

**Figure S1. Flow chart of study participants.** **\***Main covariates included study area, sex, BMI and child’s smoking at 15 years. Missing values in income variables were coded as a separate category.

**Table S1** Prior studies on hs-CRP levels and childhood allergic endpoints

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Authors (year)** | **Country** | **Study design** | **Age of hs-CRP and outcomes assessment** | **Sample size** | **Main findings** |
| Visness et al. (2009) | United States | Cross-sectional | 2-19 years | 4111 | Elevated CRP levels were associated with a significant increased risk of food allergy (OR = 1.25, 95% CI = 1.01-1.55), and a borderline significant increased risk of atopy (OR = 1.22, 95% CI = 1.00-1.49). |
| Mustonen et al. 2012 | Finland, Germany, Austria, France, Switzerland | Cross-sectional analysis in birth cohort study | 4.5 years | 653 | Children with CRP levels lower than the 75th percentile had a lower risk of sensitization to inhaled allergens and seasonal allergens compared to those with CRP levels below the detection limit. However, no significant further decrease in risk of different sensitizations was observed in those with CRP levels higher than 75th percentile. In addition, no association was detected when CRP was used as a continuous variable. |
| Mustonen et al. (2013) | Finland, Germany, Austria, France, Switzerland | Longitudinal | 1 year and 4.5 years | 636 | Increased CRP levels at the age of 1 year were associated with a decreased risk of allergic sensitization at the age of 4.5 years only in non-sensitized children at 1 year old. However, no association was observed for the overall population. |
| Livnat et al. (2015) | Israel | Cross-sectional | 6-18 years | 131 | No significant association was observed between CRP levels and current asthma in children aged 6-18 years. |
| Chawes et al. (2017) | Denmark | Longitudinal (7 follow-up years) | 6 months and 7 years | 277 | Elevated CRP levels at 7 years were associated with a concurrent (6 years) higher risk of any sensitization, aeroallergen sensitization, food sensitization, asymptomatic sensitization, allergic rhinitis, and asthma. However, CRP levels at 6 months were not associated with later development of allergy endpoints in longitudinal analyses. |

Abbreviations: CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio.

**Table S2** Baseline characteristics of the originally recruited participants and the participants from the analytic sample, n (%)

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Recruited participants** | **Analytic sample** | **p-value\*** |
| Study |  |  | <0.0001 |
| GINIplus observation | 3739 (41.2) | 582 (30) |  |
| GINIplus intervention† | 2252 (24.8) | 652 (33) |  |
| LISA | 3094 (34.1) | 721 (37) |  |
| Area |  |  | <0.0001 |
| Munich | 4413 (48.6) | 1060 (54) |  |
| Leipzig | 976 (10.7) | 205 (11) |  |
| Bad Honnef | 306 (3.4) | 91 (4.7) |  |
| Wesel | 3390 (37.3) | 599 (31) |  |
| Sex |  |  | 0.848 |
| Female | 4349 (47.9) | 957 (49) |  |
| Male | 4575 (50.4) | 998 (51) |  |
| Missing | 161 (1.8) | 0 (0.0) |  |
| Parental education§ |  |  | <0.0001 |
| Low (<10 years) | 969 (10.7) | 93 (4.8) |  |
| Medium (10 years) | 2656 (29.2) | 500 (26) |  |
| High (>10 years) | 5379 (59.2) | 1356 (69) |  |
| Missing | 81 (0.9) | 6 (0.3) |  |
| Parental history of allergic diseases¶ |  |  | <0.0001 |
| No | 4081 (44.9) | 738 (38) |  |
| Yes | 4841 (53.3) | 1199 (61) |  |
| Missing | 163 (1.8) | 18 (0.9) |  |

Abbreviations: GINIplus, the German Infant Study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy; LISAplus, the Immune System and the development of Allergies in childhood study.

\*p-value from Chi-Square test.

†Group that participated in the intervention trial with hypoallergenic formulae.

§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.

¶Definition based on either of the parents having ever doctor-diagnosed asthma, allergic rhinitis or eczema

**Table S3** Adjusted ORs with 95% CIs\* for hs-CRP levels and alternative definitions of eczema, asthma, and allergic rhinitis † estimated using generalized estimation equation models

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **hs-CRP category**§ | | | | | | |
|  |  | **I** |  | **II** | |  | **III** | |
| **Outcome** | **No. of observations** | **Reference** |  | **OR (95% CI)** | **p-value** |  | **OR (95% CI)** | **p-value** |
| Asthma | 1953 | 1 |  | 1.05 (0.76, 1.45) | 0.778 |  | 0.84 (0.54, 1.33) | 0.465 |
| Eczema | 1951 | 1 |  | 1.00 (0.77, 1.30) | 0.982 |  | 0.86 (0.60, 1.24) | 0.428 |
| Allergic rhinitis | 1948 | 1 |  | 0.92 (0.73, 1.17) | 0.506 |  | 0.84 (0.61, 1.15) | 0.275 |

Abbreviations: CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio.

\*All models adjusted for time of follow-up, study area, sex, parental income, body mass index, and child’s smoking at 15 years.

†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.

§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.

**Table S4** Adjusted ORs with 95% CIs\* for hs-CRP and allergic outcomes in participants without infections during last 7 days estimated using generalized estimation equation models

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **hs-CRP category†** | | | | | | |
|  |  | **I** |  | **II** | |  | **III** | |
| **Outcome** | **No. of observations** | **Reference** |  | **OR (95% CI)** | **p-value** |  | **OR (95% CI)** | **p-value** |
| Any sensitization | 1857 | 1 |  | 0.90 (0.75, 1.08) | 0.250 |  | 0.99 (0.77, 1.28) | 0.958 |
| Food sensitization | 1857 | 1 |  | 0.96 (0.75, 1.24) | 0.777 |  | 0.95 (0.66, 1.35) | 0.770 |
| Aeroallergen sensitization | 1857 | 1 |  | 0.94 (0.79, 1.13) | 0.534 |  | 1.07 (0.83, 1.38) | 0.594 |
| Asthma | 1836 | 1 |  | 1.01 (0.65, 1.56) | 0.982 |  | 0.82 (0.41, 1.64) | 0.583 |
| Eczema | 1821 | 1 |  | 1.18 (0.76, 1.84) | 0.465 |  | 0.86 (0.44, 1.68) | 0.653 |
| Allergic rhinitis | 1824 | 1 |  | 1.00 (0.74, 1.34) | 0.994 |  | 1.26 (0.85, 1.87) | 0.251 |

Abbreviations: CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio.

\*All models adjusted for time of follow-up, study area, sex, parental income, body mass index, and child’s smoking at 15 years.

**†**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.

**Table S5** Adjusted ORs with 95% CIs\* for hs-CRP and sensitization outcomes in participants without allergic manifestation**†** estimated using generalized estimation equation models

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **hs-CRP category**§ | | | | | | |
|  |  | **I** |  | **II** | |  | **III** | |
| **Outcome** | **No. of observations** | **Reference** |  | **OR (95% CI)** | **p-value** |  | **OR (95% CI)** | **p-value** |
| Any sensitization | 1571 | 1 |  | 0.98 (0.80, 1.20) | 0.858 |  | 1.13 (0.87, 1.48) | 0.354 |
| Food sensitization | 1571 | 1 |  | 1.10 (0.81, 1.49) | 0.544 |  | 0.97 (0.64, 1.48) | 0.884 |
| Aeroallergen sensitization | 1571 | 1 |  | 1.01 (0.82, 1.24) | 0.922 |  | 1.20 (0.92, 1.58) | 0.181 |

Abbreviations: CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio.

**\***Adjusted for time of follow-up, study area, sex, parental income, body mass index, and child smoking at 15 years.

**†**Allergic manifestation is defined as no asthma, allergic rhinitis, or eczema using two out of the following 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.

§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.

**Table S6** Additionally adjusted ORs with 95% CIs for hs-CRP levels and allergic outcomes estimated using generalized estimation equation models\*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **hs-CRP category†** | | | | | | |
|  |  | **I** |  | **II** | |  | **III** | |
| **Outcome** | **No. of observations** | **Reference** |  | **OR (95% CI)** | **p value** |  | **OR (95% CI)** | **p value** |
| Any sensitization | 1932 | 1 |  | 0.93 (0.79, 1.09) | 0.355 |  | 0.99 (0.79, 1.23) | 0.900 |
| Food sensitization | 1932 | 1 |  | 1.08 (0.86, 1.35) | 0.512 |  | 1.02 (0.75, 1.39) | 0.878 |
| Aeroallergen sensitization | 1932 | 1 |  | 0.95 (0.80, 1.12) | 0.515 |  | 1.03 (0.83, 1.28) | 0.794 |
| Asthma | 1928 | 1 |  | 0.97 (0.65, 1.45) | 0.894 |  | 0.78 (0.42, 1.43) | 0.420 |
| Eczema | 1907 | 1 |  | 1.02 (0.69, 1.49) | 0.934 |  | 0.80 (0.45, 1.44) | 0.465 |
| Allergic rhinitis | 1930 | 1 |  | 1.07 (0.82, 1.40) | 0.607 |  | 1.11 (0.77, 1.58) | 0.577 |

Abbreviations: CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio.

\*All models adjusted for time of follow-up, study area, sex, parental income, body mass index, and child’s smoking at 15 years, study, atopic parents, and parental education level.

**†** CRP categories at 10 years old: 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 old: 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.