Nonatopic eczema in elderly women: Effect of air pollution and genes

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Background: Although many risk factors have been described for atopic eczema in children, little is known about the eczema phenotype in middle-aged or elderly adults.
Objective: We sought to examine the association between air pollution, atopy, and eczema in adulthood.
Methods: This analysis was based on 834 women from the Study on the influence of Air pollution on Lung Function, Inflammation and Ageing cohort in Germany. Incident symptoms of eczema after age 55 years and prevalent symptoms of eczema 12 months or less before investigation were assessed by means of questionnaire at the second follow-up (2007-2010). Total serum IgE levels were measured at baseline (1985-1994) and in 2007-2010. Exposure to air pollution was assessed by using land-use regression. Adjusted logistic regression models were applied to estimate the association between air pollution and incident and prevalent symptoms of eczema. Weighted genetic risk scores were used to investigate the effect of atopic eczema–related risk alleles on this association.
Results: Exposures to oxides of nitrogen (nitrogen dioxide and nitrogen oxides) and particulate matter (fine particulate matter with an aerodynamic diameter of ≤2.5 μm [$PM_{2.5}$] and particulate matter with an aerodynamic diameter of <10 μm) were significantly associated with increased odds of incident eczema (eg, with $PM_{2.5}$ per 4.7 μg/m^3; odds ratio, 1.45; 95% CI, 1.06-1.99). These associations were slightly more pronounced with nonatopic eczema (eg, with $PM_{2.5}$; odds ratio of 1.65 and 95% CI of 1.15-2.34 for participants without hay fever or increased IgE levels). Associations with air pollution were stronger in carriers of fewer risk alleles for atopic eczema.
Conclusion: Nonatopic eczema in the elderly is associated with traffic-related air pollutants, and this phenotype differs from genetically driven atopic eczema. (J Allergy Clin Immunol 2019;143:378-85.)

Key words: *Atopic eczema, atopic dermatitis, adults, allergy, serum IgE, hay fever, gene-environment interactions*

Research into the causes of eczema (formerly also known as atopic dermatitis) has long been hampered by inconsistent definitions. The World Allergy Organization recognized that eczema is characterized by defective skin barrier function. At least 2 types of eczema have been identified: an atopic type with skin inflammation driven by T-cell responses and T_H2 cytokines in the initiating phase, which is usually associated with IgE-mediated sensitization to environmental allergens and high levels of total IgE and allergen-specific IgE. There is also a nonatopic type of eczema with normal levels of total IgE and a lack of sensitization to environmental allergens.[1] In children and young adults skin inflammation is largely associated with high IgE levels, with atopic eczema comprising 70% to 80% and nonatopic eczema comprising 20% to 30%.[2] However, in older patients, particularly those with chronic eczema, other nonatopic inflammatory mechanisms might be involved.[3] The World Allergy Organization called for further research into the causes and mechanisms of this nonatopic eczema.[4]

Some known and proposed risk factors for atopic eczema in children include family history, birth weight, season of birth, lack of breast-feeding,[5] socioeconomic status, second-hand smoke exposure,[6] and residence in urban as opposed to rural areas.[7] Furthermore, atopic eczema has significant genetic contributions, with heritability estimates of up to 90% in European children.[8] The strongest known risk factors are null mutations in the filaggrin gene (*FLG*) resulting in epidermal barrier deficiency.[9-11] Genome-wide association studies, which were mainly performed in children, have identified 31 additional loci that are mostly implicated in immune dysregulation.[12] Additional risk factors for atopic eczema in children include exposure to second-hand smoke and maternal smoking during pregnancy,[13] and it has been suggested that environmental pollution might also play a role in eczema.[14] However, several studies reported null effects of air pollution,[15-19] and additional research is warranted to fully understand the role of air pollution in the development of atopic eczema.

Considerably less is known about the risk factors for eczema symptoms in adults, and most studies could not differentiate between relapsing childhood eczema and eczema with a later onset.[20-23] Only our recent analysis of the Study on the influence of Air pollution on Lung Function Inflammation and Ageing

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Abbreviations used
AHR: Aryl hydrocarbon receptor
ESCAPE: European Study of Cohorts for Air Pollution Effects
GRS: Genetic risk score
IQR: Interquartile range
NO_2: Nitrogen dioxide
NO_x: Oxides of nitrogen
OR: Odds ratio
PAH: Polycyclic aromatic hydrocarbon
$PM_{2.5}$: Fine particulate matter with an aerodynamic diameter of 2.5 μm or less
PM_{10}: Particulate matter with an aerodynamic diameter of less than 10 μm
SALIA: Study on the influence of Air pollution on Lung Function Inflammation and Ageing
SNP: Single nucleotide polymorphism
WHO: World Health Organization

(SALIA)[24] considered age of onset in the characterization of eczema and showed an association between air pollution and eczema with a late onset. However, nothing is known about the role of atopy in this association, which might provide more insights into the immunopathology of eczema in the elderly.

The aim of this analysis was to examine whether exposure to air pollution was associated with the incidence of nonatopic eczema in adulthood by using a cohort of elderly women in the formerly highly industrialized Ruhr area and the Southern Münsterland of Germany.

METHODS

The SALIA cohort conducted in the Ruhr area and Southern Münsterland, Germany, has been described in detail elsewhere.[25,26] Men were not recruited to avoid bias from occupational exposures in the mining and steel industries. Baseline examinations of 4874 women aged 54 to 55 years were undertaken between 1985 and 1994. The first follow-up assessment was done through a self-administered questionnaire, which was sent to participants by post (n = 2006 replies). This analysis presents data from the clinical (second) follow-up, which was conducted in 2007-2010 in 834 women. The Medical Ethics Committee of the University of Bochum approved the follow-up examinations. All participants provided written informed consent.

Both at baseline and at the clinical follow-up examination, participants completed an interviewer-administered questionnaire that collected sociodemographic, occupational, residential, health service use, medical diagnoses, smoking, family history, reproductive data, and symptoms of diseases.

Venous blood was drawn in a subsample of participants and assayed for total serum IgE at baseline by using nephelometry (Behring, Marburg, Germany) or ELISA (Abbott, Chicago, Ill); at follow-up, ImmunoCAP (Phadia, Freiburg, Germany) was used. IgE measurements at baseline were available from 605 women and at follow-up from 350 women (see the flowchart in Fig 1).

Genome-wide genotyping was performed in 462 of the women by using the Affymetrix Axiom Precision Medicine Research Array (Affymetrix, Santa Clara, Calif). Unobserved genotypes were imputed on the 1000 Genomes reference panel (Phase III) by using Minimac3.[27] We restricted single nucleotide polymorphisms (SNPs) to variants with minor allele frequencies of greater than 1% and moderate imputation quality scores ($R^2 > 0.3$). In total, 9,665,096 SNPs remained after quality control and imputation.

Exposure assessment

Exposure to air pollution was assessed by using land-use regression according to the European Study of Cohorts for Air Pollution Effects (ESCAPE) protocols.[28,29] In brief, land-use regression models were developed for annual concentrations of nitrogen dioxide (NO_2), oxides of nitrogen (NO_x), fine particulate matter with an aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$) mass, and particulate matter with an aerodynamic diameter of less than 10 μm (PM_{10}). Levels of these air pollutants were measured during the dedicated ESCAPE monitoring campaign in 2008-2009 in the area of SALIA residential addresses. Long-term concentrations were modeled with small-scale indicators of land use (eg, traffic, industry, port, and residential density) derived from Europe-wide and local geographic information databases and validated with measured annual average pollutant concentrations at the local monitoring sites. Concentrations were modeled at each study participant's address.

These land-use regression equations were applied to the SALIA addresses. Concentrations at baseline addresses derived from these models were back-extrapolated to the years around baseline investigation by the ratio of concentrations, which occurred between the baseline years and the monitoring year. For each study participant's home address, the back-extrapolated concentration was obtained by multiplying the modeled pollutant concentration by the ratio between average annual concentrations, as derived from the routine monitoring site or sites for the period in the past and for the ESCAPE measurement period time (for details see ESCAPE[30]). The procedures applied assumed that the within-city spatial contrasts remained proportional over time, as has been shown for land-use regression models previously.[31]

Outcome assessment

The 2007-2010 dermatologic questionnaire contained symptom questions to define eczema and was developed in collaboration with dermatologists (see Table E1 in this article's Online Repository at www.jacionline.org). Specifically, trained interviewers asked "Have you ever had an itchy rash which was coming and going for at least 6 months?" and "How old were you when it occurred for the first time?" to define the incidence of eczema symptoms after the age of 55 years, which corresponded to newly developed eczema symptoms after age 55 years (between baseline and follow-up investigation). The prevalence of eczema symptoms at the follow-up examination was defined by the following question: "Have you had this itchy rash at any time in the last 12 months?"

We explored 3 increasingly strict definitions of nonatopic eczema: eczema with stricter nonatopic grade means exclusion of participants with hay fever ever, participants with hay fever ever and IgE levels of greater than 100 IU/mL at baseline, and participants with hay fever ever and IgE levels of greater than 100 IU/mL at baseline or follow-up.

Statistical methods

Logistic regression models were fitted to the eczema outcomes (see above). Coefficients were estimated per interquartile range (IQR) of air pollutants and expressed as odds ratios (ORs) with 95% CIs. We used exposure estimates for the time before or at outcome assessment. Therefore we estimated (1) the association between baseline air pollution exposure and incident symptoms of eczema between baseline and follow-up (age >55 years) and (2) the association between follow-up air pollution exposure and prevalent symptoms of eczema at follow-up. *A priori* confounders included age, body mass index, highest educational status of participant or her spouse, household heating by indoor combustion of fossil fuels, smoking (categorized as current, former, or never smoking), and exposure to second-hand smoke at home or work. Cox proportional hazard regression models were fitted to time since the first symptoms of eczema after age 55 years with the same covariates.

We conducted 2 sensitivity analyses to investigate the robustness of our findings to exposure misclassification: we conducted a sensitivity analysis in which we estimated the association between follow-up air pollution exposure and incident symptoms of eczema between baseline and follow-up (age >55 years) to investigate the robustness of our findings to a possible misclassification caused by the back-extrapolation procedure. In the second sensitivity analysis we excluded all participants who moved between baseline and follow-up investigation.

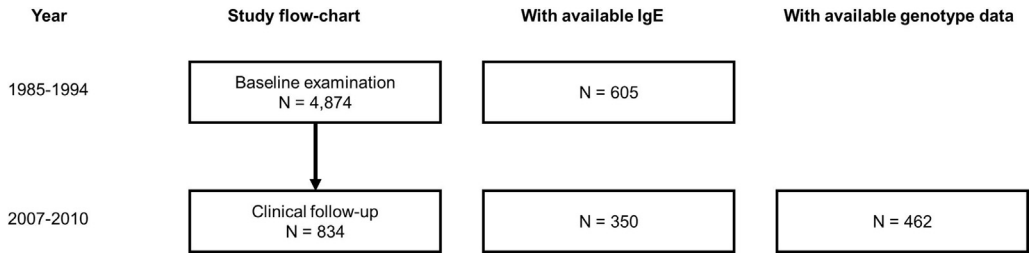

FIG 1. Flowchart of study population.

TABLE I. Description of subjects at the second SALIA follow-up (n = 834)

Covariates		
Age at second follow-up	Mean (SD); minimum-maximum	73.5 (3.0); 66.7-79.8
Age at incident eczema symptoms after age 55 y*	Mean (SD); minimum-maximum	66.9 (4.9); 58-78
Body mass index (kg/m^2)	Mean (SD); minimum-maximum	27.3 (4.5); 16.8-45.7
Heating by indoor combustion of fossil fuels at baseline	n/N (%)	137/823 (16.7)
Status, years of education†		
<10 y	n/N (%)	148/831 (17.8)
10 y	n/N (%)	404/831 (48.6)
>10 y	n/N (%)	279/831 (33.6)
Smoking		
Never	n/N (%)	668/834 (80.1)
Former	n/N (%)	143/834 (17.2)
Current	n/N (%)	23/834 (2.8)
Second-hand smoke ever	n/N (%)	503/834 (60.3)
Hay fever ever	n/N (%)	99/833 (11.9)
IgE >100 IU/mL at baseline	n/N (%)	60/605 (9.9)
IgE >100 IU/mL at follow-up	n/N (%)	47/350 (13.4)

*Corresponds to newly developed symptoms of eczema between baseline and follow-up examination.
†Highest educational status of participant or her spouse.

In the main analyses missing values for IgE were treated as IgE levels of 100 IU/mL or less, and we conducted 2 sensitivity analyses to investigate the robustness of our findings to a possible bias caused by missing IgE levels. The first sensitivity analysis was conducted of complete cases excluding those with missing IgE data, and in the second analysis missing IgE levels at baseline and follow-up investigation were imputed by using a multiple imputation procedure with the Markov Chain Monte Carlo method, as described by Schafer.[32]

To compare the common atopic eczema phenotype with air pollution–induced eczema in the elderly, we investigated the effect of atopic eczema–related SNPs on the incidence and prevalence of eczema symptoms in the elderly and particularly on the association with air pollution. To summarize the genetic risk factors for atopic eczema, we used weighted genetic risk scores (GRSs), which aggregate measured genetic effects and therefore increase the power to detect marginal genetic effects,[33] as well as gene-environment interactions.[34,35] Regression coefficients (β-estimates) were retrieved from a multiethnic genome-wide association study of 21,000 atopic eczema cases and 95,000 control subjects to calculate weighted GRSs.[12] Weighted GRSs with external weights[35] were calculated for each subject by multiplying the number of risk alleles for each of the 27 SNPs that were associated with atopic eczema[12] by the respective β-estimates and calculating the sum over all SNPs. We estimated the marginal genetic association of this GRS with incident and prevalent eczema symptoms, as well as its interaction with air pollution in adjusted logistic regression models.

All analyses were undertaken with use of SAS software (version 9.4; SAS Institute, Cary, NC) and R 3.4.1.[36]

RESULTS

Description of the study population

The subjects included in this analysis are described in Tables I and II. Mean age at follow-up was 73.5 (SD, 3.0) years. Median time between baseline and follow-up was 19.2 years (IQR, 3.6 years). After excluding those with hay fever (n = 101), there were 733 women remaining. After excluding those with increased baseline IgE levels, 684 remained, and after excluding those with increased IgE levels at follow-up, 657 remained (Fig 1 and Table II). The incidence of symptoms of eczema after age 55 years, which corresponds to newly developed symptoms of eczema between baseline and follow-up examination, was 7.4% to 7.9%, and the prevalence of symptoms of eczema up to 12 months before follow-up investigation was 8.0% to 8.8%, depending on the grade of atopy. Exposures to air pollution at baseline and follow-up are described in Table III. Annual concentrations of all pollutants decreased over the duration of follow-up.

Association between air pollution and eczema in the elderly

There were many significant associations between air pollutants at baseline and incident symptoms of eczema after age 55 years after exclusion of atopic subjects with increasing strictness (Table IV). Baseline NO_2, NO_x, PM_{10}, and $PM_{2.5}$ levels were all associated with increased odds of incident eczema. If anything, the associations were clearer and more significant for the more stringent definitions of nonatopic eczema. These associations were robust to a possible exposure misclassification caused (1) by using the back-extrapolation procedure (see Table E2 in this article's Online Repository at www.jacionline.org) and (2) by not excluding women who moved between baseline

TABLE II. Description of eczema at the second SALIA follow-up (n = 834)

Exclusion of atopic subjects with increasing strictness	n/N (%)
Incident symptoms of eczema after age 55 y*	
All participants	60/760 (7.9)
Never hay fever	50/668 (7.5)
Never hay fever and baseline IgE not >100 kU/L	46/623 (7.4)
Never hay fever and baseline IgE not >100 kU/L and follow-up IgE not >100 kU/L	45/599 (7.5)
Prevalent symptoms of eczema up to 12 mo before follow-up investigation	
All participants	73/832 (8.8)
Never hay fever	61/733 (8.3)
Never hay fever and baseline IgE not >100 kU/L	55/684 (8.0)
Never hay fever and baseline IgE not >100 kU/L and follow-up IgE not >100 kU/L	54/657 (8.2)

*Corresponds to newly developed symptoms of eczema between baseline and follow-up examination.

TABLE III. Description of air pollution exposures

	Units	No.	Median	IQR	Minimum	Maximum
Air pollutants at baseline						
NO_2	$\mu g/m^3$	834	34.7	14.8	20.3	84.1
NO_x	$\mu g/m^3$	834	60.6	43.3	26.8	216.1
$PM_{2.5}$	$\mu g/m^3$	834	33.3	4.7	22.0	41.3
PM_{10}	$\mu g/m^3$	834	50.2	6.8	32.2	65.1
Air pollutants at follow-up						
NO_2	$\mu g/m^3$	834	25.9	9.7	19.7	70.3
NO_x	$\mu g/m^3$	834	39.6	23.6	23.9	138.7
$PM_{2.5}$	$\mu g/m^3$	834	17.4	1.9	15.6	21.9
PM_{10}	$\mu g/m^3$	834	26.4	2.2	23.9	33.8

and follow-up examination (see Table E3 in this article's Online Repository at www.jacionline.org). The clearer associations with nonatopic eczema were also robust to possible bias caused by missing IgE levels: a first sensitivity analysis that excluded those with missing IgE data at baseline or follow-up and a second in which missing IgE levels were imputed by multiple imputation produced similar associations (see Tables E4-E6 in this article's Online Repository at www.jacionline.org). Analysis of time since the first symptoms of eczema and air pollution produced very similar results (see Table E7 in this article's Online Repository at www.jacionline.org).

Associations between air pollutants at follow-up and prevalent symptoms of eczema in the last 12 months showed the same trend but were not significant (Table IV and see Tables E3-E6).

Atopic eczema versus air pollution–induced eczema in the elderly

Some of the loci that were reported to be associated with atopic eczema[12] were also nominally associated ($P < .05$) with incident (3/26 available loci) and prevalent (4/26 available loci) symptoms of eczema in the elderly (see Tables E8 and E9 in this article's Online Repository at www.jacionline.org). However, none of these associations were significant after Bonferroni correction. When all atopic eczema–related SNPs were combined to a weighted GRS, this GRS was directly associated with neither incident symptoms of eczema nor in interaction with air pollution (Fig 2, *A*). With the prevalence of eczema symptoms, we also did not find a marginal genetic association of the GRS but an indication for a negative interaction with air pollution ($P_{interaction}$ = .063 for NO_2; Fig 2, *B*). Participants with a low GRS (carrier of fewer risk alleles for atopic eczema) were more susceptible to air pollution–induced prevalent eczema symptoms (OR, 1.77; 95% CI, 1.06-2.97) than participants in the general population (OR, 1.168; 95% CI, 0.861-1.584). In contrast, there was no association with air pollution in participants with a high GRS (carrier of many risk alleles for atopic eczema; OR, 0.89; 95% CI, 0.53-1.49).

DISCUSSION

This cohort of women from the Ruhr and surrounding region of Germany was followed for 19 years, during which time exposure to gaseous and particulate air pollution decreased substantially. Baseline concentrations of NO_2, NO_x, respirable particles (PM_{10}), and fine particles ($PM_{2.5}$) were significantly associated with increased odds of eczema in middle-aged or elderly women. All of these pollutants were associated with significantly increased odds of incident eczema symptoms after 55 years of age, which corresponded to newly developed eczema symptoms after 55 years of age (between baseline and follow-up investigation), and associations were stronger for nonatopic symptoms of eczema.

Polycyclic aromatic hydrocarbons (PAHs) have been identified as one of the main drivers of PM-induced inflammation.[37] The lipophilic PAHs can easily penetrate into the stratum corneum, where the inflammatory processes can lead to induction of eczema onset, as well as to an increased exacerbation rate of eczema symptoms.[38] PAHs exert their biological effects through binding to the ligand-activated transcription factor aryl hydrocarbon receptor (AHR), which activates the expression of genes encoding detoxification enzymes.[39] Activation of AHR signaling can be detrimental and, for example, lead to the generation of skin cancer, if this happens in normal uninflamed skin. However, it can also be beneficial and dampen skin inflammation if AHR activation occurs in inflamed skin, such as atopic eczema or psoriasis.[40] This Janus-faced role of AHR activation might provide one possible explanation for the present observation why the traffic-related air pollution effects are less pronounced for atopic eczema.

However, we did not find an association between air pollution and prevalent symptoms of eczema up to 12 months before the follow-up investigation. An explanation for the different associations between incidence and prevalence of eczema symptoms might be the time of onset. Incident symptoms of eczema refer to eczema symptoms with an onset at 55 years of age or later, whereas prevalent symptoms of eczema refer to current eczema symptoms without considering the time of onset. This suggests that air pollution particularly affects eczema with a late to very late onset.

Air quality in the Ruhr area improved quite substantially after closure of the coal and steel industries. For some pollutants, the back-extrapolated baseline and estimated follow-up concentrations can be compared with the air quality guidelines of the World Health Organization (WHO).[41] For example, the mean annual NO_2 concentration decreased from 37.4 $\mu g/m^3$ at baseline to 28.6 $\mu g/m^3$ at follow-up, which were both well below the WHO guideline of 40 $\mu g/m^3$. Similarly, mean annual

TABLE IV. Associations between air pollutants at baseline and incident symptoms of eczema after age 55 years following exclusion of atopic subjects, with increasing strictness from left to right

	All participants	Never hay fever	Never hay fever + baseline IgE not >100 kU/L	Never hay fever + baseline IgE not >100 kU/L + follow-up IgE not >100 kU/L
Air pollutants at baseline and incident symptoms of eczema after age 55 years*				
N	746	656	612	588
NO_2	**1.497 (1.039-2.156)**	**1.666 (1.133-2.450)**	**1.821 (1.219-2.721)**	**1.847 (1.225-2.784)**
NO_x	**1.506 (1.064-2.132)**	**1.733 (1.188-2.529)**	**1.860 (1.256-2.755)**	**1.876 (1.257-2.801)**
$PM_{2.5}$	**1.454 (1.064-1.987)**	**1.603 (1.141-2.251)**	**1.629 (1.145-2.319)**	**1.650 (1.150-2.366)**
PM_{10}	**1.356 (1.004-1.831)**	**1.523 (1.103-2.103)**	**1.573 (1.125-2.199)**	**1.582 (1.124-2.225)**
Air pollutants at follow-up and prevalent symptoms of eczema up to 12 mo before follow-up investigation				
N	818	721	673	646
NO_2	1.168 (0.861-1.584)	1.159 (0.826-1.626)	1.258 (0.888-1.783)	1.267 (0.891-1.803)
NO_x	1.144 (0.844-1.550)	1.176 (0.842-1.644)	1.274 (0.900-1.804)	1.280 (0.901-1.819)
$PM_{2.5}$	1.297 (0.931-1.806)	1.327 (0.923-1.908)	1.438 (0.984-2.100)	1.467 (0.997-2.157)
PM_{10}	1.138 (0.880-1.472)	1.206 (0.911-1.597)	1.298 (0.972-1.732)	1.307 (0.976-1.751)

ORs (95% CIs) per an increase of 1 IQR in air pollution are shown in boldface if the *P* value if less than .05. Results are adjusted for age, body mass index, highest educational status of participant or her spouse, household heating by indoor combustion of fossil fuels, smoking (categorized as current, former, or never smoking), and exposure to second-hand smoke at home or work.

*Corresponds to newly developed symptoms of eczema between baseline and follow-up examination.

PM_{10} concentrations decreased from 48.4 to 26.9 $\mu g/m^3$, which still exceeded the guideline of 20 $\mu g/m^3$, but would meet the WHO interim target-3 of 30 $\mu g/m^3$. Mean annual $PM_{2.5}$ concentrations decreased from 32.1 to 17.9 $\mu g/m^3$, which exceeded the guideline of 10 $\mu g/m^3$ but would meet the WHO interim target-2 of 25 $\mu g/m^3$. Because we did not find an association between air pollution and prevalent symptoms of eczema up to 12 months before the follow-up investigation, we could speculate that there was an improvement in eczema symptoms among the elderly women after reduction of air pollution. However, because our dermatologic questionnaire was not detailed enough to investigate this hypothesis sufficiently, more research is needed to fully understand the effect of improved air quality on eczema in the elderly.

Most of the publications related to the association between air pollution and eczema were focused on atopic eczema in children,[42] and the results were inconsistent. There was some evidence supporting adverse effects of air pollution on atopic eczema and current itchy rashes.[43-46] However, several studies also report null effects.[15-19] In addition, there are only very few studies on the association between air pollution and eczema in adults, again with contradictory results.[20-22,24] Pujades-Rodriguez et al[20] performed a population-based cross-sectional study of 2644 Nottingham adults aged 18 to 70 years in which they did not find any evidence for an association between air pollution and eczema, but 2 Chinese studies showed an association between air pollution and eczema in adults.[21,22] However, all of these studies were based on atopic eczema, and only our recent study of the SALIA cohort considered age of onset.[24]

Our analyses revealed that eczema in the elderly differs from genetically driven atopic eczema, especially its association with air pollution. First, we showed that associations with air pollution were slightly more pronounced and more consistent in nonatopic participants. Second, carriers of fewer risk alleles for atopic eczema were more susceptible to air pollution–induced symptoms of prevalent eczema in their 70s. Therefore we propose that environmental factors, such as air pollution, might be more relevant for eczema in the elderly than in children, especially for a nonatopic type of eczema. This suggests that skin barrier function, which is likely to be decreased in the elderly, is more important for development of eczema beyond 50 years of age than an atopic diathesis.

According to the literature, adult-onset eczema (between 20 and 60 years of age) is characterized mainly by female patients with a rather mild clinical phenotype and a very limited spectrum of sensitization usually accompanied by a normal total IgE level,[3] which is consistent with the phenotype described in our study population. In contrast, eczema with a very late onset (>60 years) is often accompanied by increased total IgE levels.[1,3] However, eczema in older adults seems to represent a newly defined subgroup of eczema,[1] and more research is needed to characterize this phenotype in greater detail.

The strengths of this study include the cohort design, the long duration of follow-up, estimation of air pollution exposure by using the validated ESCAPE protocols,[28,29] objective measurement of atopy based on serum IgE levels, and adjustment for relevant confounders in the multivariate analyses. However, like all cohort studies, it also has some limitations, such as attrition and survivor bias. Some of us have previously shown that those lost to follow-up tended to be older, more overweight, and have lower socioeconomic status than those who were available at follow-up.[47] Eczema was defined only by self-report, and we had no information about the severity or frequency of eczema symptoms. However, very similar questions have been validated against a standardized skin examination in children.[48] The combination of asthma with hay fever has previously been shown to reliably identify atopic asthma and to be causally associated with infantile eczema.[49]

A major limitation of our study is that IgE levels were not measured in all participants and not at every time point of investigation. Therefore more studies with more detailed information about the participants' atopy status are needed to validate our findings. Furthermore, it was necessary to back-extrapolate concentrations of baseline air pollutants, as has been successfully done in many previous ESCAPE studies, for example studies of chronic obstructive pulmonary disease,[50] acute coronary events,[51] and mortality.[31]

In conclusion, this analysis of data from a well-characterized cohort suggests strong associations between traffic-related air

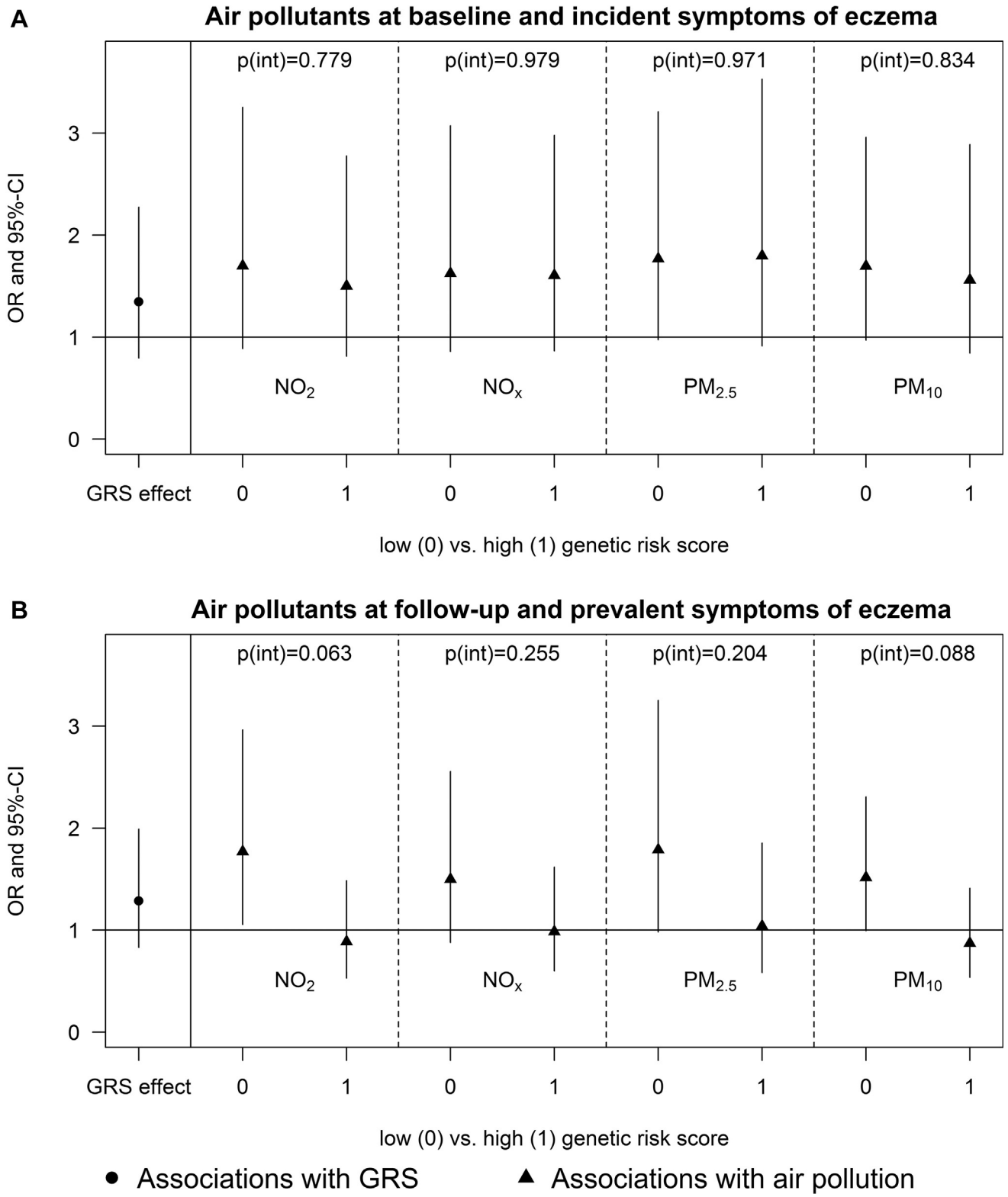

FIG 2. SNPs associated with atopic dermatitis.[12] **A,** Incident symptoms of eczema after age 55 years (n = 412). **B,** Prevalent symptoms of eczema up to 12 months before follow-up investigation (n = 452). ORs and 95% CIs are presented for the association with an increase of 1 IQR in the GRS (GRS effect) in the whole study population with genotype information and an increase of 1 IQR in air pollution stratified by a low versus high GRS (cut point: median). *P* values are given for the interaction between the GRS and air pollution on incident/prevalent symptoms of eczema. Results are adjusted for age, body mass index, highest educational status of participant or her spouse, household heating by indoor combustion of fossil fuels, smoking (categorized as current, former, or never smoking) and exposure to second-hand smoke at home or work.

pollutants and incident and nonatopic eczema in elderly women. Clearly, further research is required, particularly in men, non-European populations, and including skin examination to confirm the diagnosis of eczema. However, it would seem prudent to further reduce exposure to air pollution not just for the well-documented effects on mortality and respiratory and cardiovascular disease but also for a potential benefit on skin disease and quality of life.

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Key messages

- **Air pollution was associated with nonatopic eczema in elderly women.**
- **These women were characterized by absence of hay fever, low total IgE levels, and few risk alleles for atopic eczema.**

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TABLE E1. Section of the dermatologic questionnaire on eczema symptoms and atopic status conducted at follow-up investigation (2007-2010) used to define the eczema and hay fever variables for analyses

Variable used in analyses	Corresponding questions asked by trained interviewers
Incident eczema symptoms after age 55 years	A. Have you ever had an itchy rash that was coming and going for at least 6 months? B. How old were you when it occurred for the first time?
Prevalent eczema symptoms at follow-up examination	Have you had this itchy rash at any time in the last 12 months?
Hay fever ever	Has a doctor ever diagnosed you with hay fever?

TABLE E2. Associations between air pollutants at follow-up and incident symptoms of eczema after age 55 years following exclusion of atopic subjects, with increasing strictness from left to right

	All participants	Never hay fever	Never hay fever + baseline IgE not >100 kU/L	Never hay fever + baseline IgE not >100 kU/L + follow-up IgE not >100 kU/L
Air pollutants at baseline and incident symptoms of eczema after age 55 years*				
N	746	656	612	588
NO_2	**1.611 (1.189-2.182)**	**1.765 (1.278-2.438)**	**1.896 (1.356-2.654)**	**1.949 (1.382-2.748)**
NO_x	**1.531 (1.130-2.076)**	**1.747 (1.252-2.432)**	**1.877 (1.329-2.652)**	**1.918 (1.347-2.731)**
$PM_{2.5}$	**1.719 (1.209-2.444)**	**1.931 (1.327-2.810)**	**1.946 (1.315-2.880)**	**2.026 (1.354-3.031)**
PM_{10}	**1.376 (1.055-1.794)**	**1.549 (1.170-2.052)**	**1.587 (1.186-2.124)**	**1.616 (1.200-2.175)**

ORs (95% CIs) per an increase of 1 IQR in air pollution are shown in boldface if the *P* value is less than .05. Results are adjusted for age, body mass index, highest educational status of participant or her spouse, household heating by indoor combustion of fossil fuels, smoking (categorized as current, former, or never smoking), and exposure to second-hand smoke at home or work.

*Corresponds to newly developed symptoms of eczema between baseline and follow-up examination.

TABLE E3. Sensitivity analysis for participants who did not move between baseline and follow-up investigation: Associations between air pollutants at baseline and incident symptoms of eczema after age 55 years following exclusion of atopic subjects, with increasing strictness from left to right

	All participants	Never hay fever	Never hay fever + baseline IgE not >100 kU/L	Never hay fever + baseline IgE not >100 kU/L + follow-up IgE not >100 kU/L
Air pollutants at baseline and incident symptoms of eczema after age 55 y*				
N	636	564	526	503
NO_2	**1.613 (1.082-2.403)**	**1.833 (1.195-2.810)**	**2.074 (1.319-3.261)**	**2.145 (1.345-3.461)**
NO_x	**1.584 (1.085-2.314)**	**1.870 (1.232-2.838)**	**2.054 (1.323-3.189)**	**2.104 (1.341-3.302)**
$PM_{2.5}$	**1.492 (1.062-2.096)**	**1.632 (1.131-2.354)**	**1.685 (1.143-2.483)**	**1.708 (1.147-2.543)**
PM_{10}	1.383 (0.998-1.918)	**1.532 (1.082-2.169)**	**1.609 (1.116-2.319)**	**1.618 (1.113-2.352)**
Air pollutants at follow-up and prevalent symptoms of eczema up to 12 mo before follow-up investigation				
N	699	622	580	554
NO_2	1.157 (0.825-1.623)	1.147 (0.782-1.683)	1.263 (0.848-1.881)	1.274 (0.851-1.908)
NO_x	1.115 (0.797-1.559)	1.157 (0.796-1.684)	1.268 (0.857-1.875)	1.272 (0.856-1.890)
$PM_{2.5}$	1.290 (0.904-1.842)	1.331 (0.903-1.962)	1.460 (0.970-2.195)	1.489 (0.983-2.254)
PM_{10}	1.130 (0.854-1.494)	1.192 (0.881-1.614)	1.268 (0.857-1.775)	1.307 (0.953-1.794)

ORs (95% CIs) per an increase of 1 IQR in air pollution are shown in boldface if the *P* value is less than .05. Results are adjusted for age, body mass index, highest educational status of participant or her spouse, household heating by indoor combustion of fossil fuels, smoking (categorized as current, former or never smoking), and exposure to second-hand smoke at home or work.

*Corresponds to newly developed symptoms of eczema between baseline and follow-up examination.

TABLE E4. Sensitivity analysis for only participants with available data for IgE at baseline: Associations between air pollutants at baseline and incident symptoms of eczema after age 55 years following exclusion of atopic subjects, with increasing strictness from left to right

	All participants	Never hay fever	Never hay fever + baseline IgE not >100 kU/L	Never hay fever + baseline IgE not >100 kU/L + follow-up IgE not >100 kU/L
Air pollutants at baseline and incident symptoms of eczema after age 55 y*				
N	543	470	426	408
NO_2	1.359 (0.922-2.001)	1.498 (0.995-2.255)	**1.647 (1.072-2.529)**	**1.676 (1.078-2.606)**
NO_x	1.372 (0.945-1.991)	**1.585 (1.057-2.376)**	**1.709 (1.117-2.613)**	**1.725 (1.116-2.667)**
$PM_{2.5}$	1.400 (0.958-2.044)	**1.580 (1.030-2.423)**	**1.585 (1.017-2.469)**	**1.638 (1.036-2.592)**
PM_{10}	1.298 (0.917-1.838)	1.466 (0.998-2.152)	**1.502 (1.008-2.239)**	**1.529 (1.016-2.303)**
Air pollutants at follow-up and prevalent symptoms of eczema up to 12 mo before follow-up investigation				
N	594	518	470	451
NO_2	1.073 (0.771-1.496)	1.055 (0.731-1.522)	1.154 (0.788-1.688)	1.166 (0.792-1.717)
NO_x	1.038 (0.746-1.445)	1.072 (0.747-1.538)	1.167 (0.799-1.705)	1.175 (0.800-1.725)
$PM_{2.5}$	1.196 (0.831-1.721)	1.233 (0.828-1.835)	1.359 (0.894-2.067)	1.402 (0.914-2.150)
PM_{10}	1.094 (0.832-1.438)	1.152 (0.856-1.552)	1.250 (0.919-1.701)	1.263 (0.924-1.727)

ORs (95% CIs) per an increase of 1 IQR in air pollution are shown in boldface if the *P* value is less than .05. Results are adjusted for age, body mass index, highest educational status of participant or her spouse, household heating by indoor combustion of fossil fuels, smoking (categorized as current, former, or never smoking), and exposure to second-hand smoke at home or work.

*Corresponds to newly developed symptoms of eczema between baseline and follow-up examination.

TABLE E5. Sensitivity analysis for only participants with available data for IgE at baseline and at follow-up: Associations between air pollutants at baseline and incident symptoms of eczema after age 55 years following exclusion of atopic subjects, with increasing strictness from left to right

	All participants	Never hay fever	Never hay fever + baseline IgE not >100 kU/L	Never hay fever + baseline IgE not >100 kU/L + follow-up IgE not >100 kU/L
Air pollutants at baseline and incident symptoms of eczema after age 55 y*				
N	250	223	207	189
NO_2	1.205 (0.675-2.153)	1.261 (0.666-2.390)	1.372 (0.714-2.636)	1.411 (0.717-2.775)
NO_x	1.309 (0.746-2.299)	1.492 (0.793-2.805)	1.694 (0.871-3.294)	1.757 (0.881-3.505)
$PM_{2.5}$	1.105 (0.602-2.028)	1.059 (0.558-2.009)	1.148 (0.582-2.263)	1.187 (0.588-2.396)
PM_{10}	0.977 (0.548-1.741)	0.975 (0.532-1.788)	1.015 (0.539-1.910)	1.022 (0.532-1.964)
Air pollutants at follow-up and prevalent symptoms of eczema up to 12 mo before follow-up investigation				
N	275	246	228	209
NO_2	1.283 (0.858-1.916)	1.183 (0.749-1.869)	1.399 (0.880-2.225)	1.449 (0.902-2.327)
NO_x	1.214 (0.798-1.847)	1.203 (0.754-1.919)	1.474 (0.901-2.414)	1.500 (0.909-2.475)
$PM_{2.5}$	1.264 (0.785-2.037)	1.152 (0.686-1.937)	1.385 (0.799-2.400)	1.461 (0.828-2.577)
PM_{10}	1.166 (0.811-1.677)	1.130 (0.759-1.681)	1.269 (0.839-1.919)	1.304 (0.851-1.997)

ORs (95% CIs) per an increase of 1 IQR in air pollution. Results are adjusted for age, body mass index, highest educational status of participant or her spouse, household heating by indoor combustion of fossil fuels, smoking (categorized as current, former, or never smoking), and exposure to second-hand smoke at home or work.
*Corresponds to newly developed symptoms of eczema between baseline and follow-up examination.

TABLE E6. Sensitivity analysis for missing IgE levels at baseline and follow-up using imputation: Missing IgE levels were imputed by means of multiple imputation with the Markov Chain Monte Carlo method

	All participants	Never hay fever	Never hay fever + baseline IgE not >100 kU/L	Never hay fever + baseline IgE not >100 kU/L + follow-up IgE not >100 kU/L
Air pollutants at baseline and incident symptoms of eczema after age 55 years*				
N	746	656	603.6†	555.8†
NO_2	**1.497 (1.039-2.156)**	**1.666 (1.133-2.450)**	**1.804 (1.206-2.698)**	**1.824 (1.180-2.819)**
NO_x	**1.506 (1.064-2.132)**	**1.733 (1.188-2.529)**	**1.843 (1.243-2.732)**	**1.868 (1.220-2.859)**
$PM_{2.5}$	**1.454 (1.064-1.987)**	**1.603 (1.141-2.251)**	**1.615 (1.133-2.302)**	**1.610 (1.103-2.349)**
PM_{10}	**1.356 (1.004-1.831)**	**1.523 (1.103-2.103)**	**1.561 (1.116-2.184)**	**1.545 (1.077-2.216)**
Air pollutants at follow-up and prevalent symptoms of eczema up to 12 mo before follow-up investigation				
N	818	721	663.8†	610.9†
NO_2	1.168 (0.861-1.584)	1.159 (0.826-1.626)	1.252 (0.883-1.775)	1.268 (0.877-1.835)
NO_x	1.144 (0.844-1.550)	1.176 (0.842-1.644)	1.264 (0.892-1.790)	1.277 (0.883-1.846)
$PM_{2.5}$	1.297 (0.931-1.806)	1.327 (0.923-1.908)	1.425 (0.974-2.084)	1.449 (0.966-2.175)
PM_{10}	1.138 (0.880-1.472)	1.206 (0.911-1.597)	1.292 (0.967-1.725)	1.297 (0.952-1.766)

ORs (95% CIs) per an increase of 1 IQR in air pollution are shown in boldface if the *P* value is less than .05. Results are adjusted for age, body mass index, highest educational status of participant or her spouse, household heating by indoor combustion of fossil fuels, smoking (categorized as current, former, or never smoking), and exposure to second-hand smoke at home or work.

*Corresponds to newly developed symptoms of eczema between baseline and follow-up examination.

†Imputation was done 500 times, and *N* is the pooled mean of the imputed data sets.

TABLE E7. Associations between air pollutants at baseline and time since first symptoms of eczema after age 55 years following exclusion of atopic subjects, with increasing strictness from left to right

	All participants	Never hay fever	Never hay fever + baseline IgE not >100 kU/L	Never hay fever + baseline IgE not >100 kU/L + follow-up IgE not >100 kU/L
Air pollutants at baseline and incident symptoms of eczema after age 55 years*				
N	746	656	612	588
NO_2	**1.436 (1.02-2.022)**	**1.599 (1.118-2.289)**	**1.752 (1.209-2.537)**	**1.769 (1.213-2.58)**
NO_x	**1.443 (1.042-2.000)**	**1.659 (1.168-2.357)**	**1.796 (1.247-2.587)**	**1.802 (1.244-2.610)**
$PM_{2.5}$	**1.401 (1.031-1.904)**	**1.577 (1.128-2.206)**	**1.651 (1.158-2.352)**	**1.664 (1.159-2.389)**
PM_{10}	**1.307 (0.976-1.751)**	**1.491 (1.089-2.040)**	**1.576 (1.135-2.188)**	**1.579 (1.131-2.206)**

Hazard ratios (95% CIs) per an increase of 1 IQR in air pollution are shown in boldface if the *P* value is less than .05. Results are adjusted for age, body mass index, highest educational status of participant or her spouse, household heating by indoor combustion of fossil fuels, smoking (categorized as current, former, or never smoking), and exposure to second-hand smoke at home or work.

*Corresponds to newly developed symptoms of eczema between baseline and follow-up examination.

TABLE E8. Association between SNPs that have been associated with atopic dermatitis,[11] with incident symptoms of eczema after age 55 years in SALIA

		Atopic dermatitis in the European analysis (Paternoster et al[12])						Eczema incidence in the elderly (SALIA)		
Variant	**Locus**	**Nearest gene‡**	**EA/OA**	**N (studies)**	**EAF**	**OR (95% CI)**	***P* value**	**N (SALIA)**	**OR (95% CI)**	***P* value**
Known loci										
rs61813875	1q21.3	*CRCT1*/***LCE3E*** (*FLG*)§	G/C	93,326 (18)	0.02	1.61 (1.48-1.75)	$\mathbf{5.6 \times 10^{-29}}$	412	1.06 (0.11-9.85)	.9563
rs10791824	11q13.1	***OVOL1***	G/A	102,761 (21)	0.57	1.12 (1.09-1.15)	$\mathbf{2.1 \times 10^{-19}}$	412	0.75 (0.43-1.33)	.3271
rs12188917	5q31.1	*RAD50*/***IL13***	C/T	102,761 (21)	0.21	1.14 (1.10-1.17)	$\mathbf{4.0 \times 10^{-17}}$	412	1.28 (0.72-2.29)	.4047
rs6419573	2q12.1	*IL18R1*/***IL18RAP***	T/C	102,760 (21)	0.26	1.11 (1.08-1.14)	$\mathbf{1.5 \times 10^{-13}}$	412	1.28 (0.70-2.37)	.4242
rs2212434	11q13.5	***C11orf30***/*LRRC32*	T/C	102,761 (21)	0.45	1.09 (1.07-1.12)	$\mathbf{4.6 \times 10^{-13}}$	412	1.04 (0.61-1.79)	.8732
rs4809219	20q13.33	***RTEL1–TNFRSF6B***	C/A	102,760 (21)	0.27	0.90 (0.87-0.93)	$\mathbf{7.0 \times 10^{-13}}$	412	1.19 (0.61-2.32)	.6030
rs2918307	19p13.2	*ADAMTS10*/***ACTL9***	G/A	100,707 (20)	0.16	1.12 (1.08-1.16)	$\mathbf{4.6 \times 10^{-12}}$	412	1.07 (0.50-2.29)	.8631
rs2041733	16p13.13	***CLEC16A***	C/T	103,066 (22)	0.55	0.92 (0.90-0.94)	$\mathbf{2.5 \times 10^{-11}}$	412	0.60 (0.34-1.04)	.0699
rs12730935*	1q21.3	***IL6R***	A/G	102,760 (21)	0.39	1.08 (1.05-1.11)	$\mathbf{6.1 \times 10^{-11}}$	412	1.17 (0.68-2.02)	.5747
4:123243592†	4q27	***KIAA109*** (*IL2*)§	R/I	102,761 (21)	0.37	1.08 (1.05-1.10)	$\mathbf{4.2 \times 10^{-9}}$	412	1.37 (0.77-2.41)	.2824
rs4713555	6p21.32	***HLA-DRB1***/*HLA-DQA1*	T/G	91,217 (15)	0.27	0.91 (0.89-0.94)	$\mathbf{5.4 \times 10^{-9}}$	412	1.60 (0.88-2.91)	.1202
rs2944542	10q21.2	***ZNF365***	C/G	102,762 (21)	0.41	0.94 (0.92-0.96)	1.2×10^{-6}	412	**0.54 (0.30-0.97)**	**.0403**
rs145809981	6p21.33	***MICB***	T/C	97,697 (19)	0.14	0.91 (0.88-0.95)	1.5×10^{-6}	412	NA	NA
rs4312054	11p15.4	*OR10A3*/***NLRP10***	G/T	102,760 (21)	0.41	1.00 (0.97-1.02)	.744	412	**0.57 (0.32-1.00)**	**.0498**
rs1249910	3q13.2	***CCDC80***/*CD200R1L*	A/G	99,164 (20)	0.34	0.98 (0.96-1.01)	.137	412	**0.43 (0.22-0.86)**	**.0161**
rs2592555	11p13	***PRR5L***	C/T	102,760 (21)	0.27	0.93 (0.90-0.96)	8.7×10^{-7}	412	0.93 (0.52-1.64)	.7944
Novel loci								412		
rs2038255	14q13.2	***PPP2R3C***	T/C	102,760 (21)	0.18	1.11 (1.07-1.14)	$\mathbf{1.8 \times 10^{-10}}$	412	0.62 (0.27-1.42)	.2603
rs7127307	11q24.3	***−/ETS1***	C/T	103,066 (22)	0.47	0.93 (0.90-0.95)	$\mathbf{3.9 \times 10^{-10}}$	412	1.16 (0.68-1.98)	.5850
rs7512552	1q21.2	*C1orf51*/***MRPS21***	T/C	102,762 (21)	0.49	0.93 (0.91-0.95)	$\mathbf{9.1 \times 10^{-10}}$	412	1.99 (1.16-3.44)	.0132
rs6473227	8q21.13	*MIR5708*/***ZBTB10***	A/C	102,761 (21)	0.61	0.93 (0.91-0.95)	$\mathbf{1.4 \times 10^{-9}}$	412	0.62 (0.36-1.06)	.0804
rs6602364	10p15.1	*IL15RA*/***IL2RA***	G/C	103,065 (22)	0.45	1.08 (1.05-1.10)	$\mathbf{1.5 \times 10^{-9}}$	412	0.67 (0.39-1.15)	.1448
rs10214237	5p13.2	***IL7R***/*CAPSL*	C/T	102,761 (21)	0.27	0.93 (0.90-0.95)	$\mathbf{2.9 \times 10^{-8}}$	412	0.71 (0.40-1.27)	.2511
rs10199605	2p25.1	***LINC00299/−***	A/G	102,760 (21)	0.30	0.93 (0.90-0.95)	$\mathbf{3.4 \times 10^{-8}}$	412	1.25 (0.70-2.21)	.4474
rs4643526	2p16.1	***PUS10***	A/G	103,066 (22)	0.19	1.09 (1.06-1.12)	$\mathbf{3.5 \times 10^{-8}}$	412	1.47 (0.79-2.77)	.2274
rs12951971	17q21.2	***STAT3***	G/T	102,761 (21)	0.09	1.13 (1.08-1.17)	$\mathbf{4.1 \times 10^{-8}}$	412	1.53 (0.63-3.72)	.3425
rs7625909	3p21.1	***SFMBT1***/*RFT1*	T/C	102,761 (21)	0.32	1.07 (1.05-1.10)	$\mathbf{4.9 \times 10^{-8}}$	412	0.99 (0.55-1.77)	.9760
rs112111458	2p13.3	*CD207*/***VAX2***	G/A	102,760 (21)	0.13	0.91 (0.87-0.94)	1.4×10^{-7}	412	0.55 (0.18-1.66)	.2927

Paternoster et al: *P* values in boldface indicate genome-wide significant results; SALIA: *P* values in boldface indicate successful replication ($P < .05$ and equal effect sign).
EAF, Effect allele frequency; *EA/OA*, effect allele/other allele; *NA*, SNPs did not pass quality control in SALIA.
*In linkage disequilibrium with the known functional mutation rs2228145 ($r^2 = 0.86$).
†A nearby SNP (rs6827756, bp position 123184411) in linkage disequilibrium ($r^2 = 0.97$ in the 1000 Genomes database) was used in SALIA. rs6827756 showed a similar association in the Paternoster study (European fixed-effects $P = 3 \times 10^{-9}$).
‡The nearest genes are the 2 flanking genes, if intergenic (with the closer gene in boldface; − indicates no gene within 250 kb); single genes denote the variant is intronic.
§At 1q21.2, the variant is closest to *LCE3A*, but the previously associated filaggrin (*FLG*) is within 250 kb. At 4q27, the variant is within an intron of *KIAA109*, but the previously associated *IL2* is within 150 kb.

TABLE E9. Association between SNPs that have been associated with atopic dermatitis[11] with prevalent eczema symptoms 12 months or less before follow-up investigation in SALIA

		Atopic dermatitis in the European analysis (Paternoster et al[12])						Eczema prevalence in the elderly (SALIA)		
Variant	**Locus**	**Nearest gene‡**	**EA/OA**	**N (studies)**	**EAF**	**OR (95% CI)**	***P* value**	**N (SALIA)**	**OR (95% CI)**	***P* value**
Known loci										
rs61813875	1q21.3	*CRCT1/**LCE3E** (FLG)§*	G/C	93,326 (18)	0.02	1.61 (1.48-1.75)	$\mathbf{5.6 \times 10^{-29}}$	452	1.44 (0.16-13.29)	.7454
rs10791824	11q13.1	***OVOL1***	G/A	102,761 (21)	0.57	1.12 (1.09-1.15)	$\mathbf{2.1 \times 10^{-19}}$	452	0.73 (0.38-1.38)	.3254
rs12188917	5q31.1	*RAD50/**IL13***	C/T	102,761 (21)	0.21	1.14 (1.10-1.17)	$\mathbf{4.0 \times 10^{-17}}$	452	1.25 (0.65-2.41)	.4972
rs6419573	2q12.1	*IL18R1/**IL18RAP***	T/C	102,760 (21)	0.26	1.11 (1.08-1.14)	$\mathbf{1.5 \times 10^{-13}}$	452	**2.06 (1.07-3.96)**	**.0305**
rs2212434	11q13.5	***C11orf30**/LRRC32*	T/C	102,761 (21)	0.45	1.09 (1.07-1.12)	$\mathbf{4.6 \times 10^{-13}}$	452	0.92 (0.50-1.69)	.7858
rs4809219	20q13.33	***RTEL1–TNFRSF6B***	C/A	102,760 (21)	0.27	0.90 (0.87-0.93)	$\mathbf{7.0 \times 10^{-13}}$	452	1.21 (0.57-2.56)	.6106
rs2918307	19p13.2	*ADAMTS10/**ACTL9***	G/A	100,707 (20)	0.16	1.12 (1.08-1.16)	$\mathbf{4.6 \times 10^{-12}}$	452	0.75 (0.30-1.91)	.5517
rs2041733	16p13.13	***CLEC16A***	C/T	103,066 (22)	0.55	0.92 (0.90-0.94)	$\mathbf{2.5 \times 10^{-11}}$	452	**0.50 (0.27-0.95)**	**.0354**
rs12730935*	1q21.3	***IL6R***	A/G	102,760 (21)	0.39	1.08 (1.05-1.11)	$\mathbf{6.1 \times 10^{-11}}$	452	0.96 (0.51-1.81)	.8913
4:123243592†	4q27	***KIAA109** (IL2)§*	R/I	102,761 (21)	0.37	1.08 (1.05-1.10)	$\mathbf{4.2 \times 10^{-9}}$	452	1.25 (0.65-2.38)	.4999
rs4713555	6p21.32	***HLA-DRB1**/HLA-DQA1*	T/G	91,217 (15)	0.27	0.91 (0.89-0.94)	$\mathbf{5.4 \times 10^{-9}}$	452	1.93 (0.99-3.78)	.0546
rs2944542	10q21.2	***ZNF365***	C/G	102,762 (21)	0.41	0.94 (0.92-0.96)	1.2×10^{-6}	452	**0.48 (0.24-0.95)**	**.0353**
rs145809981	6p21.33	***MICB***	T/C	97,697 (19)	0.14	0.91 (0.88-0.95)	1.5×10^{-6}	452	NA	NA
rs4312054	11p15.4	*OR10A3/**NLRP10***	G/T	102,760 (21)	0.41	1.00 (0.97-1.02)	.744	452	**0.47 (0.24-0.91)**	**.0261**
rs1249910	3q13.2	***CCDC80**/CD200R1L*	A/G	99,164 (20)	0.34	0.98 (0.96-1.01)	.137	452	0.52 (0.25-1.09)	.0812
rs2592555	11p13	***PRR5L***	C/T	102,760 (21)	0.27	0.93 (0.90-0.96)	8.7×10^{-7}	452	1.15 (0.60-2.18)	.6783
Novel loci										
rs2038255	14q13.2	***PPP2R3C***	T/C	102,760 (21)	0.18	1.11 (1.07-1.14)	$\mathbf{1.8 \times 10^{-10}}$	452	0.72 (0.29-1.77)	.4763
rs7127307	11q24.3	***−/ETS1***	C/T	103,066 (22)	0.47	0.93 (0.90-0.95)	$\mathbf{3.9 \times 10^{-10}}$	452	1.16 (0.63-2.14)	.6243
rs7512552	1q21.2	*C1orf51/**MRPS21***	T/C	102,762 (21)	0.49	0.93 (0.91-0.95)	$\mathbf{9.1 \times 10^{-10}}$	452	2.07 (1.11-3.85)	.0217
rs6473227	8q21.13	*MIR5708/**ZBTB10***	A/C	102,761 (21)	0.61	0.93 (0.91-0.95)	$\mathbf{1.4 \times 10^{-9}}$	452	0.65 (0.35-1.18)	.1563
rs6602364	10p15.1	*IL15RA/**IL2RA***	G/C	103,065 (22)	0.45	1.08 (1.05-1.10)	$\mathbf{1.5 \times 10^{-9}}$	452	0.70 (0.38-1.30)	.2600
rs10214237	5p13.2	***IL7R**/CAPSL*	C/T	102,761 (21)	0.27	0.93 (0.90-0.95)	$\mathbf{2.9 \times 10^{-8}}$	452	0.66 (0.34-1.30)	.2322
rs10199605	2p25.1	***LINC00299/−***	A/G	102,760 (21)	0.30	0.93 (0.90-0.95)	$\mathbf{3.4 \times 10^{-8}}$	452	1.19 (0.62-2.29)	.5922
rs4643526	2p16.1	***PUS10***	A/G	103,066 (22)	0.19	1.09 (1.06-1.12)	$\mathbf{3.5 \times 10^{-8}}$	452	1.39 (0.69-2.82)	.3597
rs12951971	17q21.2	***STAT3***	G/T	102,761 (21)	0.09	1.13 (1.08-1.17)	$\mathbf{4.1 \times 10^{-8}}$	452	1.65 (0.63-4.32)	.3090
rs7625909	3p21.1	***SFMBT1**/RFT1*	T/C	102,761 (21)	0.32	1.07 (1.05-1.10)	$\mathbf{4.9 \times 10^{-8}}$	452	1.11 (0.58-2.12)	.7482
rs112111458	2p13.3	*CD207/**VAX2***	G/A	102,760 (21)	0.13	0.91 (0.87-0.94)	1.4×10^{-7}	452	0.83 (0.27-2.56)	.7482

Paternoster et al: *P* values in boldface indicate genome-wide significant results; SALIA: *P* values in boldface indicate successful replication ($P < .05$ and equal effect sign).
EAF, Effect allele frequency; *EA/OA*, effect allele/other allele; *NA*, SNP did not pass the quality control in SALIA.
*In linkage disequilibrium with the known functional mutation rs2228145 ($r^2 = 0.86$).
†Nearby SNP (rs6827756, bp position 123184411) in linkage disequilibrium ($r^2 = 0.97$ in the 1000 Genomes database) was used in SALIA. rs6827756 showed similar association in the Paternoster study (European fixed-effects $P = 3 \times 10^{-9}$).
‡The nearest genes are the 2 flanking genes if intergenic (with the closer gene in boldface; – indicates no gene within 250 kb); single genes denote the variant is intronic.
§At 1q21.2, the variant is closest to *LCE3A*, but the previously associated filaggrin (*FLG*) is within 250 kb. At 4q27, the variant is within an intron of *KIAA109*, but the previously associated *IL2* is within 150 kb.