Title: Comorbidity and persistence of allergy-related phenotypes in children in the longitudinal MeDALL study

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Body: There is evidence in the literature that eczema (E), rhinitis (R) and asthma (A) coexist. It is unknown to what extent this comorbidity could be ascribed to chance or common causal mechanisms. In 12 ongoing European birth cohorts participating in the MeDALL (Mechanisms of the Development of Allergy) consortium, we assessed comorbidities at 4 and 8 years excluding coexistence by chance, the role of sensitization in phenotypic development and the predictive value of single or comorbid phenotypes at 4 years on the presence of comorbid phenotypes at 8 years. A cross-sectional survey on 4 and 8-year-old children (n=22,417 and 18,975 respectively) investigated E, R and A from questionnaires and specific IgE to common allergens. Comorbidity defined as the coexistence of two or three allergy-related phenotypes in the same individual was estimated through the degree to which an observed frequency differs from the expected value due to chance alone. A longitudinal study of 10,099 children with data at both ages assessed persistence and comorbidity of E, R and A, using logistic regression models. The prevalence of having any phenotype (E or R or A or combined phenotypes) was 28% both at 4 and 8 years and the prevalence of comorbid phenotypes, which were more commonly observed than expected, was 4% both at 4 and 8 years. The presence of single and comorbid phenotypes at age 4 years increased the risk of having comorbid phenotypes by age 8 following a strong dose-response pattern, regardless of sensitization status. Coexisting E, R and A in the same children may have a causal relationship. The degree and distribution of the three comorbidities is independent of the presence of sensitization.