1   **„CHildhood Allergy and tolerance: bioMarkers and Predictors" (CHAMP) -A call for**
2   **prediction and quality of life**
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4   Jana Kristin Eckert*[1], Julia Kahle*[2], Andreas Böck*[1], Kathrin Zeber[1], Kathrin Urner[1],
5   Wolfgang Greiner[3], Simone Kreimeier[3], Kirsten Beyer[4], Josefine Dobbertin-Welsch[4], Eckard
6   Hamelmann[5], Ines Gellhaus[5], Christina Schorlemer[5],   Michael Kabesch[6], Parastoo
7   Kheiroddin[6], Erika von Mutius[1,7], Martin Depner[7], Daniel Walter[1], Gesine Hansen[8], Stephanie
8   DeStefano[8], Sabine Schnadt[2] and Bianca Schaub[1] for the CHAMP consortium

9   [*] shared first author
10 [1] Pediatric Allergology, Department of Pediatrics, Dr von Hauner Children's Hospital,
11 University Hospital, LMU Munich, Munich, Germany.
12 [2] German Allergy and Asthma Association, Mönchengladbach, Germany.
13 [3] Department of Health Economics and Health Care Management, School of Public Health,
14 Bielefeld University, Bielefeld, Germany.
15 [4] Department of Pediatric Pulmonology, Immunology and Intensive Care Medicine, Charité
16 Universitätsmedizin Berlin, Berlin, Germany.
17 [5] University Bielefeld, Children's Center Bethel, EvKB, Bielefeld, Germany
18 [6] KUNO Childrens University Hospital Regensburg, Department of Pediatric Pneumology and
19 Allergy Campus St Hedwig, Regensburg, Germany.
20 [7] Institute of Asthma and Allergy Prevention, Helmholtz Zentrum München, German Research
21 Center for Environmental Health, Neuherberg, Germany.
22 [8] Department of Paediatric Pneumology, Allergology and Neonatology, Hannover Medical
23 School, Hannover, Germany; Biomedical Research in Endstage and Obstructive Lung
24 Disease Hannover (BREATH), Germany; Member of the German Center for Lung Research
25 (DZL); Cluster of Excellence RESIST (EXC 2155), Hannover Medical School, Hannover,
26 Germany.
27 **Running title:** CHildhood Allergy and tolerance (CHAMP)
28 **Corresponding author**
29 Bianca Schaub
30 Dr. von Hauner Children's Hospital, LMU
31 Lindwurmstr. 4
32 80337 Munich, Germany

33 Email: bianca.schaub@med.uni-muenchen.de

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Abstract

Background: Allergic diseases are the most prevalent chronic childhood diseases resulting in a massive societal and economic burden for the community and a significant reduction of health-related quality of life (HRQoL) for affected families. The project CHAMP (**CH**ildhood **A**llergy and tolerance: bio**M**arkers and **P**redictors) was funded in 2017 by the German Federal Ministry for Education and Research.

Methods: CHAMP investigates the determinants of different allergic diseases from birth to adolescence to identify clinically relevant biomarkers predicting onset, progression, remission and severity. Data on HRQoL and patient's needs and requirements were collected, supported by the German Asthma and Allergy Association (DAAB).

Using validated questionnaires and outpatient visits, eight subprojects analysed allergic diseases in epidemiological or clinical cohorts (more than 2500 children/adolescents), sampling numerous biomaterials to assess omics on several levels. Murine models disentangled underlying mechanisms of early tolerance, translating findings from the cohorts to models and *vice versa*.

Results: The DAAB survey, including 851 participants, showed that 83% were interested in prediction of the course of different current allergic diseases and future manifestation. 86% of participants considered doctor's specialized training and their education as highly important, over 70% chose research for allergy understanding and prevention as critical. CHAMP addresses these needs. Common SOPs have been established and recruitment is ongoing.

Conclusion: The DAAB patient survey confirmed the critical need for translational allergy research. CHAMP envisions to predict onset, tolerance and remission of allergic diseases and to identify disease sub-phenotypes for future development of preventive strategies and novel avenues for therapeutic options.

Key Message

The DAAB survey shows that patient´s families are very interested in the specific allergy research questions, which CHAMP is investigating. Families care about prediction of

allergies and support searching for novel approaches for allergy prevention. CHAMP adds novel insight to the puzzle of early onset, natural tolerance and remission of different allergic diseases from birth to adolescence by identifying clinically relevant biomarkers predicting onset, progression, remission, and severity. This will lay the ground for future development of preventive strategies and shall contribute to opening up novel avenues for therapeutic options in the long term, which will clearly make an impact on the life of allergic patients and their families.

Keywords

Allergy, Biomarker, Childhood, Cohorts, Health-Related Quality of Life, Prediction, Survey

Introduction

Allergic diseases, including atopic dermatitis (AD), food allergy (FA), asthma and allergic rhinitis/rhinoconjunctivitis (AR) are the most prevalent chronic childhood diseases affecting one in four children in the Western world (1). This global health problem imposes a significant burden on patient's quality of life (2, 3), family(4), health care and society.

The current state of knowledge assumes that complex interactions between genetic and environmental factors influence a child´s immune maturation prior to the development of allergic diseases (5). The perinatal period is the first relevant time window of vulnerability, being instrumental in shaping a child´s immune system ("programming")(6–9). By identifying key markers for allergy development, it may be possible to predict subsequent development of allergic diseases already at this early stage.

In infancy and early childhood, AD and FA are common, often resolving completely within one year (10, 11). Risk factors are genetic, environmental and allergen exposure (12, 13). Blood DNA methylation biomarkers and component-specific IgE predict clinical reactivity in food-sensitized infants (14, 15). Low levels of allergen-specific IgE at diagnosis and decreasing allergen-specific IgE over a short period of time, enhance the likelihood of developing tolerance to hen's egg and cow's milk (16). Similarly, cytokine levels and circulating cells form an immune signature to predict the development of tolerance in young children (17).

Recent studies have shown that DNA methylation in asthma- and allergy-related genes change significantly early in life (18) and that epigenetic targets (e.g. FOXP3-demethylation) are critical for early life and childhood immune regulation in allergy development (19, 20). Moreover, polyvalent sensitization, increased airway hyperresponsiveness, impaired lung function, female sex and smoking reduce chances of remission(21). Also patients with multiple allergies and non-allergic comorbidities (e.g. obesity, ADHD) require consideration since comorbidities decrease the likelihood of remission and increase risk of progression to a more severe disease course(21).

For allergic rhinitis, data on remission is sparse. In a Swedish cross-sectional study, 12% of children with AR, between the age of 4 and 8 years, went into remission (22). Lately, the role of the human microbiome for onset and progression/remission of allergic diseases has received widespread attention (23, 24).

To date, no reliable predictions of allergy development exists. Current scores, including clinical features and laboratory data, have only reached limited specificity and/or sensitivity (25–28).

156 Between 2017 and 2021, the German Federal Ministry for Education and Research funded a
157 framework program for health research in children and adolescents: "Healthy for life" with
158 CHAMP (CHildhood Allergy and tolerance: bioMarkers and Predictors) being one of its
159 projects. Different CHAMP subprojects (SP1-8) including the German Allergy and Asthma
160 Association (*Deutscher Allergie- und Asthmabund*, DAAB), focus on assessment of HRQoL,
161 particular windows of vulnerability, and aim to identify biomarkers and predictors for onset,
162 tolerance and remission of allergic diseases. This article will present first results of CHAMP
163 generated by a DAAB survey on needs and expectations regarding the knowledge and
164 treatment of allergic diseases. Furthermore, we will give an overview on CHAMP and its
165 subprojects in results. Opening avenues for novel therapeutic options and preventive
166 strategies is central to patient's needs, thus being of important clinical relevance.
167

Methods
DAAB survey

An online survey, aiming at needs and expectations of families with allergic children towards health care and their professionals, was conducted (Surveymonkey, Supplement). DAAB members were contacted via E-mail, if they had children with allergic diseases (1275 invitations). Moreover, an advertisement was published on Facebook (FB), aiming at non-DAAB members as participants with children and a connection to keywords like allergy, nuts, mites, cough, itch, sneeze.

Clinical characterization: Phenotypes, questionnaires, database

In CHAMP, a number of pre-existiing cohorts (Tab. 1) were included in analysis, comprising over 2500 children. New patient cohorts were established within subproject SP4, SP5 and SP6 (Tab.3). Clinical and epidemiological questionnaires were used to collect information on health conditions, emphasizing on respiratory and atopic symptoms, sociodemographic and environmental exposures. Five different phenotypes (asthma, severe asthma, AD, FA and AR). Definition of phenotypes was based on doctor's diagnosis, phenotype-specific symptoms and disease-specific medication (except FA). For diagnosis of asthma, airflow obstruction/significant broncholysis existed. Additionally, for diagnosis of severe asthma, poor symptom control despite large doses of inhaled corticosteroid or biological treatment was required. For diagnosis of AR, elevated specific IgE-levels and respective symptoms needed to be present. FA was diagnosed based on history and/or related specific IgE and/or oral food challenge. AD was diagnosed according to Hanifin and Rajka-criteria (29). Due to the nature of the studies, cohorts may use different levels of diagnostic criteria. To address the resulting heterogeneity of phenotypes and to utilize analysis across cohorts, a common database was established, where relevant variables regarding allergic diseases and potential confounders were generated. The HRQoL survey in SP2 used in most subprojects contained a core questionnaire with detailed information on childhood allergic diseases, disease specific symptoms, medication, further supporting the comparison of phenotypes.

The following inclusion criteria apply for all cohorts: informed consent of parents or caretakers, age 6 months to 18 years, active/ passive understanding of German. Children were excluded from study visits and biomaterials in the case of fever (>38.5°C). Healthy controls (hc) were defined as children without a doctor's diagnosis or parent reported doctor's diagnosis of any allergic disease out of FA, AA, AD and AR and otherwise healthy. All studies were approved by local ethics committees. CHAMP is registered under http://www.drks.de/DRKS00015204.

204

205 **Biosamples and analysis**

206 Planned omics analysis from cord or peripheral blood comprise genome-wide association
207 studies (GWAS, GSA-chip), genome-wide methylation (EPIC-chip, Illumina), whole genome
208 expression (RNASeq), gene expression panels and microbiome analysis (16S rRNA-gene
209 sequencing). For patients with asthma, throat swabs were taken, while for FA or AD stool
210 samples and/or skin swabs were collected. Bed dust will be obtained and analysed within
211 SP4 in regards to tolerance development in FA. All samples were prepared and analysed
212 following common standard operating procedures (SOPs).

213

214

Results

Demographics and prevalences of DAAB survey participants

851 families answered the online survey conducted by DAAB via email or Facebook link. 786 families (555 DAAB-members), with n=1037 children were included after plausibility checks. Compared to DAAB-members, non-DAAB-members were younger, their children had less allergies, particularly less hay fever and had also younger children with less allergies themselves (Tab.S1/S2). Members and non-member were pooled for further considerations. Primarily mothers answered the questionnaires (94% female vs 6% male), mostly aged 30-50 years (Tab.2). About 55% of them had at least one allergic disease themself, and on average 1.3 allergic children. The most prevalent allergic disease of children was FA (74.6%), followed by AD (58.3%), AR (50.7%), and asthma (38.5%)(Tab.2). On average, the children had 2.2 out of 4 allergic diseases considered. Details regarding sex can be found in Tab S3.

Interests and needs

Interest in prediction of the course of a current allergic disease was expressed by 82% of participants (Fig.1A), even when special blood values are required. The interest for prediction of additional allergic disease development was equally high (Fig.1C). Of most interest was FA, closely followed by asthma: 42% wanted to know it any way and only 8% never (Fig.1B). When asked how satisfied people were with the current therapy of their children (Fig.2A), over 70% were satisfied or very satisfied, while less than 10% were not satisfied at all.

If a detetrioration of a current allergic disease was suspected, there was a high willingness to do something: independent of the allergic disease, 50.1% would move for better outcome, 58.7% would visit a doctor earlier and 84.2% would attend a specialist clinician. Only 2.8% of parents would take no further action (Fig.2B).

Further, the survey participants were asked about the importance of distinct research priorities and fields of action (Fig.2C). Doctor's training was ranked as most important, followed by research into health care, new drug therapy and a better understanding of allergy in general.

CHAMP Consortium comprising 8 subprojects

The CHAMP consortium consists of eight subprojects SP1-8, including the coordination project SP1 located at the children's hospital LMU Munich (Tab.3). SP2-8 cover the whole range of allergic diseases (FA, AD, asthma, and AR throughout childhood and adolescence (0-18 years)(Fig.3). Overarching are studies on HRQoL of affected children and families,

250 analyses of microbiome data within all cohorts and a translational murine project, assessing
251 pathomechanisms in different allergy models.

252

253 **SP2** assesses **HRQoL in children and adolescents with allergic diseases and quality of**
254 **life (QoL) of their parents** using different generic and disease-specific HRQoL
255 questionnaires and a core questionnaire with details on allergic disease(s) of the children.
256 Data collection on patients' HRQoL and parent' QoL-data is ongoing, consisting of a baseline
257 assessment, a one- and two-year follow-up. Baseline data are currently analyzed. In the first
258 phase of SP2, an adaption of a disease-specific HRQoL questionnaire for children suffering
259 from AA and AR for the German context was established (30).

260

261 **Microbiome data from distinct allergy cohorts and different allergic diseases (SP7**)
262 sites are characterized with respect to main bacteria species and diversity. Analysing the
263 throat microbiome in relation to immune regulation in childhood asthma, two distinct
264 phenotypes seem relevant. Faeces and skin samples from different body sites are used to
265 understand the role of the microbiome in food allergy. Here microbial features will be
266 compared between patients in progression and remission of their allergic disease (inter-
267 individual) and between time points before and after tolerance development in a subgroup of
268 patients (intra-individual comparisons).

269

270 Three projects aim at prediction of asthma, targeting the whole spectrum of severity and
271 disease course: SP3 concentrates on prediction of allergy development at birth (SP3), SP5
272 aims at severity and comorbidities of allergic diseases, while SP6 assesses asthma targets
273 during remission in children and adolescents.

274

275 For the **molecular allergy risk score, SP3** assessed differences between healthy and
276 allergic children by a combination of genome-wide genetics, epigenetic variability and gene
277 expression in two birth cohorts. In a cross-sectional cohort, children with manifestation of
278 allergic diseases (e.g. AD, asthma) will be evaluated for identical risk SNPs and an
279 epigenetic and immune signature. Finally, as replication, children will be selected based on
280 this risk score and prospectively assessed for disease development.

281

282 SP5 aims on **identification of natural progression factors and comorbidities in severe**
283 **asthma**, utilizing patients and data of the German Asthma Network (GAN) register with
284 ongoing recruitment. Within the NIKI-Cohort, children with asthma and comorbidities such as
285 obesity and attention deficit hyperactivity disorder are compared regarding underlying
286 mechanisms including functional cytokine regulation and NO-metabolism.

287

288 A **systematic detection of mechanisms and markers for allergy remission in children &**
289 **adolescents (SP6)** study collects samples of children and adolescents with atopic asthma,
290 AR and/ or AD to acquire a comprehensive picture of biological processes in remission.
291 Biomaterials from before and 6 months after start of remission are collected. The molecular
292 signatures will be validated and replicated in established cohorts.

293

294 SP4 adresses **tolerance development of FA**. In a cross-sectional design, children from the
295 EFA cohort with diagnosed hen's egg and/or peanut allergy will be rechallenged to identify
296 biomarkers as predictors for FA resolution. The identified predictors will then be evaluated in
297 a longitudinal design with children with newly determined FA. In a *proof-of concept*, identified
298 factors will be used for prediction of remission. In addition, patients who underwent oral
299 immunotherapy due to peanut allergy (31) will be assessed during long-term follow-up to
300 investigate therapeutically-induced tolerance development. SP4 will compare biomarkers and
301 environmental factors for "induced tolerance development" in peanut allergic versus "natural
302 tolerance development" in peanut- and/or hen's- egg-allergic patients.192 patients are
303 already enroled, while analyses of bio samples and clinical data will take place in parallel to
304 ongoing enrolement.

305

306 In a translational design, SP8 as murine project aims at elucidating molecular mechanisms in
307 **perinatal priming of tolerance and allergy**. Findings from the cohorts are tested in the
308 models and *vice versa*. Mechanisms of postnatal allergen-driven sensitization or tolerance
309 induction are investigated focusing on common pathways involved in the development of
310 atopic diseases as asthma, AD and FA. Furthermore, the involvment of the innate immune
311 system and especially the inflammasome with NLRP3 is investigated regarding postnatal
312 tolerance development against innocuous allergens. Results revealed hitherto unknown
313 regulatory mechanisms for NLRP3 in maternal tolerance induction and protection from
314 allergic diseases, involving both the innate and adaptive immune system.

315

Discussion

Allergic diseases are the most prevalent chronic diseases in childhood (1). They affect young patients, their families and society as a whole, resulting in immense societal and economic costs to the community.

Interactions between genetic, epigentic and environmental factors influence a child´s immune maturation. By identifying novel markers for allergy development, the CHAMP consortium aims to predict subsequent development of allergic diseases already at this early stage of maturation. The DAAB survey illustrated that families affected by allergies are highly interested in the prediction of allergies and disease development. Also, identification of novel medication and prevention of allergies are of major interest for affected families. However, current prediction scores include family history of allergic disease, clinical features and laboratory data, reaching limited specificity and/or sensitivity only (25, 26, 28).

To address these critical patient needs, we developed research projects covering all major allergic diseases and all age groups, including SP2, elucidating the impact of allergic disease on HRQoL of children and parents, respectively. Three SPs (SP3,5,6) aim at prediction of asthma by identifying novel biomarkers and predictors during onset, severity or remission. Natural or induced tolerance development is central for FA, and asthma remission (SP4/6). Recent data suggest, that changes in the microbiome are involved in allergy development. Therefore, the microbiome projects (SP7) will add data to all studies for disease prediction, mechanisms that underly disease development and environmental influence. To elucidate underlying pathomechanisms, targets, involved in allergy development, severity or tolerance development, that were identified in other projects, will be tested in SP8 in mouse models specific for the allergic disease.

We are aware, that one of the major challenges within CHAMP is the variety of cohorts, resulting in different levels of phenotype definition: specialist diagnosis, doctor's diagnosis, parent reported doctor's diagnosis. We addressed this establishing a common database and developing a core questionnaire (SP2) for all participating studies, where detailed questions on disease, symptoms and medication were asked, thus allowing the use of phenotypes for analysis across studies. Common SOPs for all biosampling and subsequent laboratory analyses were established in a collaborative process, enabling us to analyse and compare results. Yet, the variety represents also a major strength of CHAMP. The various study populations cover the whole age range and all common allergic diseases at different stages of manifestation. We established new cohorts for various allergic diseases, complemented by already established cohorts, including two longitudinal birth cohorts with excessive biosamples.

In conclusion, CHAMP aims to investigate the determinants of different allergic diseases (FA, AD, asthma, AR) across the whole pediatric age range with particular attention to primary tolerance (no onset of disease) and acquired tolerance (remission of existing disease). Thus, the CHAMP consortium has the unique opportunity to assess the development and remission of childhood allergies at all stages of childhood immune system and organ development.

Acknowledgements

Impact statement

CHAMP adds novel insight to the puzzle of early onset, natural tolerance and remission of different allergic diseases from birth to adolescence. This will lay the ground for future development of preventive strategies and shall contribute to opening up novel avenues for therapeutic options in the long term, which will clearly make an impact on the life of allergic patients and their families.

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476

478   **Figure legend**

479   **Fig. 1: Results from the DAAB survey(participants n=786): Interest of families with**
480   **allergic children in the prediction of A) developing further allergic disease (left) and if**
481   **the answer is yes/not sure, which allergic disease are you interested in (right); B)**
482   **What probability do you count as reliable; C) course of a current allergic disease, e.g.**
483   **loss (left) and if the answer is yes/not sure, which allergic disease are you interested**
484   **in (right). AD-atopic dermatitis, AR-allergic rhinoconjunctovitis, FA-food allergy**

485   **Fig. 2: Interest and needs of families with allergic children from the DAAB survey**
486   **(n=786)**

487   **Fig. 2A: Satisfaction of families with allergic children with their child's current therapy**
488   **recommended by their paediatrician depending on the allergic disease of the child**

489   **Fig. 2B: If your pediatrician expects worsening of your child's allergic disease, what**
490   **would you be willing to do?**

491   **Fig 2C: How important do you consider certain fields of action and research in health?**

492   **Fig. 3: CHAMP project: Analysing biomarkers and prediction of childhood allergy on**
493   **several layers of onset, progression and remission of allergies from birth to**
494   **adolescence**
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