

Interaction between filaggrin mutations and neonatal cat exposure in atopic dermatitis

To the Editor

Atopic dermatitis (AD) is a prevalent inflammatory skin disease. Loss-of-function mutations in the filaggrin gene (*FLG*) represent the strongest genetic risk factor for AD, being strongly associated with early disease onset and persistence into adulthood. The epidermis of individuals with mutations in *FLG* is fundamentally different from normal skin being characterized by increased penetration of allergens.

Recent birth cohort studies showed a significant interaction between cat ownership at birth and mutations in *FLG* (R501X, 2282del4) on the development of early-onset AD.¹ This finding was replicated for the 2282del4 *FLG* mutation in a Dutch cohort study and extended to further associate with risk of allergic sensitization.² We performed analyses in multiple birth cohorts to examine the consistency and overall strength of the previously observed interaction.

Consortium collaborators were invited to participate in the study,³ and 13 birth cohorts provided data on cat exposure, AD, and *FLG* mutations (Table 1 and Table S1 and S2). All cohorts had information on the most common mutations in *FLG*, R501X, and 2282del4, and the majority also had information on R2447X and S3247X (Table 1). Heterozygous, compound heterozygous and homozygous *FLG* mutation carriers were pooled as mutation carriers. Cat ownership/exposure was based on questionnaires or interviews. AD diagnoses were based on questionnaires in 10 cohorts, by physician examination in two cohorts (COPSAC2000, COPSAC2010), and a combination in one cohort (MAS). For further details, please see Supporting information.

The predetermined primary outcome was AD onset before one year of age ("AD_{early}") based on previous observations.¹ Secondary outcomes included i) current AD at seven years of age or the year of assessment closest to, but before, 7 years ("AD_{current}"), and ii) a history of AD during the first 7 years of life, or last year of assessment (AD_{ever}). For further details, please see Supporting information.

A total of 22 133 children were studied (Table 1 and Table S1). The median prevalence (range) of mutations in *FLG* was 9.4% (4.6–12.3), cat exposure 15% (7.9–29.6), AD_{early}, AD_{current}, and AD_{ever} respectively, 18% (9.7–34.6), 13.9% (3.9–20), and 39.5% (20.4–67). There was no interaction between *FLG* mutations and cat exposure on the risk of the primary outcome "AD_{early}" (OR 1.10 (95% CI 0.86–1.43),

I^2 0.0) (Figure 1 and Table S3). There was a nominally significant interaction ($P = .03$) for the secondary outcome of having AD at last time of examination or questioning at 7 years of age (AD_{current}), in the direction of increased risk of AD from cat exposure in children with *FLG* mutations (OR 1.36 (95% CI 1.02–1.82) I^2 8.6), but this was not statistically significant after adjustment for multiple testing. The *FLG*-stratified analyses showed a trend toward cat exposure being a risk factor in children with *FLG* mutations and a protective factor in children without *FLG* mutations (Figure 1 and Table S3). No interaction was found for the other secondary outcome "AD_{ever}" (OR 1.06 (95% CI 0.82–1.37), I^2 0.0).

We found no interaction between cat exposure in infancy and mutations in *FLG* on "early-onset AD" or "AD ever." A nominally significant interaction in the expected direction was found for the secondary outcome "current AD" at 7 years of age, but this did not survive adjustment for multiple testing.

A particular study strength is the large number of independent birth cohorts with prospective assessment of exposure and outcomes. Most cohorts had genotype information for the 4 most common *FLG* mutations ensuring a high degree of correct classification. It is a limitation that AD diagnoses were based on questionnaire data in most cohorts, potentially reducing diagnostic specificity. Since AD is a chronic and relapsing disease, short episodes of other eczemas, for example, due to irritant or allergic contact dermatitis, may be misinterpreted as AD by parents and caregivers, in particular in the first years of life where flexural accentuation is not yet occurring.⁴ Notably, the high prevalence of early AD in some cohorts, potentially due to unspecific diagnoses, could mask a true cat exposure-*FLG* mutation interaction. One may argue that AD measured at 7 years of age is expected to have a higher specificity due to flexural involvement.⁵ It is another limitation that cat exposure was only assessed around birth, and it is possible that later exposure to cat could have an unmeasured effect on AD. Similar, the extent of cat exposure might vary between studies and families. Other environmental factors were not included since covariate availability differed between the cohorts. Reverse causality cannot be excluded, as families who had experienced atopic disease might have avoided having pets to prevent allergic disease in their (next) child. However, one would expect families with *FLG* mutations, and thereby increased risk of eczema, to avoid cat ownership, which would tend toward an apparent protective effect of having a cat.

No association between cat ownership and AD was found in another meta-analysis of 13 studies (relative risk 0.94 [95%CI

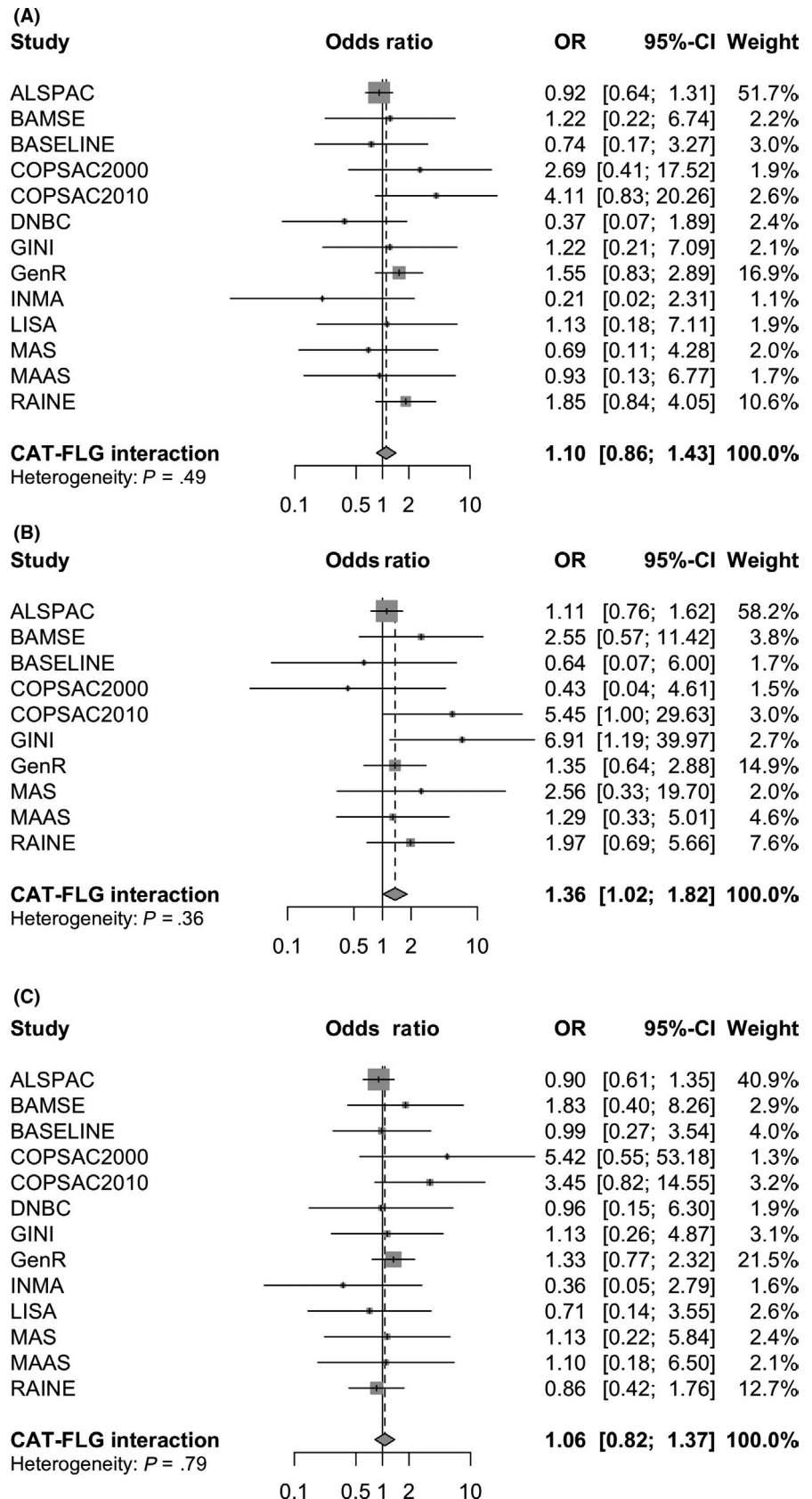
TABLE 1 Baseline characteristics of participants in birth cohorts

Cohort	ALSPAC	BAMSE	Baseline	COPSAC 2000	COPSAC 2010	DNBC	Generation R	Giniplus	INMA ^a	LISA	MAS	MAAS	Raine Study
Cohort inclusion criteria	Children from the general population	Children from the general population	Children from the general population	Children born from mothers with asthma	Children from the general population	Children from the general population	Children from the general population	Children from the general population	Children from the general population	Children from the general population	Children from the general population	Children from the general population	Children from the general population
Study year baseline	1991-1992	1994-1996	2008	2000	2010	1996-2001	2002-2006	1995-98	1997-2006 ^b	1997-99	1990	1996-1997	1989-1991
Flaggrin mutations genotyped	R501X, 2282del4, R2447X, S3247X	R501X, 2282del4, R2447X	R501X, 2282del4, R2447X, S3247X	R501X, 2282del4, R2447X, S3247X	R501X, 2282del4, R2447X, S3247X	R501X, 2282del4, R2447X, S3247X	R501X, 2282del4, R2447X, S3247X	R501X, 2282del4	R501X, 2282del4, R2447X, S3247X	R501X, 2282del4, R2447X, S3247X	R501X, 2282del4, R2447X, S3247X	R501X, 2282del4, R3247X, R2447X	R501X, 2282del4, S3247X, R5138726443
Proportion with FLAG mutations	11% (834/7743)	7.2% (138/1906)	10.8% (146/1344)	12.3% (49/396)	10.3% (72/700)	9.7% (91/935)	9.4% (268/2849)	7.0% (104/1490)	4.6% (28/606)	7.0% (69/987)	9.7% (79/813)	10.1% (87/864)	9.3% (140/1500)
Basis for atopic dermatitis diagnosis	Questionnaire	questionnaire	Questionnaire and clinical diagnosis	clinical diagnosis	clinical diagnosis	Questionnaire	Questionnaire	Questionnaire	Questionnaire	Questionnaire	Questionnaire and clinical diagnosis	Questionnaire	Questionnaire
AD 'early onset' (≤1 y) ^c	18% (1368/7743)	16.9% (323/1906)	22.7% (292/1282)	25.3% (100/396)	11.1% (78/700)	14.7% (137/935)	21.6% (545/2521)	11.3% (167/1477)	31.7% (192/606)	9.7% (94/973)	14.14% (115/813)	34.6% (160/462)	22.8% (341/1498)
AD 'current'	20% (1270/6402)	17.2% (327/1896)	15.2% (178/1168)	13.9% (55/396)	13.6% (95/700)	6.8% (65/963)	18.6% (496/2658)	5.93% (77/1298)	19.5% (118/604)	3.9% (32/825)	7.5% (58/773)	14.1% (96/681)	13.3% (184/1386)
AD 'ever (0-7 Y)'	67% (4367/6501)	39.5% (743/1878)	26.3% (354/1344)	42.2% (175/396)	27.6% (193/700)	20.4% (196/963)	41.4% (1180/2849)	35.3% (447/1266)	49.6% (307/618)	32.6% (269/826)	36.2% (294/813)	60.7% (306/504)	39.7% (596/1500)
AD assessment time-points	6, 18, 30, 42, 57, 69, 81 mo	1, 2, 4, and 8 y	6, 12, and 24 mo	1 mo, and then every 6 mo	1 mo, and then every 6 mo	6 and 18 mo, and 7 y	6 mo, and 1, 2, 3, 4, and 6 y	1, 2, 3, 4, 6, and 10 y	1, 2, And 4 y	6, 12, 18, 24 mo and 4, 6, and 10 y	1, 3, 6, 12, 18, 24 mo and then yearly	1, 3, 5, 8 y	1, 3, 5, 8 y
Child age at cat exposure assessment	During Pregnancy	At Baseline (3 mo) And/Or 1-y Follow-Up.	6 mo And 12 mo	Birth	Birth	18 mo	Age <1 y)	1 y	1 y	3 mo and 1 y	3 mo	Birth	1 y
early life cat exposure %	29.6	10.6 ^b	8.8	15	20	16.4-22.4 ^b	25.3	7.9	11.5	12.2	12.7	20.5	18

^aINMA Sub Cohorts: VAL, SAB, MEN.

^bPlease See Table S1 For Further Details.

FIGURE 1 Interaction between cat exposure and common *FLG* mutations in relation to (A) early-onset atopic dermatitis, (B) current atopic dermatitis, and (C) atopic dermatitis in the first 7 y of life



0.76-1.16)].⁶ When a compelling gene-environment interaction was observed between *FLG* mutations and cat ownership on the risk of early-onset AD in birth cohorts, it raised the possibility

that preventive measures against pediatric AD could be identified by taking the genetic susceptibility into account.^{1,2} The COPSAC2000 study, which provided the basis for the previous

report of interaction between cat and *FLG* mutations,¹ benefited from close follow-up of children and high AD diagnostic accuracy, whereas most birth cohorts in the present meta-analysis used questionnaires, potentially explaining the discrepancy between the studies.

No pathomechanism has been established for the proposed association between cat ownership and AD in *FLG* mutation carriers. Possibly, very small cat allergens might penetrate the viable layers of the epidermis, where they can exert immune effects, possibly through IL-1 β promotion.^{7,8} Studies demonstrating increased risk of peanut allergy in *FLG* mutation carriers also suggest increased peanut allergen skin penetration.⁹

In conclusion, this meta-analysis could not confirm an interaction between cat exposure in infancy and *FLG* mutations on development of early-onset AD. Gene-environment interactions in AD remain largely unknown.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Interaction between filaggrin mutations and neonatal cat exposure in atopic dermatitis

Supplementary information (online only)

Materials and methods:

Cohorts, exposures, genotypes and phenotypes

This study was performed within the framework of the Early Genetics and Lifecourse Epidemiology (EAGLE) Eczema Consortium.¹ Birth cohort studies were invited to participate in the meta-analysis if they had data on domestic cat exposure and childhood AD, as well as genotype information on common mutations in *FLG* (For details please see Table 1 and Supplementary Table 1). The 13 participating cohorts came from Australia (n=1), Denmark (n=3), Germany (n=3), Ireland (n=1), Netherlands (n=1), Spain (n=1), Sweden (n=1), and the UK (n=2). Cohorts had genotype information about the four most common loss-of-function mutations in *FLG* in Northern European descendants, R501X, 2282del4, R2447X and S3247X, except the LISA and GINIplus (only R501X and 2282del4) and BAMSE (only R501X, 2282del4, and R2447X) cohorts. Heterozygous, compound heterozygous and homozygous *FLG* mutation carriers, who all display decreased pro-filaggrin synthesis,² were pooled and referred to as mutation carriers. Each cohort provided detailed information about the proportion of children that had been exposed domestically to cat in the first year of life, and how and when cat exposure information had been obtained. Assessment of cat ownership or cat exposure was based on questionnaire data or interview. A diagnosis of AD was predominately based on questionnaire data in 10 cohorts, but by physicians in 2 cohorts (COPSAC2000, COPSAC2010) and a combination in 1 cohort (MAS) (Table 1 and supplementary Table 1).

Statistical analysis and outcomes

The predetermined primary outcome was AD onset before one year of age (AD_{early}) since this was the outcome in the initial report of this interaction.³ Secondary outcomes included i) current AD at seven years of age or the year of assessment closest to, but before, 7 years ($AD_{current}$), and ii) a history of AD during the first 7 years of life, or last year of assessment (AD_{ever}). The 7-year age range was chosen since the vast majority of pediatric AD cases are expected to have occurred at this point.⁴ A total of 9 cohorts followed the

children until 7 years of age, whereas the remaining 4 studies followed the children until age 2 (Baseline), 4 (INMA), 5 (COPSAC2010), and 6 (Generation R) years of age, respectively. We performed the cat exposure-*FLG* interaction analyses on AD assessed as '*AD_{early}*', '*AD_{current}*' and '*AD_{ever}*'. *FLG* mutation stratified analyses were performed to confirm the directionality of effect and estimates for each model.

Cat exposure × FLG mutation interaction analyses

Each cohort performed the interaction analyses between cat exposure and presence or absence of *FLG* mutations with respect to AD as the outcome (*AD_{early}*, *AD_{current}*, *AD_{ever}*), using the following logistic regression models:

$$AD_{early} (yes/no) \sim FLG (yes/no) + Cat_exposure (yes/no) + FLG*Cat_exposure (Primary)$$

$$AD_{current} (yes/no) \sim FLG (yes/no) + Cat_exposure (yes/no) + FLG*Cat_exposure (Secondary)$$

$$AD_{ever} (yes/no) \sim FLG (yes/no) + Cat_exposure (yes/no) + FLG*Cat_exposure (Secondary)$$

Stratified analyses were performed to illustrate effect size and direction of the cat vs. AD relationship in children with and without *FLG* mutations, respectively. An inverse variance fixed effects meta-analysis was conducted using the R (<https://www.r-project.org/>) based 'meta' package.⁵ Meta analyses for each model (Cat**FLG* interaction and stratified: *FLG* mutation/wild type) with AD as an outcome (early/current/ever) were performed for studies with sufficient power for each analysis. Studies with empty cells (zero observations in a given stratum) were excluded from the meta-analyses. The excluded studies from the '*AD_{current}*' analyses were DNBC, INMA and LISA. Results were reported as odds ratios (OR) with 95% confidence intervals (CI) in addition to estimated heterogeneity (I^2) and related p-value (p_1^2) observed for each meta-analysis. A p-value of 0.05 was considered statistically significant for the primary outcome, while a Bonferroni-corrected p-value considering the 3 different outcomes was used for secondary outcomes (p-value <0.017).

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Supplemetary Table 1. Atopic dermatitis diagnoses.

Cohort name	Detailed information about how diagnosis of AD was obtained
ALSPAC	Symptoms (dry, oozing or crusty rash in joints and creases of the body (or on the face forearms of shins at 6m) in the preceding 12 months reported by parents in questionnaires
BAMSE	Symptoms (dry skin and itchy rash for 2 weeks or more in typical localisation) and/or doctor diagnosis of eczema from the previous follow-up. All assessed with questionnaires answered by the parents
Baseline Study	United Kingdom Working Party Criteria for Atopic Dermatitis

COPSAC 2000	Physician diagnosed from prospective clinical follow-up. Early onset atopic dermatitis (before one year of age). Current eczema (at seven years of age) and eczema ever (ever during first 7 years of life)
COPSAC 2010	Physician diagnosed from prospective clinical follow-up. Early onset atopic dermatitis (before one year of age). Current eczema (at 5 years of age) and eczema ever (ever during first 5 years of life)
Danish National Birth Cohort (DNBC)	Has a doctor ever said that your son/daughter had atopic dermatitis or eczema, also known as allergic rash.
Generation R	Postnatal data about eczema was annually collected by questionnaires at the ages of 6 months to 6 years (response rates 71-76%). Questions about eczema were 'Has your child in the past 6 or 12 months had eczema [Yes, saw a doctor; Yes, but did not see a doctor; No, did not have eczema]?' (age 6 months to 4 years), 'Has your child ever had eczema [Yes; No]?' (age 6 years) and 'How often in the past year was your child seen by a doctor because of these complaints [Never; Once or twice; 3 times or more]?' (age 6 years). We defined ever eczema as those children of whom parents answered their child 'Yes, had eczema and saw a doctor in the past year'. Reported eczema in the previous years were used to reclassify ever eczema where appropriate. Current eczema was defined as those children with ever eczema whom in the past year were seen by a doctor because of complaints at age 6 years. Late eczema was defined as those children whom parents answered their child had eczema at 2, 3 or 4 years, but not at ages 6 months and 1 year. Early eczema was defined as those children whom parents answered their child had eczema at ages 6 months or 1 year. We defined controls as those children of whom parents answered their child 'No, never had eczema' and 'Yes, had eczema but did not see a doctor/No, did not have eczema'.
GINIplus	Parent report of doctor diagnosis for each year of life
INMA (subcohorts: VAL, SAB, MEN)	Atopic eczema (questionnaire in VAL+SAB), physician diagnosed atopic eczema (questionnaire in MEN)
LISAplus	Parent report of doctor diagnosis for each year of life

German Multicenter Allergy Study (MAS)	Early manifestation of AD was defined as onset of disease in the first 2 years of life, and severity of early AD was assessed on the basis of parental reporting of the frequency of child's scratching. An ordinal variable combining early AD and the frequency of scratching was used as the outcome variable. Furthermore, an objective severity score was assessed during the skin examination at age 2 years. At age 7 years, children with early AD were grouped into 3 disease patterns: the group with complete remission after age 2 years comprised those children who showed no AD after the age of 2 years; children with AD at every follow-up until age 7 years were categorized as having persistent AD; and all children with early AD fulfilling neither of these criteria were categorized as having intermittent AD
MAAS	Eczema status was obtained by questionnaire when the children came to the MAAS follow-up clinic. Question, "Has your child ever suffered from atopic dermatitis", Eczema EVER : Case='yes' at any timepoint (1y, 3y, 5y, 8y); Control='no' at all timepoints; Current Eczema Case='yes' at 81 months; Control='no' at 81 months; EARLY Eczema : Case='yes' at 6 or 18 months; Control='no' at 6 and 18 months; LATE Eczema: Case='yes' from 30 months and EARLY control; Control=EVER control or EARLY case
Raine Study	Parental Questionnaire: (Age: 1,2,3): Has your child had any skin rashes, dermatitis or eczema which lasted more than a couple of days? (Age 5 yrs):Has your child ever had an itchy rash which was coming and going for at least six months? Has your child had this itchy rash any time in the last 12 months? Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes? Who diagnosed your child with eczema? - Pediatricians, doctors, child health nurse/school nurse, Naturopath, Pharmacist, relative, friend or teacher. (Age 8 yrs): Has your child had eczema in the last 12 months? Has your child had eczema in the last month?

Supplementary Table 2. Cohort characteristics.

Cohort name	ALSPAC	BAMSE	Baseline Study	COPSAC 2000	COPSAC 2010	Danish National Birth Cohort (DNBC)	Generation R	GINIplus	INMA (subcohorts: VAL, SAB, MEN)	LISAplus	German Multicenter Allergy Study (MAS)	MAAS	Raine Study
Cohort inclusion criteria/study design	Pregnant women resident in Avon, UK	Children born in predefined areas of Stockholm	Children born in a single tertiary maternity hospital	Children born from mothers with asthma	Children from the general population	Children from the general population	Pregnant women with an expected delivery date between April 2002 and January 2006 living in Rotterdam	Population-based, prospective birth cohort including full-term infants	Population based birth cohort.	Population -based, prospective birth cohort including full-term infants	Prospective observational birth cohort	Prospective Cohort	pregnancy cohort
Study year baseline	1991-1992	1994-1996	2008	2000	2010	2003	2002-2006	1995-98	INMA Menorca: 1997-1998, INMA Sabadell: 2004-2006, INMA Valencia: 2003-2005	1997-99	1990	1996-1997	1989-1991
Filaggrin mutations genotyped	R501X, 2282del4, R2447X, S3247X	R501X, 2282del4, R2447X	R501X, 2282del4, R2447X, S3247X	R501X, 2282del4, R2447X, S3247X	R501X, 2282del4, R2447X, S3247X	R501X, 2282del4, R2447X, S3247X	R501X, 2282del4, R2447X, S3247X	R501X, 2282del4	R501X, 2282del4, R2447X, S3247X	R501X, 2282del4	R501X, 2282del4, R2447X, S3247X	R501X, 2282del4, R2447X, S3247X	R501X, 2282del4, S3247X, rs138726443
Proportion with FLG mutations % (n/n_total)	11% (834/7743)	7.2% (138/1906)	10.8% (146/1344)	12.3%(49/396)	10.3% (72/700)	Among children with information on AD at ages <18 months it	9.4% (268/2849)	7.0%(104/1490)	4.6%(28/606)	7.0% (69/987)	9.7% (79/813)	10.1% (87/864)	9.3%(140/1500)

						was 9.7% (91/935), and among children with information on current/ever AD at age 7 year it was 8.8% (85/963)							
Basis for diagnosis of atopic dermatitis	Questionnaire	Questionnaire	UKWPC, SCORAD	Clinical diagnosis	Clinical diagnosis	Questionnaire	Questionnaire	Questionnaire	Questionnaire	Questionnaire	Clinical diagnosis and questionnaire	Questionnaire	Questionnaire
Prevalence with AD 'ever (0-7 y)' % (no/no total)	67% (4367/6501)	39.5% (743/1878)	26.33% (354/1344)	42.2% (175/396)	27.6% (193/700)	20.4% (196/963)	41.4% (1180/2849)	35.3% (447/1266)	49.6% (307/618)	32.56% (269/826)	36.16% (294/813)	60.7% (306/504)	39.7% (596/1500)
Prevalence with AD 'early onset (<1y)' % (no/no total)	18% (1368/7743)	16.9% (323/1906)	22.7% (292/1282)	25.3% (100/396)	11.1% (78/700)	14.7% (137/935)	21.6% (545/2521)	11.3% (167/1477)	31.7% (192/606)	9.7% (94/973)	14.14% (115/813)	34.6% (160/462)	22.8% (341/1498)
Prevalence with AD 'current' % (no/no total)	20% (1270/6402)	17.2% (327/1896)	15.2% (178/1168)	13.9% (55/396)	13.6% (95/700)	6.8% (65/963)	18.6%(496/2658)	5.93% (77/1298)	19.5% (118/604)	3.9% (32/825)	7.5% (58/773)	14.1% (96/681)	13.27% (184/1386)

AD assessment time-points	6, 18, 30, 42, 57, 69, 81 months	1, 2, 4 and 8 years	6, 12 and 24 months	Diagnosed longitudinally from acute and planned visits in the research clinic	Diagnosed longitudinally from acute and planned visits in the research clinic	6 and 18 month as well as 7 years	6 months, 1, 2, 3, 4 and 6 years	1, 2, 3, 4, 6 and 10 years	1, 2, and 4 years	6, 12, 18, 24 months as well as 4, 6 and 10 years	1, 3, 6, 12, 18, 24 month and then yearly	1,3,5,8	1, 3, 5, 8 years
Definition of cat exposure	Mothers answered: 'How many cats do you have?'	That they had cat at home	Household has a cat and childminder/nursery/creche has a cat under 12 months	Cat in the household	Cat in the household	Parental report: 'What animals or pets have you had since his/her birth?'	Parental report: 'Do you have a cat in your home?'	Parental report: 'Do you currently have pets living in the house?'; 'If yes, which?' (cat)	a) cat at home at least one month from birth to age 1y (SAB+VAL); b) cat at home at any point from birth to age 1 year (MEN)	3 months: Do you currently have pets living in the house? If yes, which: cat 1 year: Did you get a pet since birth? If yes, which: cat	Parental report: 'Are there any cats living in your household?'	Questionnaire parental report of cat ownership	Parental report: 'cat in the house?; cat outside the house?; In contact with cats elsewhere?'
Child age at cat exposure assessment	During pregnancy (90% completed by 28 weeks)	At baseline (3 months) and/or 1 year follow-up.	6 months and 12 months	Birth	Birth	18 months	Prenatal cat exposure as proxy for early life (age < 1 year) cat exposure	1 year	1 year	3 months and 1 year	3 months	at recruitment (birth)	1 year
Proportion with early life cat exposure % (no/no total)	29.6%	Baseline: 9.7% 1 yrs: 7.8% Baseline and/or 1 yrs: 10.6%	8.8%	15%	20%	22.4% (outcome AD<18m) and 16.4% (outcome AD7y current/ever)	25.3%	7.9% (118/1490)	11.5%	12.2%	12.7% (103/813)	20.5% (174/847)	18%
Latest follow-up age for AD (years)	7 years	7 years	2 years	7 years	5 years	7 years	6 years	7 years	4 years	7 years	7 years	8	7 years

Reference (PMID):	22507743; 22507742	29507996	25102856	18578563	29102067	26594040	28070760	20082618	21471022,	12358337	15131576	12688622	8105165;
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Supplementary Table 3. Interaction between cat exposure and *FLG* mutations in relation to early childhood atopic dermatitis phenotypes. Results represent meta-analyses using a fixed effects model and are shown both for an interaction model and stratified on Filaggrin mutation or wildtype, respectively.

Phenotype	Interaction					Filaggrin mutation					Filaggrin wildtype				
	N	OR	95%CI	<i>P</i>	<i>P_{het}</i> (I ²)	N	OR	95%CI	<i>P</i>	<i>P_{het}</i> (I ²)	N	OR	95%CI	<i>P</i>	<i>P_{het}</i> (I ²)
AD _{early}	13	1.10	0.86-1.43	0.44	0.48 (0)	13	1.20	0.95-1.53	0.12	0.27 (16.9)	13	1.08	0.98-1.18	0.09	0.74 (0)
AD _{current}	10	1.36	1.02-1.82	0.03	0.36 (8.6)	10	1.24	0.94-1.62	0.11	0.23 (22.6)	10	0.91	0.81-1.0	0.07	0.30 (14.7)
AD _{ever}	13	1.06	0.82-1.37	0.63	0.78 (0)	13	1.01	0.79-1.29	0.90	0.84 (0)	13	0.95	0.88-1.02	0.19	0.75 (0)

N: Number of participating cohorts, CI: Confidence Interval, I²: Heterogeneity (%)