Increasing Severity of Early-Onset Atopic Dermatitis, But Not Late-Onset, Associates with Development of Aeroallergen Sensitization and Allergic Rhinitis in Childhood

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Abstract

Background: Early exposure to allergens through a defect skin barrier has been proposed as a mechanism for inducing sensitization and development of allergic diseases. We hypothesized that early-onset, severe atopic dermatitis (AD) is associated with development of aeroallergen sensitization and allergic rhinitis. **Methods**: We included 368 children from the Copenhagen Prospective Studies on Asthma in Childhood $_{2000}$ (COPSAC $_{2000}$) at-risk mother-child cohort. AD was diagnosed prospectively based on Hanifin&Rajka's criteria and severity assessed using the Scoring Atopic Dermatitis (SCORAD) index. Early-onset AD was defined as debut [?]1 year, late-onset as debut from 1-6 years. Aeroallergen sensitization and allergic rhinitis were diagnosed at ages 6-7 and 12 years. Associations between early-onset and late-onset AD and allergy endpoints were calculated using general estimating equations (GEE) models to compute the overall odds ratios (OR) for both time points. **Results**: Early-onset AD (yes/no) and severity (SCORAD) were associated with development of aeroallergen sensitization during childhood; GEE OR=1.68 [1.08; 2.62], p=0.02 and 1.08 [1.03; 1.12], p<0.001, whereas late-onset was not; GEE OR=1.65 [0.92; 2.94], p=0.08 and 1.01 [0.97; 1.06], p=0.55. The same trend was seen for allergic rhinitis with significant association between early-onset AD and allergic rhinitis; GEE OR=1.56 [1.01; 2.41], p=0.04 and severity; GEE OR=1.09 [1.05; 1.13], p<0.001, whereas late-onset AD showed no association. The effects on sensitization and rhinitis of early-onset vs. late-onset AD severity were significantly different: p-interaction $_{\text{sensitization}}$=0.03 and p-interaction $_{\text{rhinitis}}$<0.01. **Conclusion**: Increasing severity of early-onset AD, but not late-onset AD, associates with aeroallergen sensitization and allergic rhinitis later in childhood.

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Governance: We are aware of and comply with recognized codes of good research practice, including the Danish Code of Conduct for Research Integrity. We comply with national and international rules on the safety and rights of patients and healthy subjects, including Good Clinical Practice (GCP) as defined in the EU's Directive on Good Clinical Practice, the International Conference on Harmonisation's (ICH) good clinical practice guidelines and the Helsinki Declaration. Privacy is important to us which is why we follow national and international legislation on General Data Protection Regulation (GDPR), the Danish Act on Processing of Personal Data and the practice of the Danish Data Inspectorate.

ABSTRACT

Background: Early exposure to allergens through a defect skin barrier has been proposed as a mechanism for inducing sensitization and development of allergic diseases. We hypothesized that early-onset, severe atopic dermatitis (AD) is associated with development of aeroallergen sensitization and allergic rhinitis.

Methods : We included 368 children from the Copenhagen Prospective Studies on Asthma in Childhood$_{2000}$(COPSAC$_{2000}$) at-risk mother-child cohort. AD was diagnosed prospectively based on Hanifin&Rajka's criteria and severity assessed using the Scoring Atopic Dermatitis (SCORAD) index. Early-onset AD was defined as debut [?]1 year, late-onset as debut from 1-6 years. Aeroallergen sensitization and allergic rhinitis were diagnosed at ages 6-7 and 12 years. Associations between early-onset and late-onset AD and allergy endpoints were calculated using general estimating equations (GEE) models to compute the overall odds ratios (OR) for both time points.

Results : Early-onset AD (yes/no) and severity (SCORAD) were associated with development of aeroallergen sensitization during childhood; GEE OR=1.68 [1.08; 2.62], p=0.02 and 1.08 [1.03; 1.12], p<0.001, whereas late-onset was not; GEE OR=1.65 [0.92; 2.94], p=0.08 and 1.01 [0.97; 1.06], p=0.55. The same trend was seen for allergic rhinitis with significant association between early-onset AD and allergic rhinitis; GEE OR=1.56 [1.01; 2.41], p=0.04 and severity; GEE OR=1.09 [1.05; 1.13], p<0.001, whereas late-onset AD showed no association. The effects on sensitization and rhinitis of early-onset vs. late-onset AD severity were significantly different: p-interaction$_{\text{sensitization}}$=0.03 and p-interaction$_{\text{rhinitis}}$<0.01.

Conclusion : Increasing severity of early-onset AD, but not late-onset AD, associates with aeroallergen sensitization and allergic rhinitis later in childhood.

Keywords: Atopic dermatitis; early-onset; late-onset; severity; SCORAD; Filaggrin mutation; aeroallergen sensitization; specific IgE; allergic rhinitis; childhood**Abbreviations**AD = Atopic Dermatitis

COPSAC = Copenhagen Prospective Studies on Asthma in Childhood

SCORAD = Scoring Atopic Dermatitis

FLG = Filaggrin

OR = Odds Ratio GEE = General Estimating Equations sIgE = specific IgE

Introduction

Atopic dermatitis (AD) is a chronic relapsing disease, which most often debuts in early childhood and remits later in childhood. It is characterized by defects in the barrier function due to an abnormal stratum corneum in both affected and nonaffected skin[1,2]. Several lines of evidence indicate that an epidermal barrier impairment in the skin of children with AD is involved in the development of allergic sensitization[3,4]. Recently, it has been proposed that early exposure to foods via the skin in children with AD may allow penetration of food allergens through the skin leading to development of sensitization and subsequent food allergy[5,6]. This is in contrast to an early, continuous oral exposure to some allergenic foods such as peanuts and egg, which may lead to development of immune tolerance and reduced risk of food allergy in young children[6–8].

The development of specific IgE (sIgE) to environmental allergens has also been associated with a defective skin barrier function[4]; e.g. one study showed association between increasing total epidermal water loss and prevalence of sensitization to aeroallergens[4]. Another study used a chemical sensitizer to show that sensitization through the skin in AD induced a persistent skewing towards antigen-specific Th2 responses regardless of Filaggrin (*FLG*) mutation status[3]. *FLG* is a key protein that assists in the final differentiation of the epidermis and formation of the skin barrier[2]. *FLG*mutation status leads to functional loss of barrier function in the skin and other mucosal surfaces[2,9]. A previous literature review described that up to 2/3 of patients with AD will develop allergic rhinitis[10], and particularly earlier debut of AD seemed to impose a higher risk. To our knowledge, no previous studies have investigated the association between AD severity and later development of aeroallergen sensitization and allergic rhinitis, and none included *FLG* mutation status.

We hypothesized that the epidermal barrier defect in early-onset, more severe AD in infancy compared to late-onset AD may facilitate penetration of aeroallergens via the skin and increase the risk of developing aeroallergen sensitization and allergic rhinitis in childhood. To test this hypothesis, we used data from the Copenhagen Prospective Studies on Asthma in Childhood$_{2000}$(COPSAC$_{2000}$) at-risk mother-child cohort to determine whether early-onset vs. late-onset AD and severity of AD are associated with development of aeroallergen sensitization and allergic rhinitis at 6-7 and 12 years of age.

Methods

Design

COPSAC$_{2000}$ is a single-center, prospective clinical mother-child cohort study of 411 children born between August 1998 and December 2001 to mothers with a history of asthma[11–13]. The children were closely monitored from birth till age 12 years with 19 planned visits to the clinic (age 2 weeks, 1, 3, and 6 months and 1, 11/2, 2, 21/2, 3, 31/2, 4, 41/2, 5, 51/2, 6, 61/2, 7, 9 and 12 years), where the children were seen by a COPSAC research physician with dermatology training. Additional acute care visits were arranged upon onset of any asthma-, allergy-, or AD-related flare ups. Atopic disorders were diagnosed and monitored at these visits by the COPSAC physicians according to standard operating procedures.

Ethics

The Copenhagen Ethics Committee (KF 01-289/96) and The Danish Data Protection Agency (2008-41-2434) approved the study, and oral and written informed consent was obtained from both parents at enrolment.

Atopic dermatitis

AD was diagnosed prospectively at scheduled and acute care visits at age 0-6 years (prior to evaluation of our outcomes) according to Hanifin and Rajka's criteria[14] capturing age of debut and age of remission as previously detailed[15,16]. A diagnosis of AD required the presence of 3 of 4 major criteria and at least 3 of 23 minor signs. The following 4 minor signs were excluded: keratoconus and anterior sub-capsular cataracts, delayed blanch, and impaired cell-mediated immunity. The severity of AD was scored using the Scoring Atopic Dermatitis (SCORAD) index at scheduled and acute care visits[17], ranging from 0 to 83 points (excluding the subjective components of pruritus and sleeplessness from the modified SCORAD index). As we saw the children at acute care visits whenever they had an AD flare-up, we were sure to capture the highest SCORAD value in the course of their disease.

Aeroallergen sensitization Assessment of sIgE levels in blood samples was done at age 6 and 12 years by an initial screening method (ImmunoCAP Phadiatop Infant and ImmunoCAP Phadiatop, Thermo Fisher Scientific, Uppsala, Sweden)[18] followed by analysis of individual allergen sIgE levels in screening positive samples towards birch, grass, mugwort, horse, dog, cat, house dust mites (D. pteronyssinus and D. farinae) and molds (Penicillium notatum, Cladosporium herbarum, Aspergillus fumigatus and Alternaria alternata). Sensitization was defined as values of sIgE [?] 0.35 kU_A/L[13].

Allergic rhinitis

Allergic rhinitis was diagnosed at the COPSAC research unit at age 7 and 12 years based on a parental interview on history of symptoms. Allergic rhinitis was defined as substantial and reoccurring sneezing, blocked, itchy or runny nose severely affecting the wellbeing of the child in the past 12 months in periods without accompanying common cold or flu, and with congruence between symptoms, relevant exposure and aeroallergen sensitization (positive sIgE and/or skin prick test)[19–22].

*Filaggrin mutation*Genotyping for common loss-of-function mutations in *FLG* , R501X, 2282del4, R2447X and S3247X was performed as previously described.[2] A *FLG* mutation carrier was defined as having at least one gene mutation.

Statistical methods

Age at AD debut ([?]/> 1 yr), aeroallergen sensitization (yes/no) and allergic rhinitis (yes/no) were categorized as binary variables. Severity of AD by means of SCORAD was included in the models as a continuous variable including the highest SCORAD level measured in the child (early-onset from 0-1 year and late-onset from 1-6 years).

Associations between AD (binary age at onset or continuous SCORAD) and aeroallergen sensitization and allergic rhinitis were analyzed by logistic regression analyses expressing results as odds ratios (OR) with 95% confidence intervals (CI). Furthermore, we used a logistic regression general estimating equations (GEE) model to compute the overall OR for allergy endpoints using compiled data from both time points and accounting for repeated measures. All results are calculated as crude and adjusted for potential confounders including sex, older siblings, maternal allergic rhinitis, paternal allergic rhinitis, breastfeeding and smoking during 3rdtrimester.

The analysis of whether the association between AD and later sensitization/allergic rhinitis depended on the AD-debut age (yes/no) was analyzed using a logistic regression model where AD status is a three-level variable (early, late, never). The analysis of whether the association between AD and later sensitization/allergic rhinitis depended on the AD-debut age (SCORAD) was based on two models using the quantitative measure of SCORAD as a predictor; one based on early debut, and one based on late debut. As all non-AD children had a SCORAD of 0, these are excluded from the analysis. From these models the slopes are compared using

a Wald's tests associated with H0: b(early) = b(late) which hence reveal whether the association between severity and AR/sIgE is different between early and late AD-debuts.

In the analyses of early-onset AD (debut[?]1yr, yes/no) we used all the other children as a control group, whereas in the analyses of late-onset AD (debut 1-6 years, yes/no) we excluded the children with an early-onset AD debut from the control group.

We additionally stratified for *FLG* mutation. Further, effect modification by *FLG* was evaluated by second order interaction models by adding cross-products to the models.

All statistical analyses were performed with the statistical software package R version 4.0.2 and RStudio version 1.1.442 (RStudio Inc, Boston, MA, USA). Missing observations were treated as missing data. P-values <0.05 were considered statistically significant.

Results

Baseline

Assessment of allergic rhinitis was performed in 290 (71%) of the 411 children at 7 years, in 353 (86%) children at 12 years and in 368 (90%) children at either 7 and/or 12 years. The latter defined the study population. Accordingly, assessment of aeroallergen sensitization was performed in 296 (72%) of the children at 6 years, in 315 (77%) children at 12 years and in 352 (86%) children at either 6 and/or 12 years. Baseline characteristics including gender, socioeconomics, early life exposures, and allergic predisposition of the included and excluded children are outlined in **Table 1** . The excluded children (N=43) had fewer older siblings than the included children (no older siblings: 68% vs. 60%, p=0.04), but did not differ with respect to the remaining baseline characteristics.

Age at onset of AD and risk of sIgE aeroallergen sensitization

Aeroallergen sensitization measured by sIgE ([?] 0.35 kU_A/L) at 6 years was present in 29/84 (35%) children with early-onset AD compared to 45/207 (22%) children without early-onset AD: OR=1.90 [1.08; 3.31], p=0.02. At 12 years, aeroallergen sensitization was present in 48/89 (54%) vs. 92/215 (43%): OR=1.56 [0.95; 2.58], p=0.08. The GEE model of early-onset AD showed a compiled significantly increased OR for developing aeroallergen sensitization at the two timepoints of 1.68 [1.08; 2.62], p=0.02 (**Table 2**).

In children with late-onset AD (1-6 years of age), aeroallergen sensitization at 6 years was diagnosed in 15/53 (28%) compared to 28/145 (19%) without late-onset AD: OR=1.65 [0.78; 3.38], p=0.18. At 12 years, aeroallergen sensitization was present in 26/49 (53%) vs. 54/136 (40%) : OR=1.72 [0.89; 3.33], p=0.11. The GEE model showed a compiled borderline-significant OR for the two timepoints of 1.65 [0.92; 2.94], p=0.08 (**Table 2**). Early-onset and late-onset AD imposed a similar risk of development of sIgE aeroallergen sensitization (p-interaction=0.93).

AD severity and risk of aeroallergen sensitization

Among children with an early-onset AD, the highest severity score for AD (SCORAD) measured between 0-1 year showed associations with development of aeroallergen sensitization measured by sIgE. Per 1-point increase in SCORAD, the OR for aeroallergen sensitization at 6 years was 1.08 [1.03; 1.14], p<0.01, and the OR for aeroallergen sensitization at 12 years was 1.08 [1.03; 1.13], p=<0.01. The GEE model was significant with a compiled OR for the two timepoints of 1.08 [1.03; 1.12], p<0.001. Contrary, among children with a late-onset AD, the highest SCORAD measured from 1-6 years showed no significant associations with later development of aeroallergen sensitization (**Table 2**). Early-onset AD severity imposed a higher risk for development of sIgE aeroallergen sensitization than late-onset severity (p-interaction=0.03).

AD and risk of allergic rhinitis

We assessed the associations between early-onset AD, late-onset AD, and AD severity and development of allergic rhinitis at 7 and 12 years (**Table 3**). Among children with early-onset AD, 17/83 (20%) developed allergic rhinitis at 7 years (OR=2.22 [1.09; 4.46], p=0.025) and 38/98 (38%) developed allergic rhinitis at

12 years (OR=1.57 [0.95; 2.56], p=0.07). The GEE model showed a compiled OR for the two timepoints of 1.56 [1.01; 2.41], p=0.04.

Among children with late-onset AD, 8/52 (15%) developed allergic rhinitis at 7 years (OR=1.80 [0.67; 4.58], p=0.22) and 21/60 (35%) developed allergic rhinitis at 12 years (OR=1.36 [0.71; 2.56], p=0.35). The GEE model showed a compiled OR for the two timepoints of 1.76 [1.00; 3.10], p=0.05 (**Table 3**). Early-onset and late-onset AD imposed a similar risk of development of allergic rhinitis (p-interaction=0.89). Similarly, early-onset AD severity (SCORAD) was associated with development of allergic rhinitis during childhood; GEE OR=1.09 [1.05; 1.13], p<0.001, whereas late-onset severity was not; GEE OR=1.00 [0.96; 1.04], p=0.90. Early-onset AD severity imposed a higher risk of allergic rhinitis than late-onset severity (p-interaction<0.01).

Adjusting the results for sex, older siblings, maternal allergic rhinitis, paternal allergic rhinitis, breastfeeding and smoking during 3rd trimester did not alter the results noteworthy (**Table E1 and E2**).

Filaggrin mutation The results for aeroallergen sensitization stratified by *FLG*mutation are shown in **Table E3** in the Online Repository. When evaluating age at onset of AD and severity by SCORAD, *FLG*mutation did not seem to alter the results (**Table E3**).

The results for allergic rhinitis including stratification by *FLG*mutation are shown in **Figure 1** and listed in **Table E2** . When evaluating age at onset of AD (**Figure 1a**) *FLG*mutation did not seem to alter the results (p-interaction 7 years=0.30 and 12 years=0.17). However, when evaluating AD severity by SCORAD in children with early-onset AD, i.e., debut [?] 1 year, (**Figure 1b**)*FLG* positive children exhibited 24% (ORpos / ORneg = 1.34 / 1.08) and 14% (ORpos / ORneg = 1.20 / 1.05) higher odds for the association between AD severity and development of allergic rhinitis at 7 and 12 years respectively in contrast to *FLG* negative, indicating that this association is stronger among children with*FLG* mutation (p-interaction 0.06 and 0.055, respectively). Due to low numbers, we were not able to investigate the association between SCORAD > 1 year and allergy outcomes stratified by*FLG* mutation status.

Discussion

Primary findings

In this longitudinal birth cohort study of 368 high-risk children, we found that increasing severity of early-onset AD was associated with sensitization to aeroallergens and allergic rhinitis at 6-7 and 12 years, while severity of late-onset AD after age 1 year was not. These findings suggest that aeroallergens penetrate the skin inflamed from AD in infancy more so than later and that an early-onset vs. late-onset debut represent different endotypes of AD that differentially associate with subsequent risk of respiratory allergy in childhood.

Strengths and limitations

It is a major strength of the study that this is a prospective mother-child cohort design with 19 planned visits up until 12 years of age all including evaluations of AD at the COPSAC research clinic[11,15,16]. Moreover, all children were additionally seen at the COPSAC clinic at acute visits for any skin-related symptoms, which minimized the risk of parental recall bias and ensured we captured the highest SCORAD values during the children's disease course. All AD diagnoses strictly followed standard operating procedures. This careful prospective follow-up is a significant strength enabling accurate diagnosis of AD including severity (SCORAD).

Another strength is the measurement of the outcomes, aeroallergen sensitization and allergic rhinitis, at two time-points (6-7 and 12 years), which ensured conclusions based on results from both early school-age and early teens.

All mothers had a history of asthma, i.e. study participants were at risk of respiratory allergy and asthma, which may limit the generalizability of our findings.

Interpretation

We show that children with more severe, early-onset AD before age 1 year have an increased risk for developing sensitization to aeroallergens and allergic rhinitis compared to children with onset of AD after age 1 year. This is in agreement with some previous studies[23–26] as most studies found higher frequencies of allergy outcomes in early-onset vs. late-onset AD[27,28], whereas one study found no difference[29] and two other studies only found a higher risk if children with early-onset also had persistent AD[30,31]. Further, the latter study found an increased risk of sensitization to aeroallergens at 18 years among children with late-onset AD[31].

The varying findings in these previous studies can be due to several factors. Importantly, the severity of AD in early life seems to be the most important factor according to our study but was not assessed in previous studies. Also, the diagnosis of AD and allergic rhinitis was mostly based on questionnaires, and the evaluation of allergy outcomes was done at different time-points across the studies ranging from 4 to 18 years. Only one other study diagnosed sensitization and allergic rhinitis at several time points[31], but with low complete follow-up rates of 52% at 7 years, 40% at 12 years and 39% at 18 years, in contrast to a follow-up rate of 71% at 7 years and 86% at 12 years in our study. None of the previous studies assessed AD severity, which showed significantly different effects in early-onset vs. late-onset in relation to both aeroallergen sensitization and allergic rhinitis.

The possible mechanisms driving the association between AD and respiratory allergy have previously been explained by an underlying Th2-skewed immune system[10,32], which leads to an increased risk of both AD, asthma and allergic rhinitis. An inherent genetic susceptibility may also influence the risk of developing all three diseases. Thus, a GWAS study identified shared AD, asthma, and allergic rhinitis immune-related genetic variants, suggesting that these disorders may co-exist because they share genetic risk loci that result in dysregulation of immune-related genes[33]. However, this does not explain the mechanism behind age at onset and severity of AD and development of aeroallergen sensitization and allergic rhinitis.

More recently, the hypothesis explaining the association between AD and allergy has shifted to include a primary defect in the epidermal barrier in AD[34]. The epidermis provides an essential barrier to the external environment, preventing both water loss from the body and intrusion of infectious agents and allergens. When allergens are captured and processed by antigen-presenting Langerhans cells of the epidermis, they migrate to the draining lymph nodes and if not down-regulated, they can interact with naive T cells to promote Th2 immunity leading to allergies[35]. This epicutaneous sensitization has also been proposed to cause migration of Th2 memory cells from the skin to the bronchial lymphoid tissue, where subsequent inhalation of the sensitizing allergen causes a cellular and humoral response in the airways, resulting in symptoms of allergic rhinitis and asthma[10]. Finally, it has been proposed that chronic AD lesions may express thymic stromal lymphopoietin and other proinflammatory mediators, which increase the risk of developing allergic inflammation and sensitization in the lungs[36].

Our study also showed a trend of higher risk of developing allergic rhinitis with increasing SCORAD among children with a *FLG*mutation compared to children without a mutation. Indeed, *FLG*mutation is known to lead to an impaired skin barrier, which is a plausible mechanistic explanation of the observed associations. To our knowledge no previous studies have investigated the role of *FLG*mutations in the relationship between AD age at onset, severity, and development of respiratory allergy. Our results should be interpreted with caution due to low numbers, and it would be interesting to investigate this association in a larger-scale study.

To ensure that early-onset AD was not present with concomitant allergic sensitization, and that reverse causation is not driving our results, we investigated early allergic sensitization at age 6 months. However, only 2 children were sensitized to an aeroallergen at this point - one from the early-onset AD group and one who never developed AD, so that is not likely to alter our results.

Our study suggests programming in early life and that appropriate early interventions may hamper the progression of AD to aeroallergen sensitization and allergic rhinitis, especially in children with early-onset, more severe disease and *FLG* mutation. Following such thoughts, early strengthening of the epidermal barrier in high-risk infants using emollients before the onset of AD has been hypothesized to prevent development

of AD and subsequent respiratory allergy, but this could not be demonstrated in two recent randomized controlled trials[37,38].

To prevent development of aeroallergen sensitization and allergic rhinitis in children with early-onset, severe AD, an alternative possible effective intervention may reside in modulating the immune response through manipulation of the route of earliest encounter with the allergen, along the same lines as has been shown with food allergens. Thus, early environmental exposure through the skin may lead to sensitization whereas early oral exposure may led to tolerance[6–8] by stimulating regulatory T-cells induction and function in the gut[39]. A murine study has supported this hypothesis[40], and two human studies have tested this hypothesis in children using a sublingual immunotherapy mixture of house dust mite, cat and grass[41] or house dust mite alone[42,43]. The studies failed to show any effect on development of allergic sensitization, which was also less influenced by early-onset and severity of AD in our study compared to allergic rhinitis, i.e., clinically relevant sensitization. Further, they had some weaknesses including high drop-out rates, lack of compliance, the children being too old at the beginning of the study, difficulty taking the sublingual immunotherapy correctly, and difficulty identifying children at high risk for developing AD. To establish whether early sublingual exposure to aeroallergens can prevent development of sensitization and allergic rhinitis in children with early-onset, severe AD, randomized controlled trials taking all these factors into account are needed.

Conclusion

Our study suggests that increasing severity of early-onset AD is associated with the development of sensitization to aeroallergens and allergic rhinitis in childhood. Our findings imply that a skin barrier defect and/or skin inflammation from AD in infants may have important programming effects on development of respiratory allergy later in childhood. These findings call for a randomized controlled trial of early oral exposure to aeroallergens to reduce the risk for developing aeroallergen sensitization and allergic rhinitis in children, similar to what has been shown for primary prevention of food allergies.

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Figure 1: Associations between early-onset AD ([?] 1 year) and late-onset AD (1-6 years) and allergic rhinitis (AR) at 7 and 12 years. AD is either defined as a binary variable (yes/no) **(a)** or a continuous variable expressed as a severity score (SCORAD) **(b)**for AD. All the results are stratified for Filaggrin (*FLG*) mutation. The numbers indicate children with the variable present and evaluated outcome.

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AD = Atopic Dermatitis SCORAD = Scoring Atopic Dermatitis OR = Odds Ratio NA = Not Available, too few children to generate an OR AR = Allergic Rhinitis*FLG* = Filaggrin

Table 1: Baseline characteristics of included children who were assessed for allergic rhinitis at 7 and/or 12 years and excluded children.

Characteristics	**N (Total)**	**Included**	**Exclu**
	411	368	43
Gender	**Gender**	**Gender**	**Gende**
Male N (%)	411	182 (50 %)	21 (49
Socioeconomic factors	**Socioeconomic factors**	**Socioeconomic factors**	**Socioe**
Social circumstances*, mean (SD)	382	0.02 (1.0)	-0.25 (
Smoking during third trimester	**Smoking during third trimester**	**Smoking during third trimester**	**Smoki**
Yes N (%) ^	411	53 (14%)	10 (23
Older siblings	**Older siblings**	**Older siblings**	**Older**
No older siblings N (%)	385	212 (60%)	21 (68
1 older N (%)		103 (29%)	5 (16%
2 older N (%)		26 (7.3%)	1 (3.2%
3 older N (%)		13 (3.7%)	4 (13%
Maternal allergic disposition	**Maternal allergic disposition**	**Maternal allergic disposition**	**Mater**
Asthma: Yes N (%)	411	368 (100 %)	43 (100
Allergic rhinitis: Yes N (%)	410	275 (75 %)	35 (81
AD: Yes N (%)	411	174 (47%)	24 (56
Paternal allergic disposition	**Paternal allergic disposition**	**Paternal allergic disposition**	**Paterr**
Asthma: Yes N (%)	399	65 (18%)	3 (7.1%
Allergic rhinitis: Yes N (%)	397	122 (34%)	8 (20 %
AD: Yes N (%)	397	44 (12%)	8 (20%
Allergic disposition			
Filaggrin mutation: Yes N (%)	395	46 (13%)	4 (12%
Solely breastfed, mean days (SD)	354	114 (62)	96 (70)
Total breastfed, mean days (SD)	395	248 (153)	227 (18

***** Social circumstances are correlated to household income (r=0.73, p<0.001), to maternal level of education (r=0.68, p<0.001) and to maternal age (r=0.75, p<0.001). For further information, see the Online Repository

Table 2: Associations between early-onset AD ([?] 1 year) and late-onset AD (> 1 year) and allergic sensitization at 7 and 12 years. AD is either defined as a dichotomous variable (yes/no) or a continuous

variable expressed as a severity score (SCORAD) for AD. The GEE[§] model computes the overall OR for allergic rhinitis using compiled data from both time points.

	Allergic sensitization (sIgE*) at 6yrs	Allergic sensitization (sIgE*) at 6yrs	Allergic sensitization (sIgE*) at
Debut	N^	OR	95% CI
AD yes/no	AD yes/no	AD yes/no	AD yes/no
1yr	84/291 (29%)	1.90	[1.08; 3.31]
> 1yr	53/198 (27%)	1.65	[0.78; 3.38]
SCORAD	SCORAD	SCORAD	SCORAD
1yr	72/291 (25%)	1.08	[1.03; 1.14]
> 1yr	67/198 (34%)	1.04	[0.99; 1.09]

§ Logistic regression General Estimating Equations.

* sIgE [?] 0.35 kUA/L to any aeroallergen

Table 3: Associations between early-onset AD ([?] 1 year) and late-onset AD (> 1 year) and allergic rhinitis at 7 and 12 years. AD is either defined as a binary variable (yes/no) or a continuous variable expressed as a severity score (SCORAD) for AD. The GEE* model computes the overall OR for allergic rhinitis using compiled data from both time points.

	Allergic Rhinitis at 7yrs	Allergic Rhinitis at 7yrs	Allergic Rhinitis at 7yrs	Allergic Rhinitis at 7yrs	All
Debut	N^	OR	95% CI	p-value	N^
AD yes/no	AD yes/no	AD yes/no	AD yes/no	AD yes/no	AD
1yr	83/285 (29%)	2.22	[1.09; 4.46]	0.03	98/
> 1yr	52/194 (27%)	1.80	[0.67; 4.58]	0.22	60/
SCORAD	SCORAD	SCORAD	SCORAD	SCORAD	SC
1yr	71/285 (25%)	1.11	[1.05; 1.18]	<0.001	86/
> 1yr	66/194 (34%)	0.99	[0.92; 1.06]	0.85	74/

the late-onset group (> 1yr) the total N is lower as we excluded the children with early-onset AD from those calculations.

* Logistic regression General Estimating Equations.

Online Repository

Baseline table of original information used to derive the measure of social circumstances.

		COPSAC$_{2000}$	**COPSAC$_{2000}$**
	Variable type	categorical: n (%) numeric: mean (SD)	Missing data
Household income (Euros/year)	*cat*		29
Below 54.000		120 (31.41)	
54.000-81.000		153 (40.05)	
81.000-108.000		76 (19.90)	
108.000-134.000		22 (5.76)	
Above 134.000		11 (2.88)	
Maternal education	*cat*		29

		$\mathbf{COPSAC_{2000}}$	$\mathbf{COPSAC_{2000}}$
Elementary or College		220 (57.59)	
Medium		104 (27.23)	
University		58 (15.18)	
Maternal age	*num*	32.11 (4.51)	0

Social circumstances are correlated to household income (r=0.73, p<0.001), to maternal level of education (r=0.68, p<0.001) and to maternal age (r=0.75, p<0.001).

Table E1: Associations between early-onset AD ([?] 1 year) and late-onset AD (> 1 year) and allergic sensitization at 6 and 12 years. AD is either defined as a dichotomous variable (yes/no) or a continuous variable expressed as a severity score (SCORAD) for AD. The GEE§ model computes the overall aOR for allergic sensitization using compiled data from both time points. Analyses are adjusted for sex, older siblings, maternal allergic rhinitis, paternal allergic rhinitis, breastfeeding and smoking during 3rd trimester.

	Allergic sensitization (sIgE*) at 6yrs	Allergic sensitization (sIgE*) at 6yrs	Allergic sensitization (sIgE*) at
Debut	N^	aOR	95% CI
AD yes/no	AD yes/no	AD yes/no	AD yes/no
1yr	84/291 (29%)	1.96	[1.09; 3.51]
> 1yr	53/198 (27%)	1.84	[0.85; 3.92]
SCORAD	SCORAD	SCORAD	SCORAD
1yr	72/291 (25%)	1.09	[1.03; 1.16]
> 1yr	67/198 (34%)	1.06	[1.00; 1.13]

§ Logistic regression General Estimating Equations.

* sIgE [?] 0.35 kUA/L to any aeroallergen

Table E2: Associations between early-onset AD ([?] 1 year) and late-onset AD (> 1 year) and allergic rhinitis at 7 and 12 years. AD is either defined as a binary variable (yes/no) or a continuous variable expressed as a severity score (SCORAD) for AD. The GEE* model computes the overall aOR for allergic rhinitis using compiled data from both time points. Analyses are adjusted for sex, older siblings, maternal allergic rhinitis, paternal allergic rhinitis, breastfeeding and smoking during 3rd trimester.

	Allergic Rhinitis at 7yrs	Allergic Rhinitis at 7yrs	Allergic Rhinitis at 7yrs	Allergic Rhinitis at 7yrs	All
Debut	N^	aOR	95% CI	p-value	N^
AD yes/no	AD yes/no	AD yes/no	AD yes/no	AD yes/no	AD
1yr	83/285 (29%)	2.02	[0.97; 4.18]	0.06	98/
> 1yr	52/194 (27%)	2.13	[0.77; 5.69]	0.13	60/
SCORAD	SCORAD	SCORAD	SCORAD	SCORAD	SC
1yr	71/285 (25%)	1.12	[1.05; 1.23]	<0.01	86/
> 1yr	66/194 (34%)	0.98	[0.89; 1.07]	0.72	74/

the late-onset group (> 1yr) the total N is lower as we excluded the children with early-onset AD from those calculations.

* Logistic regression General Estimating Equations.

Table E3: Associations between early-onset AD ([?] 1 year) and late-onset AD (> 1 year) and allergic

sensitization at 6 and 12 years (positive sIgE) stratified by *FLG* mutation. AD is either defined as a dichotomous variable (yes/no) or a continuous variable expressed as a severity score (SCORAD) for AD.

	Allergic sensitization (sIgE*) at 6yrs	Allergic sensitization (sIgE*) at 6yrs	Allergic sensitization (s
FLG§	N^	OR	95% CI
AD yes/no [?] 1 yr	AD yes/no [?] 1 yr	AD yes/no [?] 1 yr	AD yes/no [?] 1 yr
Pos	17/38 (45%)	2.25	[0.61; 8.72]
Neg	67/252 (27%)	1.70	[0.89; 3.19]
AD yes/no > 1 yr	AD yes/no > 1 yr	AD yes/no > 1 yr	AD yes/no > 1 yr
Pos	5/20 (25%)	4.13	[0.51; 41.8]
Neg	47/177 (27%)	1.35	[0.58; 2.98]

	Allergic sensitization (sIgE*) at 6yrs	Allergic sensitization (sIgE*) at 6yrs	Allergic sensitization (sIg
FLG§	N^	OR	95% CI
SCORAD [?] 1 yr	SCORAD [?] 1 yr	SCORAD [?] 1 yr	SCORAD [?] 1 yr
Pos	17/38 (45%)	1.14	[1.00; 1.38]
Neg	55/252 (22%)	1.07	[1.01; 1.13]
SCORAD > 1 yr	SCORAD > 1 yr	SCORAD > 1 yr	SCORAD > 1 yr
Pos			NA
Neg	61/177 (34%)	1.05	[0.99; 1.11]

* sIgE [?] 0.35 kUA/L to any aeroallergen

§ *FLG* = Filaggrin mutation

Table E2: Associations between early-onset AD ([?] 1 year) and late-onset AD (> 1 year) and allergic rhinitis at 7 and 12 years stratified by *FLG* mutation. AD is either defined as a dichotomous variable (yes/no) or a continuous variable expressed as a severity score (SCORAD) for AD.

	Allergic rhinitis at 6yrs	Allergic rhinitis at 6yrs	Allergic rhinitis at 6yrs	Allergic rhinitis at 6yrs
FLG§	N^	OR	95% CI	p-value
AD yes/no [?] 1 yr	AD yes/no [?] 1 yr	AD yes/no [?] 1 yr	AD yes/no [?] 1 yr	AD yes/no [?] 1 yr
Pos	17/38 (45%)	3.27	[0.71; 18.1]	0.14
Neg	66/246 (27%)	1.92	[0.83; 4.30]	0.12
AD yes/no > 1 yr	AD yes/no > 1 yr	AD yes/no > 1 yr	AD yes/no > 1 yr	AD yes/no > 1 yr
Pos			NA	
Neg	46/173 (27%)	1.17	[0.35; 3.36]	0.78

	Allergic rhinitis at 6yrs	Allergic rhinitis at 6yrs	Allergic rhinitis at 6yrs	Allergic rhinitis at 6yrs
FLG§	N^	OR	95% CI	p-value
SCORAD [?] 1 yr	SCORAD [?] 1 yr	SCORAD [?] 1 yr	SCORAD [?] 1 yr	SCORAD [?] 1 yr
Pos	17/38 (45%)	1.34	[1.09; 2.04]	0.05
Neg	54/246 (22%)	1.08	[1.02; 1.16]	0.01
SCORAD > 1 yr	SCORAD > 1 yr	SCORAD > 1 yr	SCORAD > 1 yr	SCORAD > 1 yr
Pos			NA	
Neg			NA	

§ FLG = Filaggrin mutation