comorbidity will be more common than would be expected if these diseases were independent.

Methods

Study design and participants

This study is based on information and samples obtained from 12 longitudinal birth cohorts in eight European countries (Denmark, France, Germany, Italy, Netherlands, Norway, Spain, Sweden).[12] AMICS–Menorca,[14] BAMSE,[5] DARC,[9] ECA,[15] GINIplus,[16] LISAplus,[17] MAS,[18] and PIAMA[19] recruited children between 1990 and 1998, whereas EDEN,[20] Paris,[21] ROBBIC–Rome,[22] and ROBBIC–Bologna[22] included children from 2003 to 2006. Most studies recruited unselected population-based birth cohorts. Five cohorts (BAMSE, GINIplus, LISAplus, MAS, and PIAMA) were urban, especially in metropolitan areas, whereas the others recruited children from urban and rural backgrounds.[9,15–24] We pooled the available data for two age periods: 4 years (ranging from 3 to 5 years) and 8 years (ranging from 8 to 10 years). We used these ages because most allergic diseases develop early in life or in the preschool period.[25]

Each cohort included between 368 and 5991 children, with an overall population of 23 434. We excluded children who were not followed up at either 4 years or 8 years and those with data missing. In all participating cohorts, parents gave written informed consent and the studies were approved by local ethics review boards.

Procedures

We assessed current eczema, current rhinitis, and current asthma with questionnaires. Definitions were agreed by a panel of experts—members of MeDALL and invited external participants—using a modified version of the GA2LEN questionnaire[26] to define current asthma and ISAAC questions[27] to define current rhinitis and current eczema. Consensus about application of the MeDALL definitions was reached through discussions by a panel of coauthors (IA-M, XB, MB, JG-A, SG, CH, FK, TK, MKe, MKo, GHK, IK, EM, IM, MP, DSP, HAS, RTS, JS, MW, JB, and JMA; see appendix for further details).[28]

Comorbidity of eczema, rhinitis, and asthma was defined as the coexistence of two or three of these diseases in the same child. For the main analysis, we considered seven possible exclusive conditions: three single diseases (eczema, rhinitis, and asthma), three combinations of two diseases, and the triad.

The allergens assessed and techniques used varied for each cohort. We identified six allergens for which we considered information from each cohort to be equivalent (house dust mite, cat dander, birch pollen, grass pollen, milk, and egg). We defined sensitisation as having a specific IgE concentration of 0·35 kU_A/L (1 kU_A/L=2·4 µg/L) or greater in serum against at least one of these allergens. We recorded small differences between percentages of sensitised children detected with all available serum-specific IgEs and those detected with the limited panel. To have comparable information for these allergens in all birth cohorts, we harmonised house dust mite and grass pollen (see appendix for details).

We defined parental history of allergy as maternal or paternal history of asthma, allergic rhinitis, hay fever, or eczema; symptoms of asthma, allergic rhinitis, hay fever, or eczema; or food allergy or other allergies to pets or house dust mites.

Additional information was collected for potential confounders or effect modifiers associated with eczema, rhinitis, and asthma in childhood, including a cohort-specific indicator, socioeconomic status, maternal and paternal smoking during pregnancy, maternal and paternal smoking ever, and sex (appendix).

Statistical analysis

The analysis included a cross-sectional component and a longitudinal component. The cross-sectional analysis consisted of an assessment of comorbidity at age 4 years and 8 years overall and stratified by IgE sensitisation. We estimated relative excess comorbidity as the ratio of the observed to the expected comorbidity and we calculated absolute excess comorbidity by subtracting the percentage of expected comorbidity from the percentage of observed comorbidity. We derived the expected frequencies of the occurrence of each disease and their combinations (asthma, rhinitis, eczema, asthma and rhinitis, asthma and eczema, rhinitis and eczema, and asthma and rhinitis and eczema), assuming that the diseases were independent and using a binomial distribution with the null hypothesis of independence between diseases. The observed frequencies at age 4 years was 7·49 for eczema, 4·24 for rhinitis, and 15·8 for asthma (appendix). We first derived the expected frequency of having all three diseases by multiplying the observed frequencies of eczema, rhinitis, and asthma.

Second, we derived the expected frequencies of pairs of diseases as the product of their respective observed frequencies minus the expected frequency of all three. Finally, we obtained the expected frequencies of the individual diseases as its observed frequency minus the expected frequencies of the pairwise combinations minus the expected frequency of all three. Observed and expected frequencies were both obtained for the overall population and separately for each cohort and age period. We also assessed the extent to which the observed comorbidity departed from the expected comorbidity if no causal relation existed between diseases by plotting standardised residuals of Pearson's χ^2 test.

No sample size calculations are available for comparison between expected and observed cases. For the longitudinal assessment we calculated the sample size with GRANMO (version 7.12).[29] We assumed that 20% of children would have at least one of the three allergies and that the incidence of comorbidity for healthy participants at baseline was 1·5%. We calculated that 3920 children would need to be followed up to assess whether the relative risk for having comorbidity at age 8 years in children with one or two diseases at age 4 years (at baseline) was significant, with an α of 0·05 and a β risk of 0·2 for a two-sided test.

The longitudinal analysis included children aged 4 years at baseline and aged 8 years at follow-up with the exception of two cohorts that included children aged 10 years. This analysis was done to assess the effect of multiple diseases at age 4 years on the presence of comorbidity (as an aggregate category) at age 8 years, using pooled log-linear regression models for the overall population and stratified by IgE sensitisation. Potential confounders—cohort, socioeconomic status, maternal and paternal smoking during pregnancy, maternal and paternal smoking ever, age at follow-up, and sex—were tested by bivariate tables with both the outcome and the exposure variables; these confounders were considered for adjustment if they were related to the outcome or the exposure variables with a p value less than 0·20. Confounders were not included in the final models because they were not independently related to both the exposure and the outcome, nor modified (>10% change in relative risk) the estimates for the remaining variables (appendix).[30]

We estimated the effect of serum-specific IgE sensitisation at age 4 years on the occurrence of comorbidity at 8 years through the population attributable risk (PAR): PAR=p×(RR–1)/(p×[RR–1]+1), where p is the probability of IgE sensitisation at age 4 years and RR is an estimate of the assocation between IgE sensitisation at age 4 years and the incidence of comorbidity by age 8 years for children who did not have a comorbidity at age 4 years. The PAR can be interpreted as the proportion of children with comorbidity at 8 years that could have been avoided if IgE sensitisation at 4 years had been absent, assuming that the relation between IgE sensitisation and comorbidity is causal.

We did sensitivity analyses to assess: the robustness of the findings and to avoid misclassification bias by increasing the specificity of specific IgE categorisation (≥0·70 kU_A/L and ≥3·5 kU_A/L), the effect of parental history of asthma and allergic diseases, and the effect of heterogeneity among birth cohorts by cohort-specific models and meta-analysis. We used multiple imputation of missing values by chained equations to assess the robustness of the results to missing data and to minimise the loss of statistical power caused by missing data.[31] We used Stata 12 and R for all analyses (appendix).

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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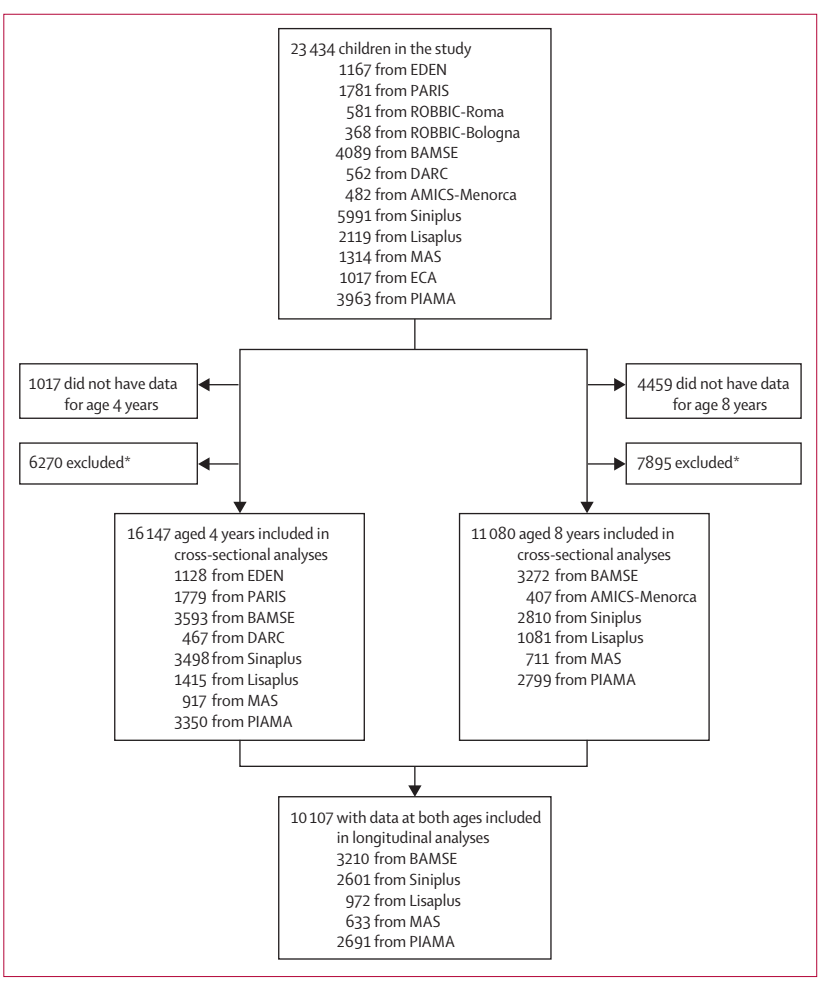

Figure 1: **Study participants**
LISAplus data were restricted to children recruited in Munich, Wesel, and Bad Honnef. *Did not have the requested variables for the definition of asthma, rhinitis, or eczema, alone and combined.

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See Online for appendix

	4 years		8 years	
	Participants (n=16 147)	Missing and non-responders (n=6270)	Participants (n=11 080)	Missing and non-responders (n=7895)
Allergy-related diseases				
None	12 385/16 147 (76·7%)	NA	8685/11 080 (78·3%)	NA
Asthma only	790/16 147 (4·9%)	NA	363/11 080 (3·3%)	NA
Rhinitis only	342/16 147 (2·1%)	NA	653/11 080 (5·9%)	NA
Eczema only	2037/16 147 (12·6%)	NA	893/11 080 (8·1%)	NA
Asthma and rhinitis	79/16 147 (0·5%)	NA	175/11 080 (1·6%)	NA
Asthma and eczema	250/16 147 (1·5%)	NA	120/11 080 (1·1%)	NA
Rhinitis and eczema	174/16 147 (1·1%)	NA	117/11 080 (1·1%)	NA
Asthma, rhinitis, and eczema	90/16 147 (0·6%)	NA	74/11 080 (0·7%)	NA
Age (months)	46·1 (5·4)	48·0 (4·6)	106·5 (12·1)	117·5 (14·9)
Girls	7843/16 147 (48·6%)	2983/6109 (48·8%)	5454/11 080 (49·2%)	3664/7733 (47·4%)
IgE (kU_A/L)				
<0·35	5772/7177 (80·4%)	1049/1272 (82·5%)	4107/6490 (63·3%)	1281/1945 (65·9%)
0·35–0·69	423/7177 (5·9%)	50/1272 (3·9%)	399/6490 (6·1%)	125/1945 (6·4%)
0·70–3·49	532/7177 (7·4%)	100/1272 (7·9%)	571/6490 (8·8%)	157/1945 (8·1%)
≥3·50	450/7177 (6·3%)	73/1272 (5·7%)	1413/6490 (21·8%)	382/1945 (19·6%)
Socioeconomic status				
Low	1887/16 044 (11·8%)	569/3836 (14·8%)	1245/11 007 (11·3%)	848/5129 (16·5%)
Medium	6980/16 044 (43·5%)	1805/3836 (47·1%)	5322/11 007 (48·4%)	2279/5129 (44·5%)
High	7177/16 044 (44·7%)	1462/3836 (38·1%)	4440/11 007 (40·3%)	2002/5129 (39·0%)
Maternal history of asthma	1450/15 982 (9·1%)	579/5983 (9·7%)	1014/10 968 (9·3%)	727/7585 (9·6%)
Paternal history of asthma	1380/15 824 (8·7%)	454/5848 (7·8%)	883/10 856 (8·1%)	629/7445 (8·5%)
Maternal history of allergic diseases	6394/15 956 (40·1%)	2445/6113 (40·0%)	4442/10 944 (40·6%)	3305/7715 (42·8%)
Paternal history of allergic diseases	5616/15 804 (35·5%)	2079/5937 (35·0%)	4072/10 833 (37·6%)	2747/7568 (36·3%)
Maternal smoking during pregnancy	2368/15 952 (14·8%)	1136/5017 (22·6%)	1578/10 931 (14·4%)	1480/6606 (22·4%)
Paternal smoking during pregnancy	4014/9069 (44·3%)	1866/3647 (51·2%)	3185/7281 (43·7%)	2037/3341 (61·0%)
Maternal smoking	1830/9026 (20·3%)	985/2321 (42·4%)	1081/5238 (20·6%)	1064/2102 (50·6%)
Paternal smoking	2609/9031 (28·9%)	1041/2309 (45·1%)	1235/5170 (23·9%)	1073/2058 (52·1%)

Data are n/N (%) or mean (SD). Missing and non-responders includes children with missing data for the variables requested for the definition of diseases and children who did not participate in the corresponding follow-up (see appendix for numbers of children with data missing for each variable). NA=not applicable.

Table 1: **Characteristics of participants at age 4 and 8 years**

Results

The study population consisted of 16 147 children aged 4 years (mean 46·1 months, SD 5·4) and 11 080 aged 8 years (mean 106·5, SD 12·1), of whom 10 107 had information available at both ages (figure 1, table 1). Generally, excluded children with missing data at ages 4 years and 8 years tended to be older, of medium or low socioeconomic status, and with higher parental smoking than participants (table 1). At both ages, excluded children were also less likely to be sensitised to IgE than were children included in the analyses (table 1). Most of the absolute differences—with the exception of parental smoking—were small (table 1) and unlikely to account for our results.

593 of 16 147 (3·7%) children aged 4 years and 486 of 11 080 (4·4%) aged 8 years had comorbidity (figure 2A). Comorbidity was more common in IgE-sensitised children at both ages compared with children without IgE sensitisation (figure 2B, 2C). When the observed and expected prevalences of each disease were compared at 4 years and 8 years, both absolute and relative co-morbidity were more common than would be expected by chance alone (figure 2D, 2G). The relative excess comorbidity was statistically significant (appendix) except for rhinitis and eczema at age 8 years. The absolute excess of any comorbidity was 1·6% (3·7% observed *vs* 2·1% expected) for children aged 4 years and 2·2% (4·4% observed *vs* 2·2% expected) for children aged 8 years (figure 2G). These data show that 43·7% of the observed comorbidity at age 4 years and 50% at age 8 years is not attributable to chance.

The proportion of children with at least one of the three diseases who were sensitised to IgE ranged from 30 (9·2%) of 326 children from the PARIS cohort to 42 (28·2%) of 149 children from the MAS cohort for participants aged 4 years and from 200 (30·4%) of 657 children from the PIAMA cohort to 80 (53·7%) of 149 children from the MAS cohort aged 8 years (appendix).

The pattern of comorbidity differed between children with and without IgE sensitisation to common allergens

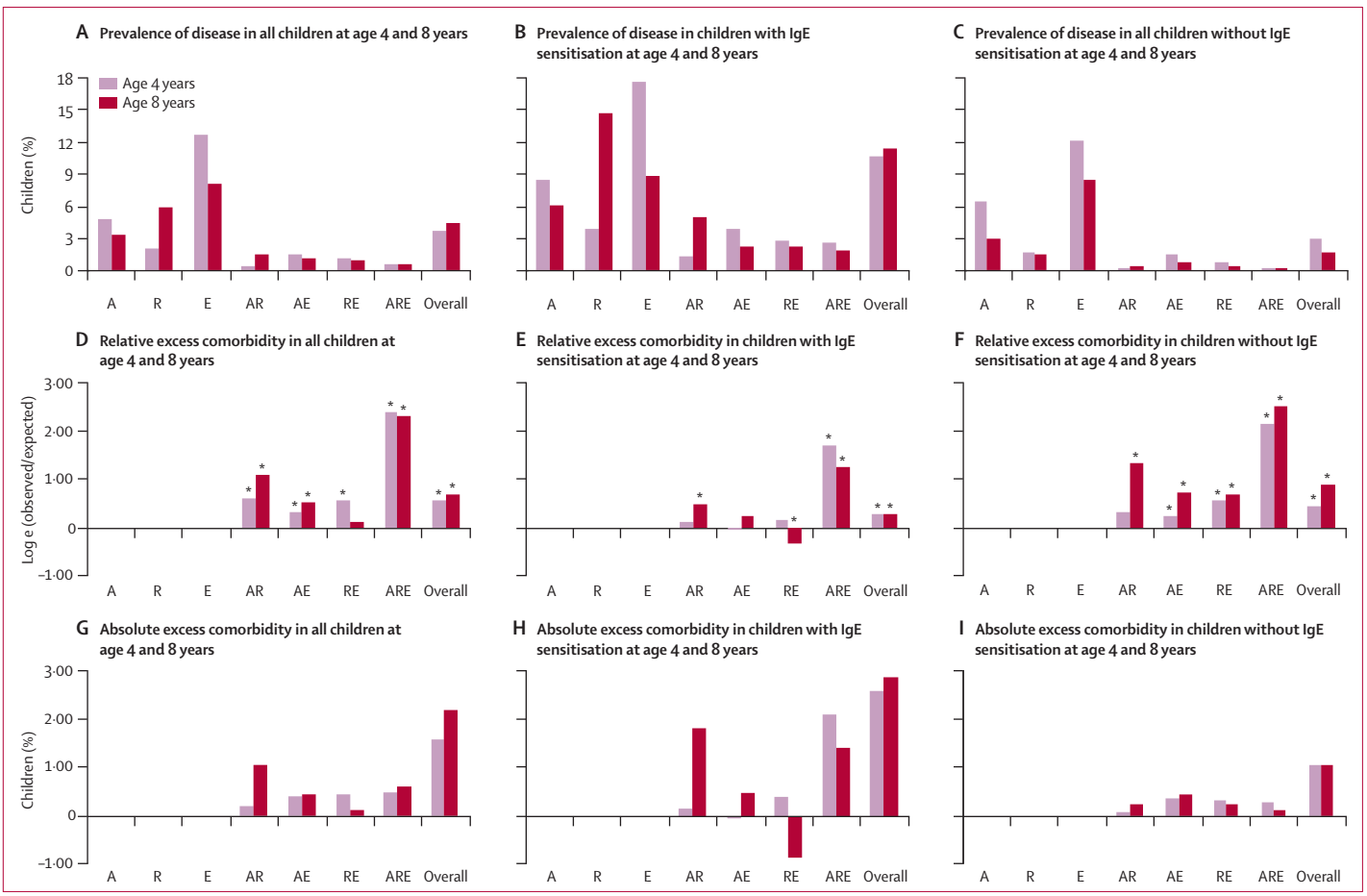

Figure 2: **Prevalence, relative excess comorbidity, and absolute excess comorbidity for children aged 4 years and 8 years**
A=asthma. R=rhinitis. E=eczema. *Statistically significant for relative excess morbidity analysis (p<0·05).

for both the relative excess comorbidity, which assesses the strength of the association between the three diseases, and the absolute excess comorbidity, which assesses the magnitude of the comorbidity (figure 2B, 2C, 2E, 2F, 2H, 2I). Those with IgE sensitisation had a small relative excess comorbidity, with the only significant increase for asthma and rhinitis at age 8 years and for asthma, rhinitis, and eczema at both ages (figure 2E), whereas those children without IgE sensitisation had significantly high relative excess comorbidity for all comorbidities except asthma and rhinitis at age 4 years (figure 2F). Although the overall relative excess comorbidity was significant for children both with and without IgE sensitisation, the differences for relative excess risks for the combined diseases suggests that the strength of the association between the three diseases is higher in the absence of IgE sensitisation.

By contrast, absolute excess comorbidity was higher in those with IgE sensitisation than in those without: absolute excess of overall comorbidity was 2·6% at age 4 years and 2·9% at age 8 years, mainly a result of asthma and rhinitis at age 8 years and asthma, rhinitis, and eczema at both ages (figure 2H). Of those without IgE sensitisation, overall absolute excess comorbidity was 1% at both ages with a similar contribution from all comorbidities (figure 2I). The pattern of absolute excess comorbidity suggests that the magnitude of excess comorbidity is higher in children with IgE sensitisation than in those without.

We analysed the longitudinal pattern of comorbidity for 10 107 children with data at both ages. The relative risk of comorbidity at age 8 years ranged from 36·2 (95% CI 26·8–48·8) for children with rhinitis and eczema at age 4 years to 63·5 (95% CI 51·7–78·1) for children with asthma, rhinitis, and eczema at age 4 years (table 2). When we included IgE sensitisation as a covariate, it was associated with comorbidities at 8 years (RR 3·5, 95% CI 2·7–4·6), suggesting that IgE sensitisation at age 4 years is an independent contributor to comorbidity at 8 years. However, when the longitudinal model was stratified by specific IgE sensitisation, the RRs were substantially higher for children without IgE sensitisation (table 2). Assuming

	All children (N=8366)*			Children with IgE sensitisation (N=1587)			Children without IgE sensitisation (N=3423)		
	n at 4 years	n at 8 years (%)	RR (95% CI)	n at 4 years	n at 8 years (%)	RR (95% CI)	n at 4 years	n at 8 years (%)	RR (95% CI)
None	6839	102 (1·5%)	1	1128	60 (5·3%)	1	2910	18 (0·6%)	1
Asthma only	316	59 (18·7%)	12·5 (9·3–16·9)	84	35 (41·7%)	7·8 (5·5–11·2)	133	12 (9·0%)	14·6 (7·2–29·7)
Rhinitis only	110	28 (25·5%)	17·1 (11·7–24·8)	36	16 (44·4%)	8·4 (5·4–13·0)	40	5 (12·5%)	20·2 (7·9–51·8)
Eczema only	859	85 (9·9%)	6·6 (5·0–8·8)	224	46 (20·5%)	3·9 (2·7–5·5)	296	13 (4·4%)	7·1 (3·5–14·4)
Asthma and rhinitis	34	22 (64·7%)	43·4 (31·7–59·4)	15	13 (86·7%)	16·3 (11·9–22·4)	6	2 (33·3%)	53·9 (15·9–182·8)
Asthma and eczema	107	65 (60·8%)	40·7 (31·9–52·1)	45	34 (75·6%)	14·2 (10·6–19·1)	27	10 (37·0%)	59·9 (30·5–117·5)
Rhinitis and eczema	63	34 (54·0%)	36·2 (26·8–48·8)	32	19 (59·4%)	11·2 (7·7–16·3)	8	6 (75·0%)	121·3 (65·9–223·2)
Asthma, rhinitis, and eczema	38	36 (94·7%)	63·5 (51·7–78·1)	23	23 (100%)	19·7 (15·4–25·2)	3	2 (66·7%)	107·8 (42·8–271·3)

RR=relative risk. The log-linear models included children who had two or three diseases and those who had none at age 8 years. Children with one disease at 8 years were excluded from the model. *3356 children had no information available for serum-specific IgE test results.

***Table 2*: Risk of comorbidity at age 8 years according to presence of disease at 4 years by log–linear models**

	n (%; N=4579)	RR (95% CI)
Allergic diseases at age 4 years		
None	3485 (76·1%)	1 (reference)
Asthma only	354 (7·7%)	7·0 (4·7–10·4)
Rhinitis only	93 (2·0%)	7·4 (4·2–13·0)
Eczema only	647 (14·1%)	4·3 (3·0–6·3)
IgE sensitisation at age 4 years		
No	3667 (80·1%)	1 (reference)
Yes	912 (19·9%)	4·1 (3·0–5·6)

Children with comorbidities at age 4 years were excluded. Only children with available IgE at 4 years were included.

***Table 3*: Risk of comorbidities at age 8 years for children without comorbidity at 4 years by multivariate log–linear model**

a prevalence of IgE sensitisation at 4 years of 912 of 4579 (19·9%) and an RR of 4·1 (95% CI 3·0–5·6) for IgE sensitisation (table 3), we obtained a PAR of 0·38, indicating that only 38% of the incidence of comorbidity at age 8 years is attributable to the presence of IgE sensitisation.

We did sensitivity analyses with imputed datasets, which led to very similar results (appendix). The longitudinal association between comorbidity at age 4 years and comorbidity at age 8 years using higher cutoffs for stratification of IgE sensitisation, maternal and paternal asthma, and parental history of allergies, and after combining serum-specific IgE and total IgE did not change, thus confirming our results (appendix), although the proportion of children with comorbidity of eczema, rhinitis, and asthma at age 8 years increased (appendix). We did meta-analyses of log-linear models to ascertain the heterogeneity between birth cohorts in the longitudinal analysis (appendix). Although heterogeneity existed, all RRs for comorbidities were large and statistically significant and the overall dose–response pattern was maintained in the largest cohorts (appendix).

Discussion

We have shown that eczema, rhinitis, and asthma coexist in the same children both at age 4 and 8 years more often than would have been expected if these diseases were independent and that the presence of comorbidity at age 4 years is a strong determinant of comorbidity at age 8 years, suggesting the existence of causal relationships between these diseases. To our knowledge, this study is the first to show that excess comorbidity of eczema, rhinitis, and asthma is present in children both with and without IgE sensitisation, as well as in children with and without parental history of allergies, suggesting that both IgE-mediated and non-IgE-mediated mechanisms are probably involved in their causal relationships. This study is also the first to show that the tendency of these diseases to overlap is stronger in children without IgE sensitisation than in those with IgE sensitisation, as shown by both relative excess comorbidity and RRs, suggesting that IgE sensitisation can no longer be considered the dominant causal mechanism of comorbidity of eczema, rhinitis, and asthma (panel).

Before ascribing our results to a causal association, chance and bias should be excluded. Regarding chance, despite our large sample size, we had few cases for some of the comorbidities after stratification by IgE sensitisation, particularly for children without sensitisation to IgE. Replication of our results and pooling with other cohorts could provide more robust estimation of the pattern of comorbidity among children with and without IgE sensitisation. Allergic diseases were classified on the basis of questionnaires and we had to harmonise requested variables to build a pooled database. Although the diseases we studied were defined by symptom-based questionnaires which could lead to misclassification, well-established international definitions[33] were agreed on by a MeDALL expert panel.[28] Unfortunately, the available information did not enable us to assess other phenotypes such as episodic viral wheeze and multitrigger wheeze,[34] which have rarely been used in birth cohort studies. We assumed

that misclassification of asthma and episodic viral wheeze would not have differed between children with and without comorbidities. A particular difficulty arises if the classification error for one of the diseases (eg, underdiagnosis of rhinitis) depends on the presence or absence of the other diseases or their surrogates (eg, underdiagnosis of asthma), leading to differential misclassification. Our opinion is that such differential misclassification could have occurred in our study—children with one disease have frequent contact with medical care and so are more likely to be diagnosed with another disease. However, whether the differential misclassification biased the results is unknown; the bias caused by differential misclassification can either exaggerate or underestimate the associations being studied.[35] In any case, bias caused by differential misclassification is unlikely to account for all of the excess risk of comorbidity we detected for five reasons: (1) the large magnitude of the excess comorbidity and associations, (2) the use of validated questionnaires, (3) minimisation of random variability and selection bias by use of a large pooled analysis, (4) the negligible role of confounding, and (5) the existence of experimental and epidemiological evidence supporting a real causal association between asthma, rhinitis, and eczema.

Data were missing for many children, probably as a result of the large number of variables requested coupled with non-response rates. However, for most variables, the absolute differences between included and excluded participants were small and unlikely to account for our results (table 1). Despite the large sample size, only 10 107 children from five birth cohorts had complete data without missing values for both ages, which is insufficient to longitudinally model all possible multiple diseases as outcomes. For this reason, we assessed comorbidity as an aggregate category of multiple diseases at age 8 years. Our study was sufficiently powered to analyse comorbidity as an aggregate category. The analysis with imputed datasets (table 2) enabled us to assess the effect of missing data and to increase the statistical power, which was especially important in the stratified analyses (appendix). The RRs were stable in the log–linear models with imputed data. Other potentially important limitations such as misclassification of IgE sensitisation and heterogeneity between birth cohorts were assessed in the sensitivity analysis, which provided very similar results to the main analysis (appendix).

Our study had several strengths. The prospective design enabled us to do both cross-sectional and longitudinal analyses. We did not do power calculations for the comparison between expected and observed frequencies, other than using the general rule of a minimum of five observations per cell, which was exceeded by far in our study both for the overall and IgE-stratified analyses. Finally, the cohorts included children with mixed rural and urban background and pooling data resulted in good coverage of Europe's population, strengthening the external validity of our results.

We are unaware of any previous study that assessed both the relative and absolute excess comorbidity of eczema, rhinitis, and asthma. Our results show that eczema, rhinitis, and asthma coexist in the same children aged both 4 years and 8 years more often than would be expected by chance. Furthermore, the presence of multiple diseases at age 4 years is a strong determinant of the presence of comorbidity at age 8 years. Most previous studies have relied on only observed comorbidity without considering the degree of comorbidity expected by chance (ie, comorbidity that would be present even if the diseases were independent). In our study, the excess comorbidity that was not a result of chance was only about half of the observed comorbidity, suggesting that previous estimations of comorbidity are probably inflated. Venn diagrams, which have often been used to depict the degree

Panel: Research in context

Systematic review

We searched PubMed from inception to July 16, 2013, with the term: "asthma" AND "rhinitis" AND "eczema OR dermatitis" AND (coexist*[tiab] OR co–exist*[tiab]) OR ((comorbidity[tiab]) OR (comorbidity[MeSH Terms])). We filtered the search to children aged 0–18 years only. We retrieved 94 citations, of which we excluded eight reviews and 16 reports published in languages other than English. Most of these final 70 studies assessed comorbidities of children with rhinitis, eczema, or asthma, or were focused on sequential progression of multiple allergic conditions. Several studies[5,32] described the prevalence of comorbidity and concluded that allergic comorbidity is common, thus supporting the hypothesis that eczema, rhinitis, and asthma are inter-related and should not be regarded as separate diseases. However, none of the studies assessed the overall pattern of excess comorbidity between eczema, rhinitis, and asthma against the null hypothesis of independence including the role of IgE sensitisation. Because they did not estimate which proportion of the observed allergic comorbidities could be attributable to chance or to causal determinants,[2] they might be based on erroneous assumptions about allergic comorbidity.

Interpretation

Our analysis has shown that eczema, rhinitis, and asthma coexist in the same child at both age periods more often than would be expected if these diseases were independent. Furthermore, the presence of comorbidity at age 4 years was strongly associated with the presence of comorbidity at age 8 years in a dose–response manner, thus increasing our confidence of the existence of causal mechanisms among these diseases. This relation was present in children with and without IgE sensitisation and in the presence or absence of parental history of allergies, suggesting that in addition to IgE other non-IgE-mediated mechanisms are probably involved in the causal relationships.

of comorbidity, do not provide information about excess comorbidity and therefore should be interpreted with caution. Although abundant, most previous evidence about comorbidity has been focused on a limited number of pair-wise relationships, mainly between asthma and rhinitis or between asthma and eczema. A study of the MAS cohort showed that allergic rhinitis in preschool children is a predictor of subsequent onset of wheezing.[36] In the CAPS cohort, children with atopic eczema were more likely than were those without atopic eczema to have a history of food allergies, allergic rhinitis, and current wheeze.[37] Similarly, in the ECA study children with rhinitis at age 10 years were much more likely to have asthma, atopic eczema, and food allergy than children without rhinitis.[38] Our study has taken the evidence one step further by longitudinally modelling the overall pattern of comorbidity of eczema, rhinitis, and asthma.

Our study provides information about the role of IgE sensitisation in allergic comorbidity during childhood. Absolute excess comorbidity was larger among children with IgE sensitisation and the independent association between serum-specific IgE at age 4 years and the development of comorbidity at age 8 years strongly supports the role of serum-specific IgE sensitisation in comorbidity of eczema, rhinitis, and asthma. The population attributable risk of IgE sensitisation was 38%. This finding suggests that, assuming that all the association between specific IgE sensitisation and comorbidity was causal, a maximum of 38% of comorbidity at age 8 years would have been avoided if those children had not been sensitised to IgE. However, of children with IgE sensitisation, only around a quarter of the observed comorbidity was not a result of chance at both ages, whereas the corresponding numbers for children without IgE sensitisation were 34·8% for those aged 4 years and 58·3% for those aged 8 years. Clarification about whether IgE sensitisation is causally related to comorbidity, or a result of reverse causation or other related factors will need much more focused research.

Our study has shown that excess comorbidity also occurs in the absence of IgE sensitisation or parental history of allergies. By contrast with IgE-sensitised children, those without IgE sensitisation had a more consistent pattern of relative excess comorbidity at both ages, which suggests that the tendency of eczema, rhinitis, and asthma to aggregate is not totally dependent on IgE sensitisation or parental history of allergies. Our results are consistent with a recent study[11] showing that children with allergic and non-allergic rhinitis have a similar risk of asthma, a finding also reported in adults.[39] By contrast with previous studies,[36,37,39] the dose–response pattern of comorbidity between the ages of 4 and 8 years was more consistent and stronger in children without IgE sensitisation than in those with IgE sensitisation, suggesting that—in agreement with data for asthma[40]—the importance of IgE sensitisation and atopy as a unifying explanation for comorbidity of eczema, rhinitis, and asthma has been overemphasised.[41] Thus, more research is needed to investigate the non-IgE-mediated mechanisms of comorbidity of eczema, rhinitis, and asthma.[42]

Overall, excess comorbidity can be broadly attributed to different causal mechanisms involving disease-to-disease causation or shared environmental or genetic risk factors.[2] Two hypotheses—the atopic march[8] and the unified airways disease[43]—have attempted to explain allergic comorbidities and are both directly or indirectly supported by our results. IgE sensitisation could either induce or perpetuate comorbidities and a different set of genes might be involved in the progression of comorbidity. Among the more than 100 genes that are associated with asthma, several are also associated with other allergic diseases.[44–47] Loss-of-function mutations in the filaggrin gene (*FLG*) have been suggested to have a role in the atopic march,[48] although filaggrin null-mutations do not modify the association between allergic rhinitis and asthma or eczema.[11] Most previous studies have investigated eczema, rhinitis, and asthma independently, in search of more specific sub-phenotypes of each disease, which is a useful approach. However, our results suggest that excess comorbidity of eczema, rhinitis, and asthma is the result of phenotypical interrelationships between these diseases and that an integrated approach including all three diseases should be also considered. The use of new approaches—eg, network topology[2] and systems biology[13]—could help unravel the inter-relationships between these diseases and improve diagnostic and control strategies.

Finally, although around 50% of the allergic comorbidity in children was attributable to chance, the frequency of absolute excess comorbidity of eczema, asthma, and rhinitis is large, affecting 1·6% children aged 4 years and 2·2% of those aged 8 years. Our study provides additional evidence for the design and implementation of health-care strategies to manage comorbidity of allergic diseases similar to those developed by ARIA[49] and the Royal College of Paediatrics and Child Health Standards in the UK.[50] Our results could also inform the management of children with these diseases, helping practitioners to realise that children with eczema, asthma, or rhinitis only are at risk of developing the other conditions irrespective of their IgE status. The study provides new information about the natural course of single diseases and comorbidities and might enable existing predictive indices of allergic diseases (eg, asthma[51,52]) to be improved by incorporating the new information about comorbidities into refined predictive models. Finally, our findings suggest that interventions for one of these diseases could prevent or improve the others, and that assessment of the effects of pharmacological interventions on comorbidities is necessary.[53]

Contributors

MP wrote the initial draft with supervision of JMA. JMA, JG-A, SG, JS, XB, and MP interpreted the findings. MB prepared the common database and did statistical analyses. JL did statistical analysis. IA-M (EDEN), CB-J,

EE (DARC), JH, SK, CGT (GINI and LISA), CH, SL, TK (MAS), IK, EM, MW (BAMSE), IM, FR, JJ (PARIS), UG, MKo, HAS, AHW (PIAMA), DP (ROBBIC–Rome), MPF (ROBBIC–Bologna), KCLC, K-HC (ECA), and MT (AMICS–Menorca) provided data. All authors provided comments, participated in the critical revision of the article, and approved the final version.

Conflicts of interest

The University of Groningen has received money for DSP for an unrestricted educational grant for research from AstraZeneca and Chiesi. DSP's travel to European Respiratory Society and American Thoracic Society meetings has been partially funded by AstraZeneca, Chiesi, GlaxoSmithKline, and Nycomed. Fees for consultancies for DSP were given to the University of Groningen by Astra Zeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Nycomed, and TEVA. Travel and lectures in China were paid for DSP by Chiesi. The other authors declare that they have no conflicts of interest.

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