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DISSERTATION

Allergic multimorbidity over 20 years and early-life determinants of asthma and allergic rhinitis 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. Information on predictors, risk and protective factors for asthma and allergic rhinitis is also scarce due to a lack of long-term prospective studies.

Objective: The objectives of the current analyses were 1) to examine the progression of coexisting allergic conditions (asthma, allergic rhinitis, eczema) into adolescence and adulthood, stratified by parental allergies and sex/gender; 2) to determine early-life predictors of asthma incidence and 3) to determine early-life predictors of allergic rhinitis incidence, both up to 20 years of age by applying time-to-event analysis.

Methods: In 1990, 1314 newborns were recruited from 5 cities 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 standardised questionnaires including validated ISAAC questions in 19 follow-up assessments up to age 20. Allergic multimorbidity was defined as the coexistence of at least 2 of the following diseases in one participant: asthma, allergic rhinitis, eczema. A Cox regression model examined the associations between early-life dietary and behavioural factors and onset of asthma and onset of allergic rhinitis separately, including sensitisation against aeroallergens.

Results: Response at age 20 was 71.6% (n=941) 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 females and males (12.7% (95%-CI 9.7-16.2%) vs. 11.6% (95%-CI 8.9-14.8%)). Asthma incidence was lower in participants who were vaccinated (measles, mumps, and rubella/tickborne encephalitis/BCG vaccine: adjusted hazard ratio [aHR], 0.66 [95%-CI, 0.47-0.93%]) and

higher in subjects who had parents with allergic rhinitis (aHR, 2.24 [95%-CI, 1.67-3.02%]), started day care early or late (before 18 months: aHR, 1.79 [95%-CI, 1.03-3.10%]; after 3 years: aHR, 1.64 [95%-CI,0.96-2.79%]), had mothers who smoked during pregnancy (aHR, 1.79 [95%-CI, 1.20-2.67%]), had poor parents (aHR, 1.55 [95%-CI, 1.09-2.22%]), and had parents with asthma (aHR, 1.65 [95%-CI, 1.17-2.31%]). Aspects of diet, pet ownership, presence of older siblings, and passive smoking were not associated with asthma. For allergic rhinitis up to age 20, we identified the following predictors: parental allergic rhinitis (adjusted hazard ratio [aHR], 2.49; 95%-CI, 1.93-3.21%), parental urticaria (aHR, 1.32; 95%-CI, 1.00-1.74%), parental asthma (aHR, 1.29; 95%-CI, 0.95-1.75%), early allergic sensitisation (aHR, 4.53; 95%-CI, 3.25-6.32%), eczema within the first 3 years of life (aHR, 1.83; 95%-CI, 1.38-2.42%), male sex (aHR, 1.28; 95%-CI, 1.02-1.61%) and birthday in summer or autumn (aHR, 1.26; 95%-CI, 1.00-1.58). Potentially modifiable factors, including pregnancy and birth details, feeding, tobacco smoke exposure, pets, vaccination, and other childhood diseases, were not associated with allergic rhinitis.

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, co-existing allergies were increasingly common throughout adolescence up to adulthood. Avoiding tobacco smoke exposure during pregnancy, receiving vaccinations in early childhood, and starting day care between 1.5 and 3 years of age may prevent or delay the development of asthma. Only non-modifiable factors, particularly early allergic sensitisation or eczema and parental allergic rhinitis, predicted allergic rhinitis up to 20 years of age.

‘Allergische Multimorbidität über 20 Jahre und frühkindliche Risikofaktoren für Asthma und allergische Rhinitis in der Geburtskohortenstudie MAS ‘ von Hannah Gough

ZUSAMMENFASSUNG

Hintergrund: Die Prävalenz der allergischen Multimorbidität, das gleichzeitige Auftreten von Asthma, allergischer Rhinitis und der atopischen Dermatitis sowie frühkindliche Risikofaktoren für Asthma und allergischer Rhinitis sind bisher nicht in einer bevölkerungsbezogenen Längsschnittstudie vom Kleinkind- bis in das Erwachsenenalter untersucht worden.

Zielsetzung: Die Ziele der gegenwärtigen Analysen waren 1) die Prävalenz von gleichzeitig auftretenden allergischen Erkrankungen zu ermitteln, stratifiziert nach elterlichen Allergien und Geschlecht, 2) Faktoren im frühen Lebensalter zu ermitteln, die das Auftreten von Asthma bis 20 Jahren beeinflussen und 3) Umwelt- und Lebensstilfaktoren im frühen Lebensalter zu ermitteln, die das Auftreten von allergischen Rhinitis beeinflussen bis 20 Jahren.

Methodik: Im Jahr 1990 wurden 1314 Neugeborene aus 5 deutschen Städten in die Multizentrische Allergie Studie (MAS) eingeschlossen. Die gezielt risikoangereicherte Stichprobe enthielt 38% Studienteilnehmer mit einem erhöhten Allergierisiko, d.h. mindestens 2 Familienmitglieder (Eltern, Geschwister) mit Allergien, verglichen mit 19% der Quellpopulation. Die restlichen 62% der MAS-Teilnehmer hatten kein oder nur ein niedriges Risiko an Allergien zu erkranken. Symptome, Medikamenteneinnahme und Arztdiagnosen wurden mit standardisierten Fragebögen zu 19 Zeitpunkten bis zu einem Alter von 20 Jahren festgestellt. Allergische Multimorbidität war definiert als das gleichzeitige Aufteten von mindestens 2 der folgenden Erkrankungen bei einem Teilnehmer: Asthma, allergische Rhinitis, atopische Dermatitis. Mit Cox-Regression-Modellen wurden die Einflüsse von Faktoren im frühen Lebensalter auf die Entstehung von Asthma und allergischer Rhiniits untersucht, einschließlich der Sensibilisierung gegen Aeroallergenen.

Ergebnisse: Die Teilnahmequote mit 20 Jahren war 71,6% (n=941). In diesem Alter hatten 18,5% (95%-CI 15,0-22,5%) aller Teilnehmer mit allergischen Eltern gleichzeitig 2 oder 3 allergische Erkrankungen verglichen mit nur 6,3% (95%-CI 4,3-9,0%) der

Teilnehmer mit nichtallergischen Eltern. In diesem Alter war die allergische Multimorbidität bei Frauen und Männern ähnlich (12,7% (95%-CI 9,7-16,2%) vs. 11,6% (95%-CI 8,9-14,8%)). Die Inzidenz von Asthma war niedriger bei Teilnehmern die geimpft waren (Mumps, Masern, Röteln/Zeckenenzephalitis/BCG Impfung: aHR, 0.66 [95%-CI, 0.47-0.93%]) und höher bei Teilnehmern mit elterlicher allergischer Rhinitis (aHR, 2,24 [95%-CI, 1,67-3,02%]), die sehr früh oder sehr spät in den Kindergarten bzw. die Kita kamen (vor dem 18. Lebensmonat: aHR, 1,79 [95%-CI, 1,03-3,10%] bzw. erst nach dem 3. Lebensjahr: aHR, 1,64 [95%-CI, 0,96-2,79%]), deren Mütter während der Schwangerschaft geraucht hatten (aHR, 1,79 [95%-CI, 1,20-2,67%]), die einkommensschwache Eltern hatten (aHR, 1,55 [95%-CI, 1,09-2,22%]), oder Eltern mit Asthma (aHR, 1,65 [95%-CI, 1,17-2,31%]). Ernährung, Haustiere und ältere Geschwister waren mit Asthma nicht assoziiert. Das Risiko bis zum 20. Lebensjahr an allergischer Rhinitis zu erkranken war höher bei: mindestens einem Elternteil mit allergischer Rhinitis (adjusted hazard ratio [aHR], 2,49; 95%-CI, 1,93-3,21%), mit Urtikaria (aHR, 1,32; 95%-CI, 1,00-1,74%), oder mit Asthma (aHR, 1,29; 95%-CI, 0,95-1,75%), frühkindlicher allergischer Sensibilisierung (aHR, 4,53; 95%-CI, 3,25-6,32%), atopischer Dermatitis innerhalb der ersten 3 Lebensjahre (aHR, 1,83; 95%-CI, 1,38-2,42%), männlichem Geschlecht (aHR, 1,28; 95%-CI, 1,02-1,61%) und einer Geburt, die im Sommer oder Herbst lag (aHR, 1,26; 95%-CI, 1,00-1,58). Alle modifizierbaren Faktoren einschließlich Schwangerschafts- und Geburtsaspekten, Ernährung, Exposition gegenüber Tabakrauch, Haustiere, Impfungen und Kinderkrankheiten waren nicht mit der allergischen Rhinitis assoziiert.

Schlussfolgerung: Das Vorhandensein von elterlichen Allergien ist nicht nur ein Risikofaktor für die Entstehung einzelner Allergien sondern erhöht insbesondere auch die Wahrscheinlichkeit, allergische Multimorbidität zu entwickeln. Die Häufigkeit von gleichzeitig auftretenden allergischen Erkrankungen stieg bis zum Erwachsenenalter an. Die Vermeidung von Exposition gegenüber Tabakrauch während der Schwangerschaft, die Durchführung von empfohlenen Impfungen im Kindesalter und der Beginn von Kinderbetreuung zwischen 1,5 und 3 Jahren könnten die Entstehung von Asthma verhindern oder verzögern. Vor allem eine frühe allergische Sensibilisierung oder eine frühkindliche atopische Dermatitis und elterliche allergische Rhinitis konnten das erstmalige Auftreten der allergischen Rhinitis bis zum Alter von 20 Jahren voraussagen. Potenziell modifizierbare Risikofaktoren für die allergische Rhinitis konnten nicht identifiziert werden.

1.0 INTRODUCTION

Due to the increasing prevalence of allergic diseases among children and teenagers across the world (1-3), a number of birth and child cohort studies have been initiated in order to better understand this rise in prevalence; however research has been almost exclusively on single allergic entities (4-10). Information on predictors, risk, and protective factors for allergic diseases such as asthma and allergic rhinitis are also scarce to due to a lack of long-term prospective studies. With this information, long-term prevention strategies could be identified and implemented in order to reduce the considerable burden allergic diseases have on quality of life and daily activities at the population level. Comprehensive prospective follow-up data from two decades of the German Multicentre Allergy Study (MAS) was used to analyse coexisting allergic diseases as well as risk- and protective factors for the development of asthma and allergic rhinitis. Studies in children on coexisting allergies, for example the Swedish BAMSE cohort (11) showed that allergies occur more often in school rather than in preschool children and 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 (12). A great number of potentially modifiable behavioural patterns and exposures during prenatal, perinatal, and postnatal periods have been suggested to either prevent or encourage the development of asthma and allergic rhinitis (13-16). Existing studies differ in study design and setting, sampling schemes, and case definitions, making it difficult to compare results and arrive at clear conclusions. Prospective birth cohorts have allowed the collection of a wealth of information over the past years, however this has been rarely analysed and presented en bloc which also hamper efforts to identify modifiable factors and identify possible prevention strategies. Some of these flaws can be targeted by using analytic techniques that are more appropriate for longitudinal studies. In line with this, the current analyses aimed to identify early-life determinants of asthma and allergic rhinitis incidence by applying time-to-event analysis, including all 19 assessments and accounting for a wide array of exposures and indicators of heredity.

2.0 OBJECTIVE

The aims of our analyses were 1) to examine the progression of coexisting allergic conditions (asthma, allergic rhinitis, eczema) into adolescence and adulthood, stratified by parental allergies and sex/gender, since the progression of allergic multimorbidity has not yet been studied from birth to 20 years of age; 2) to determine early-life predictors of asthma incidence and 3) to determine early-life predictors of allergic rhinitis incidence, both up to 20 years of age by applying time-to-event analysis. These analyses were carried out using the comprehensive prospective follow-up data from two decades of the German birth cohort study MAS.

3.0 METHODS

3.1 Study design and follow-up

The German Multicentre Allergy Study aims to describe patterns and risk factors of allergic diseases. Of 7609 children born between January and December 1990 in 5 cities across Germany, a risk-enriched population-based sample was recruited (n=1314) with 38% (n=499) 'high-risk children' and followed up for 20 years. 'High-risk' children were defined as having two immediate family members (among parents or siblings) with asthma, allergic rhinitis or eczema, or an elevated cord blood immunoglobulin E (IgE) ≥0.9kU/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. During the 20-year follow-up period, clinical examinations were carried out and at 19 time points the participants' exposure to environmental and behavioural factors was assessed using face-to-face, paper, telephone, and online questionnaires. Six clinical evaluations were carried out in the first two years, after this the study participants were assessed annually until 13 years of age using questionnaires and thereafter at 15 and 20 years of age. The questionnaires included items regarding allergic phenotypes, physical activity, diet, living conditions, immunisation status and smoking behaviour. To ensure a high long-term response rate at the 20-year follow-up, local residents' registration offices, the national database for changes of address, delivery room documentation and social media platforms were used. Parents and participants provided written informed consent. The study was approved by local ethics committees in all study centres.

3.2 Outcome definitions

Allergic multimorbidity at each time point was defined as the coexistence of at least 2 of the following 3 diseases in the same participant: asthma, allergic rhinitis, eczema.
The classification of allergic diseases was based on the disease symptoms recorded using questions that have been widely used by European population-based birth cohort studies on asthma and allergies, including validated ISAAC-based (International Study of Asthma and Allergies in Childhood) questions (17-19). 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. The outcome of allergic rhinitis was based on parent- and self-reported nasal symptoms: 1) 'In the past 12 months, did

your child/you have problems with sneezing, or a runny or blocked nose when he/she/you did not have a cold or the flu?' and 2) 'In the past 12 months, has your child/have you been disturbed by a runny/itchy/blocked nose or itchy/watery/red eyes in daily activities?', with both items being answered with yes. Items on asthma, allergic rhinitis and their indicative symptoms were considered too unspecific as outcomes before the age of 3 years. Eczema was defined as having an itchy rash which 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.

3.3 Statistical methods

The data were analysed with SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA). In the following, a description of methods is cited from previous papers (20-22). When analysing allergic multimorbidity, the characteristics of the study participants and prevalence of symptoms of single allergic diseases were first described with summary statistics. The frequency of the 3 major allergic entities and their overlap was presented in Venn diagrams for different time points during the first 20 years of life. Stratification by parental allergy status (at least one allergic parent vs. non-allergic parents) and sex/gender was carried out. The association between early-life predictors and onset of allergic diseases was evaluated using time-to-event analysis with a Cox proportional (continuous time) hazards model, with raw and adjusted hazard ratios (HRs) and respective 95% CIs based on Wald tests as the main effect estimator. A separate model was estimated for each predictor, for which potential confounders were selected by using directed acyclic graphs. Thereafter, stepwise selection excluded those not significantly linked to the outcome (entry/exclusion threshold, P = .05).

4.0 RESULTS

Of 1314 newborns recruited, 941 (71.6%) remained in the MAS birth cohort until the age of 20. 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. 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. Participants lost to follow-up also came from less educated families, with 27.3% of parents having low education status compared with 19.4% among the complete responders.

4.1 Allergic multimorbidity

Allergic multimorbidity became more prevalent with increasing age in all strata.
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 females and males (12.7% (95%-CI 9.7-16.2%) vs. 11.6% (95%-CI 8.9-14.8%)); however males with allergic parents were 3.6 times (95%-CI 2.0-6.4%) and females 2.3 times (95%-CI 1.3-4.1%) more likely to have coexisting allergies than those with non-allergic parents. 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 occurred more frequently with coexisting allergic rhinitis and/or eczema than as a single entity from pre-puberty to adulthood.

4.2 Early-life determinants of asthma

Parental asthma, allergic rhinitis, and eczema were strong risk factors for asthma up to age 20 years, whereas parental self-reported food hypersensitivity and urticaria showed no association. Total IgE level in cord blood, but not positive parental IgE level at birth, was an independent predictor of asthma development up to age 20 years. Asthma incidence was lower in participants who were vaccinated (measles, mumps, and rubella vaccine/tickborne encephalitis vaccine/BCG vaccine: adjusted hazard ratio [aHR], 0.66 [95%-CI, 0.47-0.93%]). Up to age 20 years, asthma incidence was higher in subjects

who had parents with allergic rhinitis (aHR, 2.24 [95%-CI, 1.67-3.02%]), started day care early or late (before 18 months: aHR, 1.79 [95%-CI, 1.03-3.10%]; after 3 years of age: aHR, 1.64 [95%-CI,0.96-2.79%]), had mothers who smoked during pregnancy (aHR, 1.79 [95%-CI, 1.20-2.67%]), had poor parents (aHR, 1.55 [95%-CI, 1.09-2.22%]), and had parents with asthma (aHR, 1.65 [95%-CI, 1.17-2.31%]). Aspects of diet (breast-feeding, weaning, diet in pregnancy, and parental food hypersensitivity), pet ownership (cat or dog), presence of older siblings, and passive smoking were not associated with asthma.

4.3 Early-life determinants of allergic rhinitis

From infancy to young adulthood, symptoms indicative of rhinitis (sneezing and runny/blocked nose in the last 12 months) were reported with increasing frequency, reaching a high of 47.1% at 20 years of age. Participants from both rich and poor backgrounds (grandparents and parents) had the same risk of AR as those from average-income families. The risk of allergic rhinitis was higher with a parental history of allergic rhinitis (adjusted hazard ratio [aHR], 2.49; 95%-CI, 1.93-3.21%), urticaria (aHR, 1.32; 95%-CI, 1.00-1.74%), or asthma (aHR, 1.29; 95%-CI, 0.95-1.75%). Early allergic sensitisation (aHR, 4.53; 95%-CI, 3.25-6.32%), eczema within the first 3 years of life (aHR, 1.83; 95%-CI, 1.38-2.42%), male sex (aHR, 1.28; 95%-CI, 1.02-1.61%) and birthday in summer or autumn (aHR, 1.26; 95%-CI, 1.00-1.58) were independent predictors of allergic rhinitis up to 20 years of age. All investigated potentially modifiable exposures and behaviours, including pregnancy and birth details, feeding, pollution, tobacco smoke exposure, pets, vaccination, and other childhood diseases, were not associated with allergic rhinitis. In contrast to allergic rhinitis alone, allergic rhinitis plus asthma was particularly associated with thyroxine intake (aHR, 2.04 vs. 1.20) and smoking during pregnancy (self-reported smoking aHR, 1.75 vs. 1.22; cord blood cotinine aHR, 1.91 vs. 1.34). Participants with early or late start of day care seemed to have a higher incidence of allergic rhinitis combined with asthma (imprecise estimates reflected in wide CIs).

5.0 DISCUSSION

The MAS study is the first longitudinal birth cohort to examine multimorbidity of asthma, allergic rhinitis and eczema up to 20 years of age and provides sex-specific prevalence data as well as valuable information about modifiable risk factors linked to allergic diseases.

5.1 Allergic multimorbidity

The present analyses showed 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. Apart from an allergic predisposition, sex/gender and allergic sensitisation, 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 (23). 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) (24-26) did not seem to have much influence on the prevalence of coexisting multiple allergic diseases in the same individual.

5.2 Prediction and prevention of asthma

Of a large number of perinatal and early-life factors that were evaluated, only a few showed associations with asthma up to age 20 years using time-to-event analysis. Wheezing, eczema, or allergic sensitisation all within the first 3 years were strong predictors for earlier onset of asthma up to adulthood in our current study (data not shown for the latter 2). These findings confirm the recently published results from a Danish birth cohort study up to age 26 years (27). A lower risk of allergy and asthma in 5-year-old children who were vaccinated against measles, mumps, and rubella has been shown before in our birth cohort, as well as for BCG vaccination in a large survey of children starting school in 1994 (28,29). The results of our current analyses showed that this protective effect for asthma seems to last until adulthood for participants who

received at least some whole-organism vaccines in early childhood (measles, mumps, and rubella; tuberculosis; and tick-borne encephalitis) compared with those who did not receive any at all.

5.3 Prediction and prevention of allergic rhinitis

The risk of developing allergic rhinitis was close to 3-fold in families with parental allergic rhinitis. Modifiable risk factors were only linked to allergic rhinitis with concurrent asthma, for which primary prevention seems possible by starting day care between 18 and 36 months of age, following vaccination recommendations for live vaccines and avoiding smoking in pregnancy. The strongest non-modifiable predictors of allergic rhinitis up to age 20 years, besides allergic sensitisation to cow's milk, hen's egg (or both) were parental allergic rhinitis, which confirmed previous reports, and to a lesser extent, parent-reported asthma and urticaria (30-31). Because sensitisation to cow's milk and hen's egg, which is common in infancy, was not closely connected to aeroallergens, early sensitisation to these foods, alongside early eczema within the first 3 years could be used as an independent predictor and might be modifiable through upstream interventions.

5.4 Strengths and limitations

The strengths of the current analyses include the use of stringent epidemiological definitions 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, 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 currently suffering from allergic diseases may be more likely to continue participating (regular assessments to check progress of allergic condition may seem more relevant from the study participant's point of view). However, our relatively high response rate at 20 years of age (71.6% of all children recruited at birth) may have reduced but cannot exclude a possible response bias. Secondly, due to the allergy risk-enriched sampling strategy the MAS study sample as a whole is not representative of the population of the 5 cities where families were recruited from. However, adjusting or as we did stratifying for parental allergy status leads to more generalisable prevalence estimates for e.g. participants with allergic and with non-allergic family history. Also, this (risk-enriched)

approach was expected to increase the number of allergic children with the intention to strengthen the estimation of risk and protective factors, the main reason this long-term birth cohort was started approximately 25 years ago. To our knowledge, this is the first time-to-event analysis of risk factors for allergic rhinitis spanning the first 20 years, the age period during which about 80% of lifetime disease has commenced (32). Such a model properly accounts for timing of disease onset, as well as early or temporary discontinuation of follow-up.

5.5 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. 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. The risk of developing asthma could be reduced by avoiding prenatal tobacco smoke exposure, starting day care between 1.5 and 3 years of age, and receiving the recommended vaccinations in early life. A positive parental history of allergies and low household income were non-modifiable risk factors for asthma beyond childhood and adolescence. On the basis of our results for risk factors of allergic rhinitis, no recommendations can be made regarding modifiable exposures and behaviours as there were no links to this allergic disease.

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Anteilserklärung an den erfolgten Publikationen

Hannah Gough hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Gough H, Grabenhenrich L, Reich A, Eckers N, Nitsche O, Schramm D, Beschorner J, Hoffmann U, Schuster A, Bauer C-P, Forster J, Zepp F, Lee Y-A, Bergmann RL, Bergmann KE, Wahn U, Lau S, Keil T. Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. *Pediatr Allergy Immunol* 2015 May 22. doi: 10.1111/pai.12410. [Epub ahead of print]
Beitrag im Einzelnen (bitte kurz ausführen):

- Datenerhebung im Rahmen der (20-Jahre) Follow-Up Untersuchung: Telefoninterviews durchgeführt, Fahrt nach Mainz um Kreiβsaal Dokumentation zu besichtigen, ausführliche Suche nach Studienteilnehmern mit Hilfe dieser Informationen und des Einwohnermeldeamtes.
- Schreiben und Revision des Papers
- Statistische Auswertungen mit dem Programm SAS

Publikation 2: Grabenhenrich LB, Keil T, Reich A, et al. Prediction and prevention of allergic rhinitis: A birth cohort study of 20 years. *J Allergy Clin Immunol* 2015 pii: S0091-6749(15)00492-3. doi: 10.1016/j.jaci.2015.03.040 (Epub ahead of print)
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- Kritische Durchsicht des Papers, Verbesserungsvorschläge im Rahmen des Schreibens und Revisionsprozesses

Publikation 3: Grabenhenrich LB, Gough H, Reich A, et al. Early-life determinants of asthma from birth to age 20 years: a German birth cohort study. *J Allergy Clin Immunol* 2014: 133(4):979-88.
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Unterschrift, Datum und Stempel des betreuenden Hochschullehrers/der betreuenden Hochschullehrerin

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Unterschrift des Doktoranden/der Doktorandin

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Publikation 1: Gough H et al., 2015

Gough H, Grabenhenrich L, Reich A, Eckers N, Nitsche O, Schramm D, Beschorner J, Hoffmann U, Schuster A, Bauer C-P, Forster J, Zepp F, Lee Y-A, Bergmann RL, Bergmann KE, Wahn U, Lau S, Keil T. Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. *Pediatr Allergy Immunol* 2015 May 22. doi: 10.1111/pai.12410. [Epub ahead of print].

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Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht

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Publikationsliste

Als Erstautorin:

	IF
1) Gough H, Grabenhenrich L, Reich A, Eckers N, Nitsche O, Schramm D, Beschorner J, Hoffmann U, Schuster A, Bauer C-P, Forster J, Zepp F, Lee Y-A, Bergmann RL, Bergmann KE, Wahn U, Lau S, Keil T. Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. *Pediatr Allergy Immunol* 2015 May 22. doi: 10.1111/pai.12410. [Epub ahead of print]	3,859

Als Co-Autorin:

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1) Grabenhenrich LB, Keil T, Reich A, Gough H, Beschorner J, Hoffmann U, Bauer CP, Forster J, Schuster A, Schramm D, Nitsche O, Zepp F, Lee YA, Bergmann R, Bergmann K, Wahn U, Lau S. Prediction and prevention of allergic rhinitis: A birth cohort study of 20 years. *J Allergy Clin Immunol* 2015: pii: S0091-6749(15)00492-3. doi: 10.1016/j.jaci. 2015.03.040. [Epub ahead of print]	11,248
2) Grabenhenrich LB, Gough H, Reich A, Eckers N, Zepp F, Nitsche O, Forster J, Schuster A, Schramm D, Bauer CP, Hoffmann U, Beschorner J, Wagner P, Bergmann R, Bergmann K, Matricardi PM, Wahn U, Lau S, Keil T. Early-life determinants of asthma from birth to age 20 years: a German birth cohort study. *J Allergy Clin Immunol* 2014; 133 (4):979-88. doi: 10.1016/j.jaci.2013.11.035. Epub 2014 Jan 22.	11,248

Eidesstattliche Versicherung

„Ich, Hannah Gough, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: *‚Allergic multimorbidity over 20 years and early-life determinants of asthma and allergic rhinitis in the German birth cohort MAS*‘ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
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Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

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