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Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS

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Abstract

Background: The occurrence of allergic multimorbidity (coexistence of asthma, allergic rhinitis and eczema) has not been evaluated longitudinally from early childhood up to adulthood in a population-based study sample. We aimed to determine the prevalence of allergic multimorbidity up to age 20 stratified by parental allergies and sex/gender using extensive prospective follow-up data from two decades of a birth cohort study.

Methods: In 1990, we recruited 1314 healthy newborns from 6 maternity wards across Germany for the population-based MAS birth cohort study. The sample was purposely risk-enriched by increasing the proportion of children at high allergy risk (i.e. at least 2 allergic family members among parents and siblings) from 19% in the source population to 38% in the final sample. The remaining 62% of all MAS children had a low or no allergy risk. Symptoms, medication and doctor's diagnoses of allergic diseases have been assessed using standardized questionnaires including validated ISAAC questions in 19 follow-up assessments up to age 20. Allergic multimorbidity at each time point was defined as the coexistence of at least 2 of the following diseases in one participant: asthma, allergic rhinitis and eczema.

Results: Response at age 20 was 72% (n = 942) of all recruited participants. At age 20, 18.5% (95% CI, 15.0–22.5%) of all participants with allergic parents had 2 or 3 concurrent allergies as compared to only 6.3% (95% CI, 4.3–9.0%) of those with non-allergic parents. At this age, allergic multimorbidity was similar in women and men (12.7% (95% CI, 9.7–16.2%) vs. 11.6% (95% CI, 8.9–14.8%)), whereas single allergic diseases were slightly more common in women than men (24.2% (95% CI, 20.2–28.5%) vs. 20.1% (95% CI, 16.6–24.0%)). Asthma occurred more frequently with coexisting allergic rhinitis and/or eczema than as a single entity from pre-puberty to adulthood.

Conclusion: Having parents with allergies is not only a strong predictor to develop any allergy, but it strongly increases the risk of developing allergic multimorbidity. In males and females alike, coexisting allergies were increasingly common throughout adolescence up to adulthood. Particularly asthma occurred in both sexes more frequently with coexisting allergies than as a single entity.

The past several decades have seen an increase in the prevalence of allergic diseases among children and teenagers across the world with the highest prevalence being observed in Anglo-American countries (1–4). Although a number of birth and child cohort studies have been initiated to better understand this high prevalence, research has been almost exclusively on single allergic entities (5–11). The coexistence of asthma, allergic rhinitis and eczema has rarely been specifically targeted in longitudinal investigations. Few prospective cohort studies have looked at allergic multimorbidity such as asthma and concurrent rhinitis or asthma and concurrent eczema but mostly in early childhood and never beyond 12 years of age (12–16). Ballardini et al. found in the Swedish BAMSE cohort that coexisting allergies occurred more often in school rather than in preschool children (12). Analyses of combined European birth cohort data by the EU-funded MeDALL consortium showed that the coexistence of asthma, rhinitis and eczema in the same child at age 4 and 8 was more prevalent than expected by chance alone, suggesting that these diseases share common mechanisms (17). Latent class analyses of UK birth cohort data identified temporal patterns of coexisting allergies up to age 11 (18). The progression of these coexisting conditions into adolescence and adulthood and the influence of parental allergies or sex/gender have not yet been studied. Therefore, the purpose of the current analysis was to investigate the prevalence of current allergic multimorbidity throughout childhood and adolescence up to age 20 stratified by parental allergies and by sex/gender using the comprehensive prospective follow-up data from two decades of a German birth cohort study.

Methods

MAS-90 study participants

The German Multicentre Allergy Study began with the recruitment of 1314 newborns between January and December 1990 in maternity wards from university hospitals in 5 German cities – Berlin, Düsseldorf, Freiburg, Mainz and Munich – and has been described in detail elsewhere (19) including follow-up methods (7). The MAS birth cohort was risk-enriched with 38% (n = 499) 'high-risk' children, defined as having two immediate family members (parents or siblings) with asthma, allergic rhinitis or eczema, or an elevated cord blood immunoglobulin E (IgE) ≥0.9 kU/l, as compared to approximately 19% 'high-risk' children in the source population. The remaining 62% (n = 815) were drawn as a random sample from all 'low-risk' children of all study centres.

Ethical approval was obtained from local ethics committees.

Follow-up assessments and questionnaires

Following six clinical evaluations in the first 2 years, the study participants were assessed once every year from age 3 until 13, and thereafter at 15 and 20 years of age. Questionnaires and/or interviews were completed at each time point, which included ISAAC-based questions (International Study of Asthma and Allergies in Childhood (20)) on allergic phenotypes and items regarding family history of allergies, physical activity, diet, living conditions and smoking behaviour. Up until the age of 15, the questionnaires were completed by (or with) the accompanying adult. At the age of 20, all participants gave written informed consent; before that, a parent or guardian had given consent.

Outcome definitions

The classification of allergic multimorbidity was based on standardized parent- and self-reported questions that have been suggested and widely used by European population-based birth cohort studies on asthma and allergies (21) and have been validated in the ISAAC project in many languages worldwide.

Current asthma was defined as satisfying at least two of the following 3 criteria: (1) doctor's diagnosed asthma ever, (2) any indicative symptom in the last 12 months (wheezing, shortness of breath, dry cough at night) and (3) asthma medication in the last 12 months (22–24).

Current allergic rhinitis was defined as having a runny, itchy or stuffed nose without a cold in the last 12 months (2).

Current eczema was defined as an itchy rash that persisted for at least 6 months and was located in the antecubital or popliteal fossae, wrists, ankles, neck or face during the last 12 months (2).

Statistical methods

The data were analysed with SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA). The characteristics of the study participants and prevalence of symptoms of allergic diseases were described with summary statistics. The frequency of the 3 major allergies and their overlap was presented in Venn diagrams for different time points during the first 20 years of life. We stratified by parental allergy status (at least one allergic parent vs. non-allergic parents) and by sex/gender of the study participant.

Results

General characteristics of study participants

942 questionnaires (72% of base cohort) were evaluated during the most recent assessment at 20 years of age. The characteristics of the study participants who completed the 20-year assessment were compared to those who did not complete the follow-up at 20 years of age (Table 1). There were no considerable differences in sex ratio, number of older siblings, paternal rhinitis or maternal/paternal asthma. Participants in the 20-year follow-up were, however, more likely to have a family history of eczema and maternal rhinitis than those who did not participate.

Prevalence of allergic multimorbidity

As shown in Figs 1 and 2, allergic multimorbidity became more prevalent with increasing age in all strata. From early puberty up to adulthood, asthma occurred more often in

Table 1 Characteristics of study participants who completed 20-year follow-up (n = 942) compared with those who did not (n = 372) in German MAS birth cohort

Characteristic	Study participants who did not complete 20-year follow-up (n = 372) % (absolute number)	Study participants who completed 20-year follow-up (n = 942)
Male sex	51.3 (191)	52.4 (494)
One or more older sibling	40.1 (149)	41.5 (391)
Maternal rhinitis	22.3 (83)	27.3 (250)
Paternal rhinitis	24.2 (90)	24.0 (218)
Maternal asthma	8.3 (31)	8.2 (75)
Paternal asthma	6.5 (24)	6.6 (60)
Maternal eczema	4.8 (18)	7.4 (67)
Paternal eczema	1.9 (7)	4.5 (40)

conjunction with other allergic diseases than as a single entity. At least a third to half of all participants with allergic rhinitis had concurrent asthma and/or eczema from school age onwards. Eczema was less associated with other allergic diseases (Figs 1 and 2). We also found that allergic rhinitis was strongly linked with concurrent eye symptoms (conjunctivitis). At age 9, 59.9% of all subjects with current allergic rhinitis had current conjunctivitis; at 12 and 15 years of age, 66.4%; and at 20 years of age, 61.8%.

Allergic multimorbidity by parental allergies and by sex/gender

From 3 years of age up to 20 years of age, male participants with a positive parental history of allergy were more likely to develop coexisting allergic diseases (multimorbidity) than those with a negative parental history. At age 20, 11.6% (95% confidence interval (CI), 8.9–14.8%) of all male and 12.7% (95% CI, 9.7–16.2%) of all female MAS participants had 2 or 3 coexisting allergic diseases (Fig. 2); however, males with allergic parents were 3.6 times (95% CI, 2.0–6.4%) (females 2.3 times (95% CI, 1.3–4.1%)) more likely to have coexisting allergies than those with non-allergic parents (Table 2). At age 20, 18.5% (95% CI, 15.0–22.5%) of all participants with allergic parents had 2 or 3 concurrent allergies as compared to only 6.3% (95% CI, 4.3–9.0%) of those with non-allergic parents (Fig. 2). Sex/gender seemed to be more associated with single allergic diseases than with allergic multimorbidity. Among female participants 24.2% (95% CI, 20.2–28.5%) had only one of the 3 allergic diseases compared to 20.1% (95% CI, 16.6–24.0%) in male participants. Asthma alone was

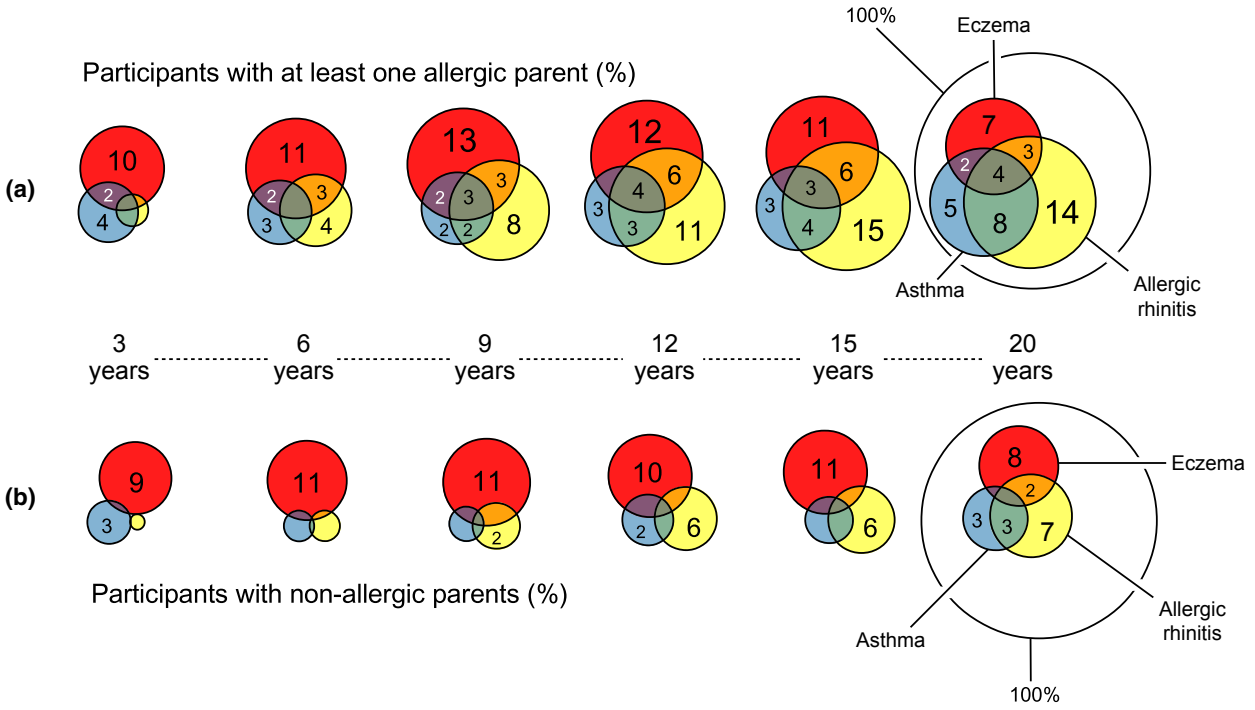

Figure 1 (a) Percentages of all participants with allergic parent(s), (b) Percentages of all participants with non-allergic parents; Multimorbidity of asthma, eczema and allergic rhinitis up to 20 years of age (n = 941), by parental allergy and age. Current asthma was defined as satisfying at least two of the following 3 criteria: (1) doctor's diagnosed asthma ever, (2) any indicative symptom in the last 12 months (wheezing, shortness of breath, dry cough at night) or (3) asthma medication in the last 12 months (22–24). Current allergic rhinitis was defined as having a runny, itchy or stuffed nose without a cold in the last 12 months (20). Current eczema was defined as an itchy rash that persisted for at least 6 months and was located in the antecubital or popliteal fossae, wrists, ankles, neck or face during the last 12 months (2). Based on Figure 4 in *Ballardini N* et al. from Swedish BAMSE birth cohort (12). Overlapping areas without numbers: prevalence <1.5%.

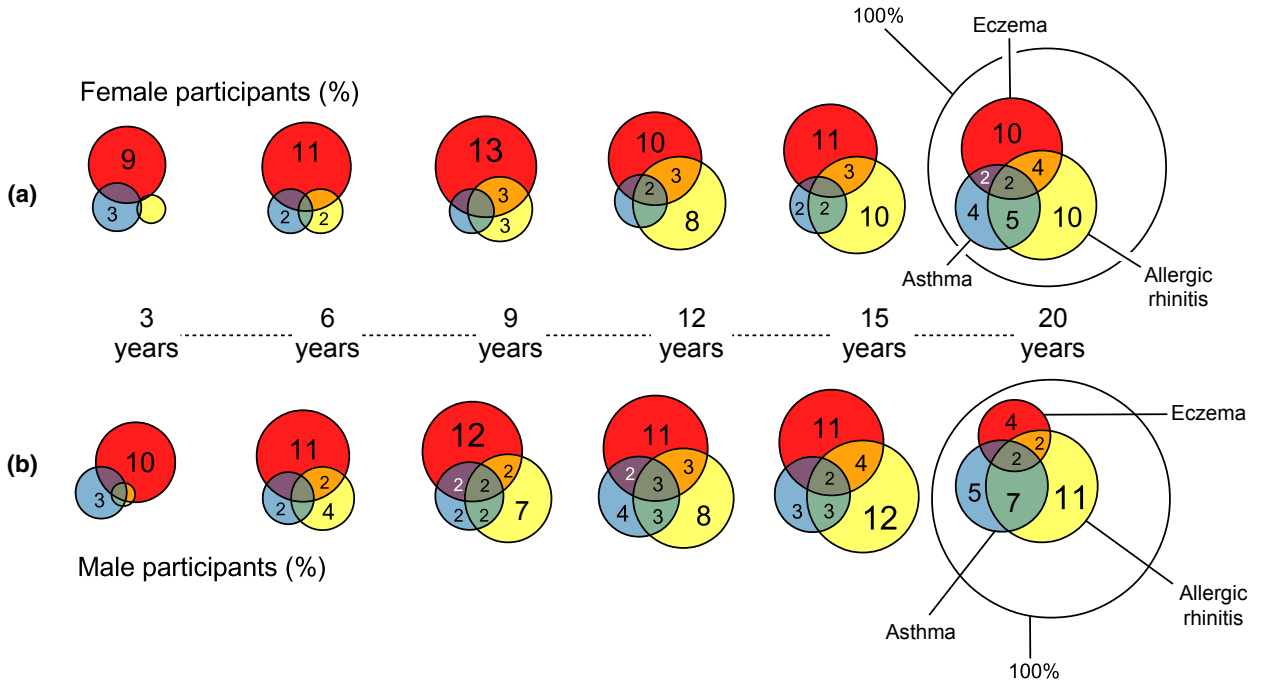

Figure 2 (a) Percentages of all female participants, (b) Percentages of all male participants; Multimorbidity of asthma, eczema and allergic rhinitis up to 20 years of age (n = 941), by sex and age. Current asthma was defined as satisfying at least two of the following 3 criteria: (1) doctor's diagnosed asthma ever, (2) any indicative symptom in the last 12 months (wheezing, shortness of breath, dry cough at night) or (3) asthma medication in the last 12 months (22–24). Current allergic rhinitis was defined as having a runny, itchy or stuffed nose without a cold in the last 12 months (20). Current eczema was defined as an itchy rash that persisted for at least 6 months and was located in the antecubital or popliteal fossae, wrists, ankles, neck or face during the last 12 months (2). Based on Figure 4 in *Ballardini N* et al. from Swedish BAMSE birth cohort (12). Overlapping areas without numbers: prevalence <1.5%.

Table 2 Prevalence of asthma, rhinitis and eczema as single entity and allergic multimorbidity (in %), by age, allergic family history and sex

Age (years)	3		6		9		12		15		20	
Allergic family histroy	pos	neg	pos	neg	pos	neg	pos	neg	pos	neg	pos	neg
MALES												
Asthma (A) only	3.2	3.8	2.5	1.6	1.4	2.6	3.2	4.0	4.1	2.1	6.8	2.7
Rhinitis (AR) only	0.4	0.0	5.9	2.3	12.0	3.1	10.8	6.0	15.6	7.5	13.6	8.8
Eczema (E) only	12.0	9.1	9.7	11.7	13.0	10.5	13.4	10.0	12.2	11.0	3.6	5.4
A + AR	0.0	0.0	1.3	0.4	3.4	0.4	4.3	1.0	4.8	2.1	10.0	3.8
AR + E	0.0	0.0	3.4	0.0	3.4	0.4	6.5	0.0	8.2	0.7	1.8	1.5
A + E	1.6	0.0	2.5	0.0	3.4	0.4	2.2	1.5	2.0	0.7	1.4	0.0
A + AR + E	1.6	0.0	2.1	0.0	4.3	0.9	5.9	0.5	4.8	0.0	5.5	0.0
None	81.2	87.1	72.6	84.0	59.1	81.6	53.8	77.0	48.3	76.0	57.3	77.8
FEMALES												
Asthma (A) only	3.8	2.1	2.6	0.9	1.8	0.0	2.6	0.0	2.7	0.8	3.9	3.4
Rhinitis (AR) only	1.2	0.9	3.0	0.5	4.9	1.1	10.9	5.4	15.3	3.9	15.0	4.8
Eczema (E) only	8.8	8.6	13.2	9.5	13.5	12.6	9.8	9.5	10.7	10.9	9.9	11.1
A + AR	0.4	0.0	0.9	0.0	0.4	0.0	2.6	0.0	4.0	0.8	6.9	2.4
AR + E	0.0	0.0	1.7	0.5	3.6	1.6	4.7	1.2	4.7	0.8	4.7	2.9
A + E	1.5	0.4	1.3	0.9	1.3	0.0	0.0	0.6	0.0	0.8	3.0	1.0
A + AR + E	0.0	0.0	0.4	0.0	2.2	0.0	2.6	0.6	1.3	0.8	2.6	1.0
None	84.2	88.0	77.0	87.7	72.2	84.7	66.8	82.7	61.3	81.3	54.1	73.4
Males: 2 or 3 of A, AR, E	3.2	0.0	9.3	0.4	14.4	2.2	18.8	3.0	19.7	3.4	18.6	5.4
Females: 2 or 3 of A, AR, E	1.9	0.4	4.3	1.4	7.6	1.6	9.8	2.4	10.0	3.1	17.2	7.2

At 20 years of age: males n = 494, females n = 447 and participants with negative family history n = 488, positive family history n = 453.

more common among males than females at almost all assessment time points (Fig. 2). The prevalence of eczema tended to increase with age in the female population, whereas a decrease was observed among males. Although eczema was more common in female than male participants, males with eczema tended to have asthma and/or rhinitis more often than females with eczema (Fig. 2). There was no considerable difference in prevalence of coexisting allergies between children who had only an allergic mother and those who had only an allergic father (data not shown).

Discussion

Main findings

The MAS study was the first longitudinal birth cohort to examine multimorbidity of asthma, allergic rhinitis and eczema up to 20 years of age and provided sex-specific prevalence data. We found that having parents with allergies is not only a strong predictor to develop any allergy, but it strongly increases the risk of developing allergic multimorbidity. At 20 years of age, participants with allergic parents developed coexisting allergies three times more often than those with non-allergic parents. In adulthood, the prevalence of allergic multimorbidity seemed similar in both sexes, whereas single allergic diseases were slightly more common in women than men. Asthma occurred more frequently with coexisting allergic rhinitis and/or eczema than as a single entity from pre-puberty to adulthood. More than twice as many female participants suffered from eczema at the age of 20 as compared to male participants.

Comparison with other studies

The BAMSE birth cohort study from Sweden examined the development of coexisting allergic diseases in children up to the age of 12 and found that 7.5% of the study population had at least two of these diseases (12). This was similar to the prevalence of 8.5% (95% CI, 6.6–10.7%) in our risk-enriched study population of the same age. Interestingly, several findings from BAMSE on allergic multimorbidity in childhood were confirmed for adolescence and adulthood by our results. Firstly, coexisting allergies continue to become more prevalent with age; secondly, asthma occurs more often with coexisting allergies than as a single allergic entity; and thirdly, parental allergy remains a strong predictor for allergic multimorbidity up to adulthood. Also, sex/gender differences known to play a distinguished role in the prevalence of single allergic entities (i.e. male predominance in childhood versus female predominance in adolescence and adulthood) do not seem to have much influence on the prevalence of coexisting multiple allergic diseases in the same individual (12, 25–28).

The British MAAS birth cohort has previously shown for 5-year-old children that more than half of those with asthma symptoms had coexisting rhinitis and/or eczema (29).

With UK data from 9801 ALSPAC and MAAS birth cohort children up to the age of 11 years, Belgrave et al. highlighted the fact that the commonly used term 'atopic march' may reflect the natural history and progression of eczema, asthma and allergic rhinitis on a cross-sectional, population-based level rather than the trajectory of disease development in individuals. Using latent class analyses, they were able to group 16% of children aged 8–11 years in classes with 2 or 3 coexisting allergies. The two groups of children with persistent eczema and wheeze as well as persistent eczema and rhinitis showed a female predominance, whereas the group of children with persistent wheeze and rhinitis included more males than females (18).

An earlier analysis of our cohort at early school age showed the lack of an association between gender and coexisting allergic respiratory symptoms such as rhinitis and concurrent wheeze (30).

An international collaborative population-based cohort data analysis including 12 European birth cohorts showed that half of the allergic multimorbidity (asthma, allergic rhinitis and eczema) at 8 years of age was not a result of chance. Additionally, this study found that allergic sensitization (i.e. the presence of specific IgE against common allergens in serum) only accounted for 38% of comorbidity in 8-year-old children (17). These findings suggest that there are non-IgE-mediated mechanisms associated with the development of allergic multimorbidity.

Apart from an allergic predisposition (e.g. family history), sex/gender and allergic sensitization, further potential risk or protective factors including environmental and psycho-social determinants have not been examined for allergic multimorbidity as a primary outcome. There still exists a lack of knowledge with respect to allergic multimorbidity and genetic determinants; however, a study from Dizier et al. in participants with a positive family history of asthma identified a statistically significant association of eczema with 11p14 genetic variants (31). Further investigation is needed in this area to confirm such findings and to explore the relationship of genetic determinants for coexisting eczema and asthma.

Strengths and limitations

The strengths of the current analysis include the use of stringent epidemiological definitions (20) to determine allergic outcomes and the large number of assessments (n = 19) in a 20-year time period, which is unique for a birth cohort study and reduces potential recall bias.

However, several limitations have to be considered. Firstly, due to the allergy risk-enriched sampling strategy, the MAS cohort as a whole is not representative of the population of the 5 cities where families were recruited from. However, A stratifying for parental allergy status leads to more generalizable prevalence estimates for the 2 subgroups of children and adolescents with allergic and with non-allergic parents.

Secondly, loss due to follow up in an observational birth cohort study over 20 years can have a considerable effect on the estimated prevalence of diseases. Study participants suffering from allergic diseases may be more likely to continue participating (in regular follow-up assessments to check progress of

their allergic condition). Our relatively high response rate at 20 years of age (72% of all children recruited at birth) may have reduced but cannot exclude a possible response bias. Furthermore, most of the basic characteristics of the study participants compared to non-participants were similar, with the exception of parental eczema and maternal rhinitis which were more common among the participants than those lost to follow-up at the last assessment.

Thirdly, information regarding non-allergic comorbidities has not been assessed in detail in previous follow-ups of MAS but will be included in future assessments during adulthood as non-allergic comorbidity of asthma and allergies is becoming of more clinical and public health relevance with increasing age. A nationwide survey in Germany showed recently that almost 50% of all adults with asthma reported coexisting gastrooesophageal reflux disease in the last 12 months (32). The existence of an association between asthma and chronic rhinosinusitis has also been demonstrated (33), and possible mechanisms causing systemic spread of upper airway disease with subsequent asthma, including staphylococcal superantigens, have been explored (34).

Conclusions

The MAS birth cohort study showed that allergic multimorbidity in the same individual was increasingly common through school age and adolescence up to adulthood. Particularly asthma occurred in both sexes more often in conjunction with other allergies than as a single entity. A positive parental history of allergy is not only a predictor to develop any allergy but also a strong determinant to develop coexisting allergic diseases. Sex/gender does not seem to be associated with the prevalence of current allergic multimorbidity as it is with single allergic entities.

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Contributions

Conceived and initiated the birth cohort: RB, KB, UW. Designed, conducted and supervised the current study: RB, KB, UW, SL, TK, LG, AR, UH, CB, JF, FZ, ON, UH, YAL. Collected data for the 20-year follow-up: ON, JB, UH, AS, HG, NE, YAL. Analysed the data: HG, LG, AR. Wrote the first draft of the manuscript: HG. Interpreted the results and critically reviewed the manuscript: HG, LG, AR, NE, ON, DS, JB, UH, AS, CB, JF, FZ, YAL, RB, KB, UW, SL, TK.

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