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High-Sensitivity C-Reactive Protein and Allergic Endpoints in German Adolescents

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Keywords
High-sensitivity C-reactive protein · Eczema · Asthma · Allergic rhinitis · Allergic sensitization · Adolescent

Abstract
Background: Assessing high-sensitivity C-reactive protein (hs-CRP) in relation to allergic endpoints can shed light on both the mechanisms of allergic disease development and early non-communicable disease prevention. However, only a few epidemiological studies so far have investigated the relationship in children and adolescents, and the results were mixed. ***Objectives:*** We sought to examine the interrelation between hs-CRP levels and allergic outcomes using a larger population size and a longitudinal study design. ***Methods:*** Complete data were available on 1,955 participants from the 15-years follow-up of the 2 large population-based German birth cohorts – GINIplus and LISA. Serum hs-CRP concentrations were measured using the immunoturbidimetric high-sensitive assay. Six allergic endpoints were used – doctor-diagnosed asthma, doctor-diagnosed eczema, doctor-diagnosed allergic rhinitis, food sensitization, aeroallergen sensitization, and any sensitization. We used generalized estimation equation models to assess the asso-

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ciations between hs-CRP levels and allergic endpoints. ***Results:*** Our longitudinal analyses did not detect any significant association between hs-CRP levels and any of the studied allergic outcomes (e.g., asthma, eczema, allergic rhinitis, food sensitization, aeroallergen sensitization, and any sensitization). The results were consistent in a series of sensitivity analyses. ***Conclusions:*** Our study suggests that there is no association between hs-CRP levels and any of the allergic endpoints in German adolescents. However, whether allergic diseases are inflammatory conditions and which markers might be most sensitive, remain to be confirmed in future studies.

Introduction

According to the hygiene hypothesis, infections in childhood might be beneficial for modulating immune tolerance and the subsequent development of allergic disorders [1]. High-sensitivity C-reactive protein (hs-CRP) is a marker of low-grade systemic inflammation, which has been closely linked to many non-communicable diseases (NCD) [2]. Childhood allergic diseases are considered the earliest debuting NCD [2]. Thus, exploring the relationship between hs-CRP and allergies may be valuable not only for understanding the mechanisms of allergic disease development but also for initiating early NCD prevention. However, only a handful of epidemiological studies so far have investigated the relationship between hs-CRP levels and concurrent or later allergic outcomes in children and adolescents, and the findings were mixed (these findings are summarized in online suppl. Table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000497320) [3–7]. Most of these studies adopted a cross-sectional design [3, 4, 7] and had a small sample size [3–6]. Therefore, we sought to re-examine the interrelation between hs-CRP levels and allergic outcomes using a larger population size and a longitudinal study design.

Methods

Study Population

The current analysis is based on the data from 2 ongoing multicenter population-based prospective birth cohort studies in Germany: the "German Infant Study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy development" (GINIplus) study and the "Influence of Life-Style Factors on the Development of the Immune System and Allergies in East and West Germany" (LISA) study. Detailed information on the cohorts has been published elsewhere [8, 9].The GINIplus is a 2-armed study consisting of 5,991 healthy full-term and normal birth weight newborns recruited at selected maternity wards in Munich and Wesel between 1995 and 1998. The interventional arm included newborns with family history of allergy. The newborns participated in the randomized, double-blind controlled intervention trial with hydrolyzed formulas, including partially hydrolyzed whey, extensively hydrolyzed whey, extensively hydrolyzed casein, or a conventional cow's milk. The observational arm included newborns without family history of allergy, and those whose parents declined participation in the intervention trial. The LISA cohort is a population-based cohort consisting of 3,094 full-term and normal birth weight newborns recruited at selected maternity wards in Munich, Leipzig, Wesel, and Bad Honnef from 1997 to 1999.

In both cohorts, parent-completed questionnaires were administered at birth and when children were 1, 2, 3, 4, 6, 10, and 15 years of age in GINIplus and at 6, 12, 18, and 24 months and 4, 6, 10, and 15 years of age in LISA. Additionally, blood samples were drawn at 6, 10, and 15 years from subgroups of the cohorts.

Approvals for the 2 cohorts have been obtained from the local Ethics Committees (Bavarian General Medical Council, University of Leipzig, Medical Council of North-Rhine-Westphalia). All families have signed informed consent.

Hs-CRP Assessment

Serum hs-CRP concentrations at 10- and 15-years were measured using the Roche (Mannheim, Germany) Tina-quant CRP (latex) high-sensitivity assay. The measured hs-CRP concentrations had highly right-skewed distribution, as many hs-CRP observations were below the detection limits. To facilitate data analysis, we categorized hs-CRP levels into 3 age- and sex-specific levels [10]. The hs-CRP categories at 10 years were CRP-I, below detection limit (<0.02 mg/dL); CRP-II, ≥0.02 mg/dL and <75th sex-specific percentile of those with CRP ≥0.02 mg/dL; and CRP-III, ≥0.02 mg/dL and ≥75th sex-specific percentile of those with CRP ≥0.02 mg/dL. Hs-CRP categories at 15 years old were: CRP-I, below detection limit (<0.016 mg/dL); CRP-II, ≥0.016 mg/dL and <75th sex-specific percentile of those with CRP ≥0.016 mg/dL; and CRP-III, ≥0.016 mg/dL and ≥75th sex-specific percentile of those with CRP ≥0.016 mg/dL.

Allergic Endpoints

For the main analysis, all allergic endpoints were defined based on the information collected at the 10- and 15-year follow-ups. Doctor-diagnosed eczema and asthma were defined based on a positive response to the question "In the past 12 months, was your child diagnosed with eczema/asthma?" Doctor-diagnosed allergic rhinitis was defined based on a positive response to the following question: "In the past 12 months, has your child been diagnosed with hay fever/allergic rhinitis?"

Specific IgE against common allergens was assessed in serum collected at the 10- and 15-year follow-up sessions using the standardized CAP-RAST FEIA method (ThermoFischer, Freiburg, Germany). Allergic sensitization to aeroallergens (SX1: house dust mites, cats, dogs, mold, birch, rye, mugwort and timothy grass), as well as allergic sensitization to food allergens (FX5: milk, peanut, eggs, soya, cod and wheat flour), was defined as a specific IgE value above 0.35 kU/L against SX1 and FX5 allergens respectively.

Any sensitization was defined as an allergic sensitization to either aero- or food allergens.

For a sensitivity analysis, eczema, asthma, and allergic rhinitis were defined based on the information collected from birth (eczema) or from 3 years onwards (asthma and allergic rhinitis) [11]. This was done due to the difficulty of accurate diagnosis of asthma and allergic rhinitis at very young ages [12]. Each of these 3 outcomes was defined as satisfying 2 out 3 following criteria: (1) doctor diagnosis ever, (2) having symptoms in the last 12 months, and (3) taking medication in the last 12 months.

Covariates

The following potentially important covariates were considered for this analysis: sex, study (GINIplus intervention vs. GINIplus observation vs. LISA), study area (Munich vs. Leipzig vs. Wesel vs. Bad Honnef), time-specific net equivalent household income defined as time- and city-specific income tertiles due to large income difference among cities, time-specific body mass index (kg/m^2), time-specific exposure to tobacco smoke at home in the last 12 months, child's smoking status (as ever smoking) at 15 years, parental education level (based on highest parental level of education: both parents with less than 10 years of school [low], at least 1 parent with 10 years of school [medium], at least 1 parent with more than 10 years of school [high], classified according to the German education system), and parental history of allergic diseases (self-report of doctor diagnosis of asthma, allergic rhinitis, or eczema, collected at birth). Missing values in income variables, which were many, were coded as a separate category.

Statistical Analysis

We used generalized estimation equation (GEE) models [13] with log link and exchangeable correlation structure to assess the associations between hs-CRP levels and allergic endpoints at 10 and 15 years of age because of the longitudinal design of the current study (i.e., exposure and outcomes). Thus, the results are presented as ORs with corresponding 95% CIs.

We adjusted main models for time of follow-up and the covariates, which were associated with hs-CRP, as well as at least one of the outcome endpoints. Thus, the main models were adjusted for sex, study area, net equivalent household income, body mass index, and child's smoking at 15 years. We also performed several sensitivity analyses. First, we re-ran the models for eczema, asthma, and allergic rhinitis using alternative definitions. This was done to achieve larger power to detect possible associations, as prevalence of asthma and eczema based exclusively on doctor diagnosis in the past 12 months were low. Second, participants who had infections during the last 7 days prior to blood collection at 10 or 15 years, or participants with such information missing were excluded from the analytic sample, as their CRP levels could have been affected. Third, participants who had asthma, eczema, and allergic rhinitis (alternative definitions), or participants with such information missing, were excluded from the analysis with sensitization outcomes. Fourth, models were additionally adjusted for the covariates, which were associated with either hs-CRP or at least one of the allergic endpoints – study, parental education level, and parental history of allergic diseases. Finally, we explored cross-sectional associations in 10- and 15-year old participants separately by running logistic (instead of GEE) models.

We performed all the statistical analyses using the program R, version 3.5.0 (Vienna, Austria) [14]. GEE models were fitted by the *geeglm* function from the *geepack* package [15].

Results

Compared to the original GINIplus and LISA participants (n = 9,085), samples included in the current analysis (n = 1,955; online suppl. Fig. S1) were more likely to be from the GINIplus intervention or LISA studies, to have atopic parents and parents with high school education (online suppl. Table S2). Approximately 41.7 and 13.7% of the study participants had hs-CRP levels below detection limit at the age of 10 and 15 years, respectively (Table 1). The prevalence rates of eczema, asthma, and allergic rhinitis were similar at 10 and 15 years. The prevalence of food sensitization was higher at 10 years than in 15-year participants; aeroallergen sensitization showed an opposite trend.

We did not detect any significant association between hs-CRP levels and any of the studied allergic outcomes in the main analysis (Table 2). This finding was consistent across sensitivity analyses (using different definitions for asthma, eczema, and allergic rhinitis (online suppl. Table S3); restricting analyses to participants without infections during the last 7 days (online suppl. Table S4); restricting analyses to participants without asthma, allergic rhinitis or eczema for sensitization outcomes only (online suppl. Table S5); and including additional adjustment (online suppl. Table S6). Similarly, no associations were detected when associations in 10- and 15-year old adolescents were tested cross-sectionally (data not shown).

Discussion

In agreement with our findings, Livnat and associates failed to detect any significant association between hs-CRP levels and current asthma in 131 Israeli children aged 6–18 years [3]. In an analysis of 277 Danish children, higher hs-CRP levels at 7 years was associated with an elevated risk of concurrent allergic rhinitis, asthma, and sensitization to aeroallergens, food allergens, or any allergen; yet, no associations were observed between CRP levels at 6 months with later development of allergic outcomes until 7 years [6]. However, in 2 analyses by Mustonen et al. [4, 5], children with elevated hs-CRP levels were at a decreased risk of allergic sensitization, though

Table 1. Characteristics of the study participants (n = 1,955)

Variable	Baseline		10 years		15 years	
	n/N or mean	% or SD	*n*/N or mean	% or SD	*n*/N or mean	% or SD
Covariates						
Area						
Munich	1,060/1,955	54.2	–	–	–	–
Leipzig	205/1,955	10.5	–	–	–	–
Bad Honnef	91/1,955	4.7	–	–	–	–
Wesel	599/1,955	30.6	–	–	–	–
Study						
GINIplus observation	582/1,955	29.8	–	–	–	–
GINIplus intervention[a]	652/1,955	33.4	–	–	–	–
LISA	721/1,955	36.9	–	–	–	–
Gender, female	957/1,955	49.0	–	–	–	–
Parental history of allergic diseases, yes	1,199/1,937	61.9	–	–	–	–
Parental education[b]						
Low (<10 years)	93/1,949	4.8	–	–	–	–
Medium (10 years)	500/1,949	25.7	–	–	–	–
High (>10 years)	1,356/1,949	69.6	–	–	–	–
Child smoking, yes	–	–			142/1,955	7.3
Household income						
Low	–	–	563/1,955	28.8	545/1,955	27.9
Medium	–	–	659/1,955	33.7	587/1,955	30.0
High	–	–	583/1,955	29.8	585/1,955	29.9
Missing	–	–	150/1,955	7.7	238/1,955	12.2
BMI, kg/m^2[c]	–	–	17.33	2.43	20.79	3.18
Infections last 7 days, yes	–	–	437/1,898	23.0	425/1,955	21.7
Hs-CRP[d]						
I	–	–	815/1,955	41.7	267/1,955	13.7
II	–	–	884/1,955	45.2	1,260/1,955	64.5
III	–	–	256/1,955	13.1	428/1,955	21.9
Outcomes						
Any sensitization, yes	–	–	854/1,955	43.7	943/1,955	48.2
Food sensitization, yes	–	–	359/1,955	18.4	220/1,955	11.3
Aeroallergen sensitization, yes	–	–	760/1,955	38.9	916/1,955	46.9
Asthma, yes[e]	–	–	72/1,904	3.8	75/1,911	3.9
Asthma using alternative definitions, yes[f]	–	–	118/1,923	6.1	131/1,909	6.9
Eczema, yes[e]	–	–	89/1,900	4.7	61/1,896	3.2
Eczema using alternative definitions, yes[f]	–	–	215/1,924	11.2	176/1,907	9.2
Allergic rhinitis, yes[e]	–	–	199/1,882	10.6	211/1,884	11.2
Allergic rhinitis using alternative definitions, yes[f]	–	–	224/1,881	11.9	351/1,888	18.6

[a] Group that participated in an intervention trial with hypoallergenic formulae.

[b] Definition based on highest parental level of education: both parents with less than 10 years of school (low), at least one parent with 10 years of school (medium), at least one parent with more than 10 years of school (high), classified according to the German education system.

[c] Mean ± SD.

[d] CRP categories at 10 years: CRP-I, below detection limit (<0.02 mg/dL); CRP-II, ≥0.02 mg/dL and <75th sex-specific percentile of those with CRP ≥0.02 mg/dL; CRP-III, ≥0.02 mg/dL and ≥75th sex-specific percentile of those with CRP ≥0.02 mg/dL. CRP categories at 15 years: CRP-I, below detection limit (<0.016 mg/dL); CRP-II, ≥0.016 mg/dL and <75th sex-specific percentile of those with CRP ≥0.016 mg/dL; CRP-III, ≥0.016 mg/dL and ≥75th sex-specific percentile of those with CRP ≥0.016 mg/dL.

[e] Defined as a parental report of doctor diagnosis during the last 12 months.

[f] The definitions are based on satisfying two out of three criteria: (1) ever doctor diagnosis from 1 (eczema) or 3 years onwards (asthma and allergic rhinitis), (2) medication use during last 12 months, and (3) allergic diseases symptoms during last 12 months.

BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; GINIplus, the German Infant Study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy; LISA, the Immune System and the development of Allergies in childhood study.

Table 2. Adjusted ORs with 95% CIs for hs-CRP levels and allergic endpoints estimated using generalized estimating equations models[a]

Endpoint	Number of observations	hs-CRP category[b]				
		I	II		III	
		reference	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Any sensitization	1,955	1	0.93 (0.79–1.09)	0.353	0.99 (0.80–1.23)	0.929
Food sensitization	1,955	1	1.09 (0.87–1.36)	0.453	1.04 (0.77–1.41)	0.810
Aeroallergen sensitization	1,955	1	0.95 (0.81–1.11)	0.513	1.03 (0.83–1.28)	0.762
Asthma	1,951	1	0.98 (0.66–1.46)	0.927	0.77 (0.42–1.41)	0.400
Eczema	1,929	1	1.03 (0.70–1.51)	0.894	0.85 (0.48–1.52)	0.592
Allergic rhinitis	1,953	1	1.07 (0.82–1.39)	0.609	1.11 (0.79–1.58)	0.549

[a] All models adjusted for time of follow-up, study area, sex, parental income, body mass index, and child smoking at 15 years.

[b] CRP categories at 10 years: CRP-I, below detection limit (<0.02 mg/dL); CRP-II, ≥0.02 mg/dL and <75th sex-specific percentile of those with CRP ≥0.02 mg/dL; CRP-III, ≥0.02 mg/dL and ≥75th sex-specific percentile of those with CRP ≥0.02 mg/dL. CRP categories at 15 years: CRP-I, below detection limit (<0.016 mg/dL); CRP-II, ≥0.016 mg/dL and <75th sex-specific percentile of those with CRP ≥0.016 mg/dL; CRP-III, ≥0.016 mg/dL and ≥75th sex-specific percentile of those with CRP ≥0.016 mg/dL.

hs-CRP, high-sensitivity C-reactive protein.

not with atopic dermatitis and asthma. In addition, a study of 4,111 US children and adolescents (2–19 years) reported that increased hs-CRP levels were significantly associated with an elevated risk of atopy and food allergy [7]. The exact reasons for the mixed findings across the previous studies and our current analysis are unclear but may be related to heterogeneity in study design, participants' age at assessment of hs-CRP and allergic endpoints, study area, or genetic background; furthermore, chance findings cannot be excluded.

Our study had several strengths in terms of the following 3 aspects: first, while most of the previous studies collected data on hs-CRP or allergic outcomes once, we utilized repeated measurements on both hs-CRP levels and allergic outcomes; second, the population size of our study was large and a rich set of covariates was considered, which reduced a potential for residual confounding; and third, we performed several sensitivity analyses, in particular, to reduce reverse causality (online suppl. Table S5) and to increase power (online suppl. Table S3), which demonstrated consistency of the effect estimates.

However, our study is not without limitation. First, although our analysis was based on repeatedly collected data from the prospective cohorts and were analyzed using GEE models, we had data on hs-CRP and allergic outcomes collected around the same time, which may have compromised the ability to judge the direction of the studied associations. Second, there can be a critical window (e.g., the first 1,000 days of life) for early programing of the immune system [16], thus measuring of the hs-CRP levels at 10 and 15 years may be too late to reflect the low-grade systemic inflammation status of early childhood. This can also help to explain the null findings observed in our study. Third, study participants were more likely to be initially recruited (and to further participate in the studies) from the families with higher socio-economic status compared to the general German population, which therefore reduces the generalizability of our findings. Fourth, we used only a single marker (hs-CRP) to reflect systemic inflammation, which is actually characterized by a range of indicators, such as higher levels of interleukin 6, interleukin 1B, Tumor Necrosis Factor, and adiponectin [2]. Hs-CRP is an acute-phase protein that rises quickly after a stimulus up to 48 h, with the plasma half-life of 19 h. There might hence be an association with other markers of systemic inflammation but not with hs-CRP.

Conclusions

In summary, our study suggests that there is no association between hs-CRP levels and any of the allergic endpoints including allergic sensitization, asthma, eczema, and allergic rhinitis in German adolescents. More studies are needed to reach a definite conclusion on whether allergic diseases are inflammatory conditions and which markers, and at which ages, might be most sensitive.

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Statement of Ethics

Subjects have given their written informed consent. The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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Author Contributions

B.-Y.Y., I.M., and J.H. conceived, designed the study, and conducted analysis. B.-Y.Y. and I.M. wrote the paper. C.H., M.S., T.S., S.K., G.H., C.-P.B., A.B., D.B., and G.-H.D. critically reviewed and revised the manuscript. All authors gave their agreement to the manuscript and conclusions. All authors read and approved of the final manuscript.

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