

Prediction of the incidence, recurrence, and persistence of atopic dermatitis in adolescence: A prospective cohort study

Astrid S. Peters, MD, MSc,^{a,*} Jessica Kellberger, Dipl-Stat,^{a,*} Christian Vogelberg, MD,^b Holger Dressel, MD, MPH,^a Doris Windstetter, MD,^a Gudrun Weinmayr, PhD, MPH,^c Jon Genuneit, MD,^c Dennis Nowak, MD,^a Erika von Mutius, MD, MSc,^d and Katja Radon, PhD, MSc^a *Munich, Dresden, and Ulm, Germany*

Background: Although it is known that atopic dermatitis (AD) can develop during adolescence, research on its course and predictors in this age group is thus far limited.

Objective: We aimed to describe the course of AD over puberty and prospectively determine risk factors for the incidence, recurrence, and persistence of AD until adolescence in a population-based cohort study.

Methods: German participants of the International Study of Asthma and Allergies in Childhood Phase II were followed prospectively. The final dataset comprised 2857 adolescents, of whom 2433 were unaffected by AD at baseline. Bivariate and multivariate prediction models for the incidence, recurrence, and persistence of AD using early-life factors, family history of atopic diseases, and job history as predictors were developed.

Results: The incidence of AD between ages 9 to 11 and 16 to 20 years was 1.7%, and recurrence was 2.4%. AD persisted in 47.6% of adolescents with AD symptoms at baseline ($n = 424$). High socioeconomic status, female sex, asthma symptoms and a positive skin prick test response at baseline, parental history of rhinitis/AD, and having worked in a high-risk job were significant predictors for the course of disease. With all the factors present, the probability of the incidence of AD was 21.4% (95% CI, 1.8% to 80.2%) and increased up to 81.7% (95% CI, 47.0% to 95.8%) for recurrence of AD and 87.6% (95% CI, 63.4% to 96.6%) for persistence of AD among those affected by AD. Early-life exposures did not predict the course of AD over puberty.

Conclusion: Genetic factors, early allergen sensitization, and having worked in a high-risk job seem to be more important for disease development in late adolescence than other early-life exposures. (*J Allergy Clin Immunol* 2010;126:590-5.)

Key words: Atopic dermatitis, adolescence, disease prediction, occupational exposure

The incidence of atopic dermatitis (AD) in Western countries, especially in Germany, has been increasing over the past decades.¹ To date, research in the field of AD concentrated on the course of disease in the vulnerable stages of infancy and early childhood, as well as on genetic factors.²⁻⁴ However, it has been suggested that 10% to 20% of European children and teenagers are affected by AD until adolescence.^{5,6}

Several especially environmental factors, such as indoor allergens,⁷ dust exposure,⁸ and environmental tobacco smoke (ETS),^{9,10} have a relevant influence on the development of AD in infancy and childhood. In addition, the presence of asthma and rhinitis symptoms in patients and a positive family history for those diseases are linked to the incidence of AD.¹¹ Siblings and day care attendance are known to have a protective effect on the development of AD in early life.^{12,13} Dietary factors, such as breast-feeding, and infections or vaccinations early in life were found to be associated with a reduced incidence of AD.^{14,15} Later in life, job exposure as a risk factor for the development of AD in adolescents seems also to be relevant,^{16,17} although the evidence is not as strong as for the other risk factors. However, data on predictors of the course of AD later in life are sparse.

Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC) was designed as a multicenter study to investigate the prevalence of allergies and asthma in children attending fourth-grade classes (aged mainly 9-11 years).¹⁸ The Study on Occupational Allergy Risks (SOLAR; started in 2002) was the first follow-up of ISAAC Phase II investigating German adolescents aged 16 to 20 years. This approach provided the opportunity to study the incidence of AD over adolescence. Factors predicting the individual risk of AD were assessed. We used this dataset to evaluate the course of AD over puberty and to determine risk factors for new onset, recurrence, and persistence of AD at age 16 to 20 years and the individual probability of the course of AD to support clinicians, especially pediatricians, in advising patients and their parents accordingly.

METHODS

Baseline survey (ISAAC Phase II)

The population for SOLAR was based on the population of ISAAC Phase II in Germany (Munich and Dresden), which examined primary school children in 1995-1996. Details of this study have been described previously.^{18,19} Briefly, parents of 6399 children aged 9 to 11 years completed a questionnaire asking for demographic and environmental factors and health outcomes. In addition, children were examined for sensitizations by means of skin prick tests

From ^athe Unit for Occupational and Environmental Epidemiology and Net Teaching, Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University Hospital of Munich (LMU); ^bUniversity Children's Hospital, Dresden; ^cthe Institute of Epidemiology, Ulm University; and ^dDr. v. Haunersches Kinderspital, University Hospital of Munich.

*These authors contributed equally to this work.

Supported by the Federal Office for Occupational Safety and Occupational Medicine and Federal Ministry of Labour and Social Affairs (Germany).

Disclosure of potential conflict of interest: E. von Mutius is a consultant for GlaxoSmithKline, UCB, Protectimmun, and Novartis and receives research support from Airsonett AB. The rest of the authors have declared that they have no conflict of interest.

Received for publication April 8, 2010; revised May 28, 2010; accepted for publication June 1, 2010.

Reprint requests: Astrid Peters, MD, MSc, Unit for Occupational and Environmental Epidemiology and Net Teaching, Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Ziemssenstr. 1, 80336 Munich, Germany. E-mail: sekretariat-radon@med.uni-muenchen.de.

0091-6749/\$36.00

© 2010 American Academy of Allergy, Asthma & Immunology
doi:10.1016/j.jaci.2010.06.020

Abbreviations used

AD:	Atopic dermatitis
AUC:	Area under the curve
ETS:	Environmental tobacco smoke
ISAAC:	International Study of Asthma and Allergies in Childhood
ROC:	Receiver operating characteristic
SES:	Socioeconomic status
SOLAR:	Study on Occupational Allergy Risks
SPT:	Skin prick test

(SPTs) and specific IgE measurements in blood serum, for AD by means of skin examination, and for asthma by measuring spirometric values and bronchial responsiveness with nebulized hypertonic saline.

The questionnaire assessed the presence of AD symptoms during the past 12 months with explicit description of the predilection areas and physician-diagnosed AD in the children. Despite the fact that parents without a medical background had to state their child's skin status, using this approach and the long time range of 1 year for skin symptoms provided sufficient validity for a correct classification for this item. However, one has to keep in mind that it is difficult to diagnose AD during a single medical examination because symptoms of AD come and go.²⁰

SPT results ($n = 4401$ [69%]) were the only clinical parameters from the clinical examination at age 9 to 11 years used for the present analysis because specific IgE data were only available in a smaller subset of the population (60%).¹⁸

Follow-up survey (SOLAR)

In 2002-2003, all ISAAC Phase II participants in Munich and Dresden whose parents agreed to be contacted were contacted once again and were invited to fill out a postal questionnaire; a medical examination was not scheduled for this follow-up. SOLAR and the demographic information of the cohort have been described in detail elsewhere.^{17,21} Overall, 4,893 (87%) adolescents in Dresden and Munich were eligible for participation, of whom 3,785 finally took part in the study. The SOLAR questionnaire included 118 items, mostly on respiratory health, allergies, and potential occupational and environmental risk factors. Most items were taken from the European Community Respiratory Health Survey and ISAAC.^{22,23} Thorough arrangements (reminder letters and up to 5 reminder telephone calls) were set to maximize response. Informed consent was obtained according to age either from the participants only (age ≥ 18 years) or additionally from their legal guardians (age < 18 years; see Fig E1 and Table E1 in this article's Online Repository at www.jacionline.org for a diagram and additional information of the ISAAC Phase II and SOLAR participants and dropouts).

Definition of outcome and potential predictors

The dataset was analyzed according to AD symptoms at baseline and follow-up and a physician's diagnosis before ISAAC Phase II. AD was defined as a diagnosis of AD by a physician and the indication of characteristic skin alterations in the typical predilection skin areas (face, neck, and flexural folds of the extremities) for more than 6 months during the 12 months before the ISAAC Phase II (baseline) and SOLAR (follow-up) surveys, respectively.

Those children without a medical diagnosis of AD who had no skin symptoms at baseline but did have skin symptoms and a physician's diagnosis at follow-up were assigned as incident cases of AD. Participants with skin symptoms but without a physician's diagnosis of AD were not assessed separately to avoid overestimation of the AD outcomes caused by possible misclassification.

Disease persistence was defined as having a physician's diagnosis and symptoms throughout the study from baseline until follow-up.

Recurrence of AD was defined as a prior medical diagnosis of AD but no symptoms at baseline and presence of skin symptoms at follow-up.

The dataset was divided according to disease status and analyzed separately to assess the individual risk factors (see Fig 1 for comparison groups and AD distribution).

The incident cases were compared with those children who had never had either a physician's diagnosis or symptoms of AD. Recurrent cases were compared with children with a physician's diagnosis before baseline who did not have symptoms either at baseline or at follow-up. The reference group for the persistent cases consisted of those patients who had symptoms at baseline but not at follow-up.

The following variables were considered as potential risk factors for each of the possible AD outcomes:

- parental history of asthma (yes/no);
- parental history of rhinitis (yes/no);
- parental history of AD/eczema (yes/no);
- kindergarten attendance (yes/no);
- breast-feeding (ever/never);
- presence of siblings ($0/\geq 1$);
- exposure to ETS until baseline (yes/no);
- asthma symptoms, such as wheezing or whistling in the chest, 12 months before baseline (yes/no), as defined according to the ISAAC protocol²³;
- rhinitis symptoms 12 months before baseline (nasal symptoms, such as sneezing or having a runny or blocked nose in the absence of additional infectious disease symptoms);
- socioeconomic status (SES; high SES is defined as at least 1 parent with ≥ 12 years of schooling);
- positive SPT response (wheal size ≥ 3 mm after subtraction of the negative control¹⁹) of at least 1 of the allergens *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, *Alternaria tenuis*, mixed tree pollen, and mixed grass pollen; and
- occupational exposure until follow-up, which was assessed according to the Asthma Specific Job Exposure Matrix.²⁴ The whole job history was taken into account, including holiday jobs or vocational training periods lasting for at least 8 hours per week for 1 month. Jobs were ranked as high-risk jobs (nursing, health care assistance, bakery, and cleaning) or low-risk jobs (others) according to the results of a previous analysis on this dataset.¹⁷

Statistical methods

Because the prevalence of AD and risk factors in different cultures and countries showed large variations, participants without German citizenship were excluded from the dataset before the analyses, reducing the number of eligible participants from 3785 to 3492.

Missing data. Missing questionnaire data for the relevant parameters under study were considered to be missing at random and were multiply imputed (see the Methods section of this article's Online Repository at www.jacionline.org for additional statistical information). Medical data were not imputed because of the complexity of the data with associations between different variables and potential confounders. Therefore 635 participants with incomplete medical information were excluded from further analyses, leaving 2857 teenagers for the analyses.

Bivariate and multivariate analyses

For the bivariate analyses, cross-tabulation and χ^2 tests for the potential association among all possible baseline risk factors and the incidence, recurrence, and persistence of AD were performed.

Those parameters with P (χ^2) values of less than .1 in any of the bivariate analyses were included in logistic regression models for any of the 3 outcomes by means of stepwise forward fitting, starting with the variable with the lowest P value. To evaluate the goodness of fit of the respective models, the Akaike information criterion was used to decide which variable to keep in the model. SES and sex were *a priori* kept for all analyses. Effect modification by sex was also tested. However, no indication for effect modification was seen (data not shown). Because 86% of the teenagers were between 16 and 18 years old, adjustment for age was not performed.

In the next step the individual risk of the incidence, recurrence, and persistence of AD was calculated according to Formula 1.

Formula 1: Risk model.

$$\text{Logit } P(\text{atopic dermatitis}) = \beta_0 + \beta_1 * x_1 + \beta_2 * x_2 + \beta_3 * x_3 + \dots + \beta_n * x_n$$

In this model all parameters that contributed significantly to the goodness of fit of the logistic model were kept. In addition, receiver operating

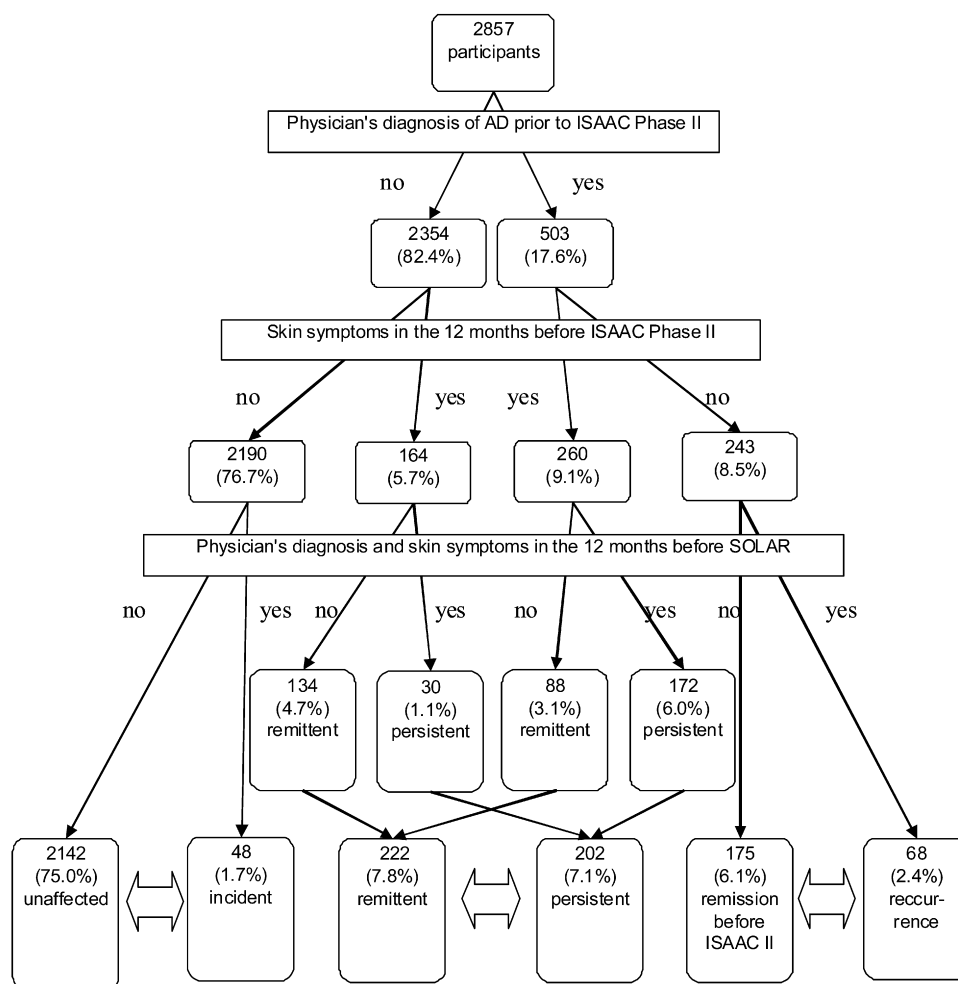


FIG 1. Distribution of AD in ISAAC Phase II and SOLAR. Double arrows at the bottom indicate the comparison groups for further analyses.

characteristic (ROC) curves and the corresponding area under the curve (AUC) values were used to evaluate the goodness of fit for the final risk model. The ROC takes the sensitivity and specificity of the corresponding model into account. A high AUC value represents a good and correct classification of all adolescents in the dataset as either healthy or affected by AD.

The calculation of probabilities for a combination of several risk factors was then performed according to Formula 2.

Formula 2: Calculation of probabilities for several risk factors.

$$P(\text{Atopic dermatitis}|x_1 \dots x_n) = \frac{\exp(\beta_0) \times (OR_1 \times OR_2 \times \dots \times OR_n)}{1 + [\exp(\beta_0) \times (OR_1 \times OR_2 \times \dots \times OR_n)]}$$

β_0 intercept, $\beta_1 \dots \beta_n$ regression coefficients of the risk factors $x_1 \dots x_n$. OR odds ratio

Statistical analyses were performed with SAS software (SAS version 9.1; SAS Institute, Inc, Cary, NC) and R software (version 2.7.0, www.r-project.org).

RESULTS

Natural course of AD

The distribution of incident, remittent, persistent, and recurrent, as well as unaffected, participants is demonstrated in Fig 1. Seventy-five percent of the participants showed no AD symptoms

in ISAAC Phase II and SOLAR, incidence of AD over puberty was 1.7%, persistence of AD reached 7.1%, remission of AD before ISAAC Phase II was 6.1% and that after ISAAC Phase II was 7.8%, and recurrence of AD was 2.4%.

Prediction of AD

Prediction of the incidence of AD. In the bivariate analyses ETS, high SES, parental history of allergic rhinitis, and having ever worked in a high-risk job were the main risk factors for the incidence of AD (Table I).

After adjustment, the multivariate model included additionally female sex, a positive SPT response, and the absence of allergic rhinitis symptoms at baseline, whereas ETS was excluded. The probability of the incidence of AD for adolescents ranged from 0.14% in the absence of any of the assessed risk factors up to 21.4% with all risk factors present (Table II). The AUC value of the ROC reached 0.68 (data not shown), representing a moderate fit for the incidence model.

Overall, the contribution of a single risk factor seems to be marginal for the incidence of AD, whereas the presence of various risk factors can add up to a moderate risk for the development of AD in adolescence.

TABLE I. Bivariate ORs for the incidence, recurrence, and persistence of AD for all potential risk factors considered

	Incidence (n/N = 48/2190), OR (95% CI)	Recurrence (n/N = 68/243), OR (95% CI)	Persistence (n/N = 202/424), OR (95% CI)
Sex (female)	1.22 (0.69-2.17)	1.83 (1.03-3.25)	1.09 (0.74-1.59)
Study center (Munich)	0.88 (0.50-1.56)	1.12 (0.63-2.00)	1.04 (0.70-1.53)
ETS exposure until age 9-11 y	0.53 (0.28-0.99)	0.92 (0.52-1.63)	0.67 (0.46-1.00)
SES (high vs low)	2.29 (1.22-4.29)	1.27 (0.70-2.29)	1.20 (0.81-1.78)
Breast-feeding	0.96 (0.45-2.07)	0.75 (0.34-1.63)	1.28 (0.73-2.23)
Kindergarten attendance	—*	—*	0.22 (0.02-2.02)
Siblings	0.84 (0.41-1.70)	0.62 (0.27-1.44)	0.97 (0.56-1.69)
Parental history of:			
Asthma	1.12 (0.44-2.87)	1.29 (0.61-2.73)	1.03 (0.60-1.78)
AD	0.81 (0.32-2.06)	1.29 (0.73-2.27)	1.63 (1.08-2.47)
Allergic rhinitis	1.96 (1.10-3.48)	1.28 (0.72-2.26)	1.58 (1.08-2.33)
Positive SPT response	1.77 (0.96-3.25)	3.40 (1.87-6.17)	1.83 (1.22-2.73)
Asthma symptoms at baseline	0.56 (0.08-4.13)	3.95 (1.58-9.88)	1.48 (0.70-3.12)
Rhinitis symptoms at baseline	0.34 (0.05-2.49)	2.72 (1.20-6.14)	1.51 (0.80-2.83)
Risk job	3.08 (1.19-7.98)	3.39 (0.88-13.03)	2.68 (1.01-7.12)

Values in boldface indicate relevant items of the bivariate analyses.

OR, Odds ratio.

*No ORs were computable because there were no observations in one of the corresponding groups.

TABLE II. Probabilities and adjusted ORs for incidence of AD over puberty compared with those without symptoms or AD diagnosis ever*: Single risk factors and all risk factors combined (final multivariate model)

AD	Probability, % (95% CI); (incidence)	Adjusted OR (95% CI)
β0 (intercept)†	0.1	
SES (high)	0.3 (0.1-0.5)	2.0 (1.0-3.7)
Sex (female)	0.2 (0.1-0.3)	1.2 (0.7-2.3)
Positive SPT response	0.3 (0.2-0.6)	3.2 (1.2-8.6)
No rhinitis symptoms at baseline	0.8 (0.1-6.0)	1.9 (1.1-3.4)
Parental history of allergic rhinitis	0.3 (0.2-0.5)	2.2 (1.2-4.2)
Risk job	0.5 (0.2-1.2)	6.0 (0.8-45.8)
All risk factors listed above present	21.4 (1.8-80.2)	195.8 (13.2-2907.2)

Items in boldface indicate a statistically significant result.

OR, Odds ratio.

*See Fig 1 for an illustration of group distribution and comparison between the groups.

†exp(β0) = 0.0014.

Recurrence of AD. The bivariate analyses for recurrence of AD comprised female sex, a positive SPT response in ISAAC Phase II, and rhinitis and asthma symptoms at baseline (Table I).

The multivariate model additionally contained the variable of high SES but excluded rhinitis symptoms at baseline as a relevant risk factor for the recurrence of AD. The probabilities for the recurrence of AD in the group of children with AD at school age ranged from 9.3% for adolescents without any risk factor to 81.7% for those with all risk factors present (Table III). The AUC showed a value of 0.71, representing a moderate fit for this model.

Persistence of AD. The persistence of AD in the bivariate analyses was influenced by a parental history of AD/eczema and rhinitis, a positive SPT response at baseline, and having ever worked in a high-risk job (Table I).

The final multivariate model additionally included female sex and high SES as relevant for the prediction of the persistence of

AD, whereas parental history of rhinitis was not included. The probability for the persistence of AD in the group of children with AD at school age ranged from 28.3% for teenagers without any of the risk factors to 87.6% for those with all risk factors present (Table IV). The AUC had a value of 0.63 for the final model.

The exact probabilities of the incidence, recurrence, and persistence of AD for other combinations of risk factors can be calculated according to Formula 2 (see above).

DISCUSSION

We present follow-up data of a population-based study describing the natural course of AD from age 9 to 11 years to age 16 to 20 years. Furthermore, relevant risk factors for the incidence, recurrence, and persistence of AD over adolescence were evaluated.

About 7% of all participants ever having AD had symptoms during adolescence. Sex-specific differences in the prevalence of AD could be shown at neither age 9 to 11 years nor age 16 to 18 years for this dataset, although female sex was associated with a higher risk for all disease occurrences. In infancy boys are more affected by AD than girls,²⁵ and the switch to a female predominance in adolescence is consistent with other European studies.^{11,26}

Overall, nearly 5% of adolescents who were symptom free at baseline had symptoms until follow-up. These results confirm the observations from cross-sectional studies that although many cases of AD occur early in life, an important number of cases still might occur during adolescence.²⁷

As in previous studies focusing on disease onset early in life,^{11,25} a positive family history of AD increased the probability of the incidence and recurrence of AD over puberty in our study. However, in contrast to these earlier studies mainly focusing on new onset of disease early in life, we could not show modifiable childhood factors contributing to the development of AD over adolescence. It might therefore be possible that all the common childhood factors are no longer relevant in the assessed age group.

In the age group under study, genetic factors (indicated by parental history of AD and rhinitis) and sensitization to allergens at age 9 to 11 years (indicated by positive SPT responses) seemed

TABLE III. Probabilities and adjusted ORs for recurrence of AD over puberty compared with those in disease remission before ISAAC II*: Single risk factors and all risk factors combined (final multivariate model)

AD	Probability, % (95% CI; recurrence)	Adjusted OR (95% CI)
$\beta 0$ (intercept) [†]	9.3	
SES (high)	12.9 (7.2-22.1)	1.4 (0.8-2.8)
Sex (female)	21.3 (12.4-34.0)	2.6 (1.4-5.0)
Positive SPT response	27.1 (16.1-41.9)	3.6 (1.9-7.0)
Asthma symptoms at baseline	24.5 (10.7-46.8)	3.2 (1.2-8.6)
All risk factors listed above present	81.7 (47.1-95.8)	43.7 (8.7-219.9)

Items in boldface indicate a statistically significant result.

*See Fig 1 for an illustration of group distribution and comparison between the groups.

[†] $\exp(\beta 0) = 0.1025$.

TABLE IV. Probabilities and adjusted ORs for persistence of AD over puberty compared with those remitted after ISAAC II*: Single risk factors and all risk factors combined (final multivariate model)

AD	Probability, % (95% CI; persistence)	Adjusted OR (95% CI)
$\beta 0$ (intercept) [†]	28.3	
SES (high)	32.9 (24.5-42.6)	1.2 (0.8-1.9)
Sex (female)	33.9 (25.4-43.6)	1.3 (0.9-2.0)
Positive SPT response	42.0 (32.2-52.6)	1.8 (1.2-2.8)
Parental history of allergic rhinitis	35.2 (26.6-44.9)	1.6 (1.1-2.5)
Parental history of AD	39.0 (29.4-49.4)	2.7 (1.0-7.4)
Risk job	51.9 (28.4-74.6)	1.4 (0.9-2.1)
All risk factors listed above present	87.6 (63.4-96.7)	17.9 (4.4-73.0)

Items in boldface indicate a statistically significant result.

*See Fig 1 for an illustration of group distribution and comparison between the groups.

[†] $\exp(\beta 0) = 0.3953$.

to be the most relevant childhood predictors for the course of disease over puberty.

Furthermore, our data support the atopic march hypothesis, with AD often representing the starting point of the atopic march because especially those children without rhinitis symptoms at baseline were at risk for AD.^{28,29} In contrast, we could not support the findings of Barberio et al³⁰ that asthma might precede AD at older ages. The finding that a positive SPT response was highly associated with AD was consistent with previous cross-sectional studies.³¹ However, one might argue that a positive SPT response is part of the causal pathway rather than a predictor of AD.

In any case, having worked in one of the high-risk jobs contributed to an increase in the incidence of AD.¹⁷ This was also confirmed in a study by von Linstow et al.³² Therefore according to our results, this seems to be the only factor that can be tackled after childhood to reduce the probability for AD in adolescence and adulthood. Pediatricians and work consultants should keep this in mind when advising youngsters.

As demonstrated in the multivariate analyses, single risk factors only contributed to a minor extent, especially to the individual risk for AD. The probabilities increased strongly with multiple risk factors present, such as parental atopy and having worked in a high-risk job. However, because of the relatively low

number of cases, especially for the incidence of AD, the 95% CIs were partly extremely large.

Strengths and limitations

One of the strengths of this study is its sample size, with follow-up data for more than 2300 adolescents. Additionally, a follow-up period of up to 8 years contributes to the assessment of a real distinction of the occurrence of AD (ie, incidence, persistence, and remission from childhood to adolescence).

Another advantage of this study was the use of validated and well-established protocols for the medical examination and the questionnaires.^{19,33} In ISAAC Phase II SPTs were used to assess atopic sensitization in the children in addition to questionnaire data. A standardized and rater-independent scheme was used to avoid misclassification.¹⁸ Because ISAAC Phase II and SOLAR data concerning clinical symptoms only referred to the corresponding past 12 months, recall or reporting bias by the minors and parents could be minimized. Study arrangements (eg, written and telephone reminders) were set to increase the response as much as possible to decrease selection bias.³⁴

Some limitations have to be taken into account. Although a large number of subjects could be followed, the number of participants with incident, recurrent, and persistent AD was limited. Therefore the reduced power resulted in large CIs, especially for the incidence and recurrence of AD, where, for example, odds ratios for kindergarten attendance were not computable because of the lack of observations in these small groups.

Unfortunately, medical data were only available for ISAAC Phase II, and therefore we decided to use only questionnaire data for the definition of AD to use the same definition with identical questions in both subsamples. In addition, no information was available for the nonrespondents in SOLAR, which again reduced the size of the remaining dataset. However, the questions used for the assessment of AD allowed valid and reliable results on a population level.³⁵ AD was defined as a physician's diagnosis of AD and the presence of skin symptoms 12 months before each survey. Although these questions were validated for ISAAC Phase II and were used in the European Community Respiratory Health Survey study,³⁶ they are not validated in adolescents. Therefore some misclassification of the outcome might have occurred. For example, hand eczema might have been misclassified as AD. Furthermore, although parents answered the questions at baseline, the adolescents themselves answered the questionnaire at follow-up. This also might result in misclassification of the outcome.^{37,38} However, one-time skin inspection might miss an important proportion of cases because one characteristic of AD is that symptoms come and go.²⁰

Although we included a number of potential childhood risk factors, we might have missed others. One of these factors might be vaccination, which has been reported to be a potential protective factor for the development of AD.³⁹ However, we used study center (Munich or Dresden) as a proxy for vaccination. Dresden, as a major city in the former German Democratic Republic, had a higher vaccination coverage than Munich because of compulsory medical surveillance in infancy and early childhood until reunification in 1990. In any case, having grown up in Dresden showed no association with a lower risk for AD.

The questionnaire-based skin information had been obtained at age 9 to 11 years; the potentially most vulnerable phase for AD in infancy and early childhood was not covered in these results. For

ISAAC Phase II, only those children who reported current skin symptoms and a previous physician's diagnosis of AD were taken as AD cases. Children with symptoms in infancy or with present symptoms but without medical diagnosis were not classified as AD cases. Therefore we cannot exclude that some of our incident cases were in fact recurrent cases of early childhood AD, which could result in an overestimation of the incidence of AD. However, because our aim was to support physicians in advising parents of primary school children with AD about the course of AD over puberty and its potential risk factors, this does not have a major effect on our results. Likewise, we do not have detailed data available on the course of AD between the 2 surveys. Because the results of this study regarding the course of AD over adolescence corresponded to those of other studies,⁴⁰ it can be assumed that the follow-up study design of SOLAR caught the majority of AD development in the study participants.

Conclusion

In adolescents early-life factors seem to be less important for the course of AD than in children. Occupational exposures, even of limited duration and intensity (eg, on holidays and during short-term vocational training), seem to be relevant. Therefore these data will support the pediatrician in advising patients with AD with respect to their job selection.

Parts of this paper have been used for the PhD thesis of Jessica Kellberger.

Clinical implications: Genetic factors, early allergen sensitization, and having worked in a high-risk job seem to be more important for disease development in late adolescence than other early-life factors.

REFERENCES

- Williams H, Stewart A, von Mutius E, Cookson W, Anderson HR. Is eczema really on the increase worldwide? *J Allergy Clin Immunol* 2008;121:947-54, e15.
- Sublett JL. The environment and risk factors for atopy. *Curr Allergy Asthma Rep* 2005;5:445-50.
- Weidinger S, O'Sullivan M, Illig T, Baurecht H, Depner M, Rodriguez E, et al. Filaggrin mutations, atopic eczema, hay fever, and asthma in children. *J Allergy Clin Immunol* 2008;121:1203-9, e1.
- Halkjaer LB, Lohdal L, Buchvald FF, Agner T, Skov L, Strand M, et al. Development of atopic dermatitis during the first 3 years of life: the Copenhagen prospective study on asthma in childhood cohort study in high-risk children. *Arch Dermatol* 2006;142:561-6.
- Buggiani G, Ricceri F, Lotti T. Atopic dermatitis. *Dermatol Ther* 2008;21:96-100.
- Finn Schultz L, Jon MH. Epidemiology of atopic dermatitis. *Immunol Allergy Clin North Am* 2002;22:1-24.
- Capristo C, Romei I, Boner AL. Environmental prevention in atopic eczema dermatitis syndrome (AEDS) and asthma: avoidance of indoor allergens. *Allergy* 2004;59(suppl 78):53-60.
- Harris JM, Williams HC, White C, Moffat S, Mills P, Newman Taylor AJ, et al. Early allergen exposure and atopic eczema. *Br J Dermatol* 2007;156:698-704.
- Arruda LK, Sole D, Baena-Cagnani CE, Nasipz CK. Risk factors for asthma and atopy. *Curr Opin Allergy Clin Immunol* 2005;5:153-9.
- Kimata H. Cessation of passive smoking reduces allergic responses and plasma neurotrophin. *Eur J Clin Invest* 2004;34:165-6.
- Girolomoni G, Abeni D, Masini C, Sera F, Ayala F, Belloni-Fortina A, et al. The epidemiology of atopic dermatitis in Italian schoolchildren. *Allergy* 2003;58:420-5.
- Sebok B, Schneider I, Harangi F. Familial and environmental factors influencing atopic dermatitis in the childhood. *J Eur Acad Dermatol Venerol* 2006;20:418-22.
- Benn CS, Melbye M, Wohlfahrt J, Björkstén B, Aaby P. Cohort study of sibling effect, infectious diseases, and risk of atopic dermatitis during first 18 months of life. *BMJ* 2004;328:1223.
- Leonardi S, Miraglia del Giudice M, La Rosa M, Bellanti JA. Atopic disease, immune system, and the environment. *Allergy Asthma Proc* 2007;28:410-7.
- Wahn U, von Mutius E, Lau S, Nickel R. The development of atopic phenotypes: genetic and environmental determinants. *Nestle Nutr Workshop Ser Pediatr Program* 2007;59:1-11, 15.
- Roberts H, Frowen K, Sim M, Nixon R. Prevalence of atopy in a population of hairdressing students and practising hairdressers in Melbourne, Australia. *Australas J Dermatol* 2006;47:172-7.
- Radon K, Riu E, Dressel H, Windstetter D, Weinmayr G, Weiland S, et al. Adolescents' jobs and the course of dermatitis symptoms throughout puberty. *Scand J Work Environ Health* 2006;32:132-7.
- Weiland SK, von Mutius E, Hirsch T, Duhme H, Fritzsche C, Werner B, et al. Prevalence of respiratory and atopic disorders among children in the East and West of Germany five years after unification. *Eur Respir J* 1999;14:862-70.
- Weiland SK, Björkstén B, Brunekreef B, Cookson WO, von Mutius E, Strachan DP. Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II): rationale and methods. *Eur Respir J* 2004;24:406-12.
- Weiland SK, Husing A, Strachan DP, Rzehak P, Pearce N. Climate and the prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema in children. *Occup Environ Med* 2004;61:609-15.
- Vogelberg C, Hirsch T, Radon K, Dressel H, Windstetter D, Weinmayr G, et al. Leisure time activity and new onset of wheezing during adolescence. *Eur Respir J* 2007;30:672-6.
- Burney P. Ten years of research on asthma in Europe. *The European Community Respiratory Health Survey. Rev Epidemiol Sante Publique* 1998;46:491-6.
- Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;8:483-91.
- Kennedy SM, Le Moual N, Choudat D, Kauffmann F. Development of an asthma specific job exposure matrix and its application in the epidemiological study of genetics and environment in asthma (EGEA). *Occup Environ Med* 2000;57:635-41.
- Hagendorens MM, Bridts CH, Lauwers K, van Nuijs S, Ebo DG, Vellinga A, et al. Perinatal risk factors for sensitization, atopic dermatitis and wheezing during the first year of life (PIPO study). *Clin Exp Allergy* 2005;35:733-40.
- Werner S, Buser K, Kapp A, Werfel T. The incidence of atopic dermatitis in school entrants is associated with individual life-style factors but not with local environmental factors in Hannover, Germany. *Br J Dermatol* 2002;147:95-104.
- Shamssain M. Trends in the prevalence and severity of asthma, rhinitis and atopic eczema in 6- to 7- and 13- to 14-yr-old children from the north-east of England. *Pediatr Allergy Immunol* 2007;18:149-53.
- Galli E, Gianni S, Auricchio G, Brunetti E, Mancino G, Rossi P. Atopic dermatitis and asthma. *Allergy Asthma Proc* 2007;28:540-3.
- Illi S, von Mutius E, Lau S, Nickel R, Gruber C, Niggemann B, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004;113:925-31.
- Barberio G, Pajno GB, Vita D, Caminiti L, Canonica GW, Passalacqua G. Does a "reverse" atopic march exist? *Allergy* 2008;63:1630-2.
- Zutavern A, Hirsch T, Leupold W, Weiland S, Keil U, von Mutius E. Atopic dermatitis, extrinsic atopic dermatitis and the hygiene hypothesis: results from a cross-sectional study. *Clin Exp Allergy* 2005;35:1301-8.
- Von Linstow ML, Porsbjerg C, Ulrik CS, Nepper-Christensen S, Backer V. Prevalence and predictors of atopy among young Danish adults. *Clin Exp Allergy* 2002;32:520-5.
- Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet* 1998;351:1225-32.
- Radon K, Goldberg M, Becklake M, Pindur U, Hege I, Nowak D. Low acceptance of an internet-based online questionnaire by young adults. *Epidemiology* 2002;13:748-9.
- Flohr C, Weinmayr G, Weiland SK, Addo-Yobo E, Annesi-Maesano I, Björkstén B, et al. How well do questionnaires perform compared with physical examination in detecting flexural eczema? Findings from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two. *Br J Dermatol* 2009;161:846-53.
- Jarvis D, Chinn S, Luczynska C, Burney P. The association of smoking with sensitization to common environmental allergens: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999;104:934-40.
- Heinrich J, Hoelscher B, Frye C, Meyer I, Wjst M, Wichmann HE. Trends in prevalence of atopic diseases and allergic sensitization in children in Eastern Germany. *Eur Respir J* 2002;19:1040-6.
- Oien T, Storro O, Johnsen R. Assessing atopic disease in children two to six years old: reliability of a revised questionnaire. *Prim Care Respir J* 2008;17:164-8.
- Bernsen RM, de Jongste JC, Koes BW, Aardoom HA, van der Wouden JC. Diphtheria tetanus pertussis poliomyelitis vaccination and reported atopic disorders in 8-12-year-old children. *Vaccine* 2006;24:2035-42.
- Maziak W, Behrens T, Brasky TM, Duhme H, Rzehak P, Weiland SK, et al. Are asthma and allergies in children and adolescents increasing? Results from ISAAC phase I and phase III surveys in Munster, Germany. *Allergy* 2003;58:572-9.

METHODS

Time frame

The ISAAC Phase II study in Germany took place from 1995 to 1996, and the participants we included in our analyses were aged 9 to 11 years (mean age 9.7 years). The follow-up survey SOLAR was carried out between 2002 and 2003, with participants now aged between 15 and 18 years (mean age of our study population, 16.6 years). The mean follow-up time of all participants included in our analyses was 6.99 years (95% CI, 6.97-7.00).

Multiple imputation

The amount of missing data differed for each variable. The extent ranged from 35 (1.9%) missing entries for parental history of allergic rhinitis up to 308 (8.9%) for parental history of asthma. For the multiple imputation, sex, study center, and age were used as requisite information. The parameters SES, parental history of asthma/AD/allergic rhinitis, kindergarten attendance, ETS, siblings, and breast-feeding were imputed. Rather than imputing

only 1 parameter, different plausible values were used for replacing the missing values, resulting in 5 complete datasets. All of the subsequent analyses were carried out on each of the 5 datasets, and the results were then combined according to standard imputation procedures.^{E1,E2} The results for the bivariate analyses revealed nearly identical results. Therefore only 1 random dataset is shown to simplify the presentation. Multivariate analyses were performed in 2 steps. First, analyses were carried out on each of the 5 datasets. Second, these results were combined, and the final results are presented.

REFERENCES

- E1. Horton N, Lipsitz S. Multiple imputation in practice: comparison of software packages for regression models with missing variables. *Am Stat* 2001;55:244-53.
- E2. Yuan, Y. Multiple imputation for missing values: Concepts and new development. SAS Institute Inc., SAS User Group International Proceedings 2000, Indianapolis, Indiana P267-25.

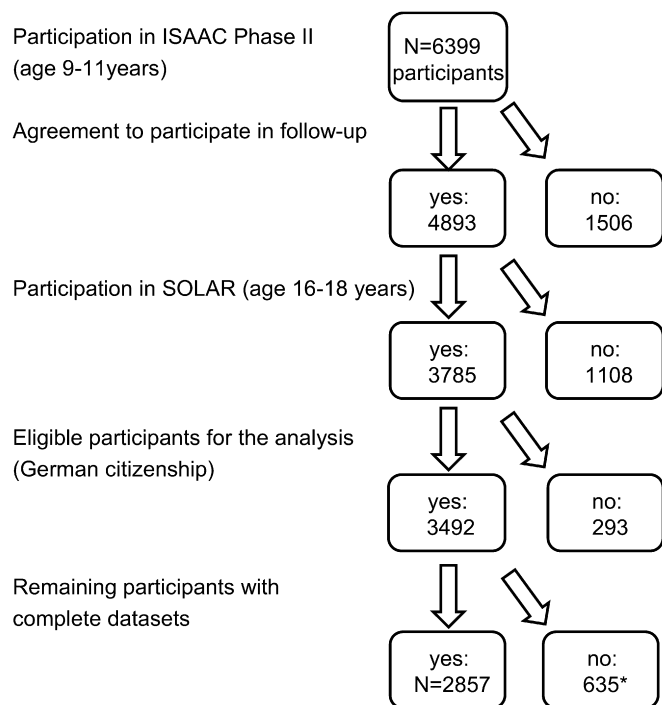


FIG E1. ISAAC Phase II and the SOLAR cohort: participants included in the analyses, dropouts, and nonresponders. *Dropouts caused by missing relevant medical information on SPTs.

TABLE E1. Descriptive information of the final study sample and the excluded participants

	Included participants (n = 2,857), % (95% CI)	Excluded participants (n = 928), % (95% CI)*
Sex (female)	52.1 (50.3-54.0)	53.2 (50.0-56.5)
Study center (Munich)	48.6 (46.9-50.4)	70.6 (67.6-73.5)
ETS exposure until age 9-11 y	42.7 (40.9-44.5)	44.4 (41.1-47.7)
SES (high)	54.3 (52.5-56.1)	51.1 (47.8-54.3)
Breast-feeding	84.4 (83.1-85.8)	83.6 (81.1-86.0)
Kindergarten attendance	99.1 (98.7-99.4)	95.6 (94.2-96.9)
Siblings	83.1 (81.8-84.5)	84.4 (82.0-86.8)
Parental history of:		
Asthma	10.6 (9.2-12.1)	9.2 (7.2-11.2)
AD	17.7 (16.2-19.3)	13.5 (11.3-15.7)
Allergic rhinitis	33.1 (31.4-34.8)	31.0 (28.0-34.0)
Positive SPT response	24.9 (23.3-26.5)	17.7 (13.7-21.7)
Asthma symptoms at baseline	4.6 (3.8-5.3)	5.7 (4.2-7.1)
Rhinitis symptoms at baseline	6.9 (6.0-7.9)	7.7 (6.0-9.4)
Risk job	3.9 (3.2-4.6)	4.0 (2.7-5.3)

*Varying number of observations caused by missing information for the individual items.

2. Herczenik E, van Haren SD, Wroblewska A, Kaijen P, van den Biggelaar M, Meijer AB, et al. Uptake of blood coagulation factor VIII by dendritic cells is mediated via its C1 domain. *J Allergy Clin Immunol* 2012;129:501-9.
3. Dasgupta S, Navarrete AM, Bayry J, Delignat S, Wootla B, André S, et al. A role for exposed mannans in presentation of human therapeutic self-proteins to CD4⁺ T lymphocytes. *Proc Natl Acad Sci U S A* 2007;104:8965-70.
4. James EA, Kwok WW, Ettinger RA, Thompson AR, Pratt KP. T-cell responses over time in a mild hemophilia A inhibitor subject: epitope identification and transient immunogenicity of the corresponding self-peptide. *J Thromb Haemost* 2007;5:2399-407.
5. Ettinger RA, James EA, Kwok WW, Thompson AR, Pratt KP. Lineages of human T-cell clones, including T helper 17/T helper 1 cells, isolated at different stages of anti-factor VIII immune responses. *Blood* 2009;114:1423-8.
6. Meems H, Meijer AB, Cullinan DB, Mertens K, Gilbert GE. Factor VIII C1 domain residues Lys 2092 and Phe 2093 contribute to membrane binding and cofactor activity. *Blood* 2009;114:3938-46.
7. Medzihradsky KF, Besman MJ, Burlingame AL. Structural characterization of site-specific N-glycosylation of recombinant human factor VIII by reversed-phase high-performance liquid chromatography-electrospray ionization mass spectrometry. *Anal Chem* 1997;69:3986-94.

Available online February 14, 2012.
doi:10.1016/j.jaci.2011.12.1004

CD27: A new player in the field of common variable immunodeficiency and EBV-associated lymphoproliferative disorder?

To the Editor:

CD27 is routinely used as a marker of memory B cells. On the basis of its functions and expression in T, B, and natural killer cells and the phenotype of a CD27^{-/-} mouse, a human defect of CD27 might have a substantial effect on cellular and humoral immunity,¹⁻⁵ which is supported by clinical and laboratory data presented by van Montfrans et al⁶ on human CD27 deficiency in the March 2012 issue of the *Journal* and our own observations. Because it is highly important for patients with hypogammaglobulinemia or severe courses of EBV infection, I would like to report briefly the parallel findings in a Viennese family of Turkish origin with an underlying CD27 mutation different from the one in the presented Dutch/Moroccan family, in whom the immunologic and genetic workup, including next-generation sequencing, was performed recently (Wolf et al, manuscript in preparation; Seidel, Haas, Pickl, Borkhardt, and Boztug, unpublished data).

Two months after undergoing infectious mononucleosis at the age of 15 months, a normally thriving girl presented with signs of EBV-associated hemophagocytosis (fever, increased ferritin and triglyceride levels, reduced fibrinogen levels, pancytopenia, and organomegaly), pneumonia, systemic inflammatory response syndrome and lymphoproliferative disorder (LPD) that responded to high-dose steroids only transiently. Because of moderate hypogammaglobulinemia, intravenous immunoglobulin (IVIG) substitution was initiated. After tapering steroids, life-threatening EBV-associated LPD recurred with fever, oliguria, ascites, and pancytopenia. Steroids were readministered successfully, and IVIG was continued. B lymphocytes were found to lack CD27 surface expression (Wolf et al, manuscript in preparation) and to show a common variable immunodeficiency (CVID)-like distribution with markedly increased transitional and CD21⁺ B cells (Seidel and Pickl, unpublished data). A few months later, the girl presented again with fever and EBV-associated LPD. The girl was treated with one course of the anti-CD20 antibody rituximab (375 mg/m² administered weekly 4 times) and responded immediately. The fever stopped, lymph node and spleen sizes shrunk visibly, and during the 9- to 10-month phase of B-cell

aplasia and complete physical health, EBV was undetectable in plasma. However, when B cells reappeared in the peripheral blood, the symptoms slowly recurred, and full-blown EBV-associated LPD with fever and systemic inflammatory response syndrome was present 1 year after the first application of rituximab. The then-4-year-old girl received a second course of rituximab, again followed by complete clinical remission. This remission has been ongoing for >1 year until today, although peripheral B cells and low-range EBV viremia became detectable 4 months ago. It is unclear, to date, whether the girl's immune system learned to regulate its aberrant response to EBV or whether she will eventually require hematopoietic stem cell transplantation for a chance of definite cure.

Together, these observations suggest that autosomal recessive CD27 deficiency should be considered in patients with CVID who lack CD27⁺ B cells and/or patients with severe courses of EBV infection, who might be treatable with IVIG and rituximab. It remains to be elucidated how the lack of (functional) CD27 contributes to the pathogenesis of CVID and EBV-associated LPD.

Markus G. Seidel, MD

From the St Anna Children's Hospital, Vienna, Austria, and Pediatric Hematology-Oncology, Medical University of Graz, Austria. E-mail: markus.seidel@medunigraz.at. Disclosure of potential conflict of interest: The author declares that he has no relevant conflicts of interest.

REFERENCES

1. Bigler RD, Bushkin Y, Chiorazzi N. S152 (CD27). A modulating disulfide-linked T cell activation antigen. *J Immunol* 1988;141:21-8.
2. Camerini D, Walz G, Loenen WA, Borst J, Seed B. The T cell activation antigen CD27 is a member of the nerve growth factor/tumor necrosis factor receptor gene family. *J Immunol* 1991;147:3165-9.
3. Prasad KV, Ao Z, Yoon Y, Wu MX, Rizk M, Jacquot S, et al. CD27, a member of the tumor necrosis factor receptor family, induces apoptosis and binds to siva, a proapoptotic protein. *Proc Natl Acad Sci U S A* 1997;94:6346-51.
4. Hendriks J, Gravestein LA, Tesselaar K, van Lier RA, Schumacher TN, Borst J. CD27 is required for generation and long-term maintenance of T cell immunity. *Nat Immunol* 2000;1:433-40.
5. Gravestein LA, Borst J. Tumor necrosis factor receptor family members in the immune system. *Semin Immunol* 1998;10:423-34.
6. van Montfrans JM, Hoepelman AIM, Otto S, van Gijn M, van de Corput L, de Weger RA, et al. CD27 deficiency is associated with combined immunodeficiency and persistent symptomatic EBV viremia. *J Allergy Clin Immunol* 2012;129:787-93.

Available online February 25, 2012.
doi:10.1016/j.jaci.2012.01.053

Reply

To the Editor:

Seidel¹ reports mutation of CD27 in a patient unrelated to the 2 patients with CD27 deficiency on whom we reported in the March 2012 issue of the *Journal*. Similar to the patients we describe,² this case also presented during early childhood with complicated EBV infection and hypogammaglobulinemia. Although only limited information on the patient reported by Seidel is available, the existence of an unrelated case with a similar clinical phenotype corroborates that CD27 deficiency predisposes to abnormal adaptive human immunity. It further directs research toward identifying which of CD27's pleiotropic functions are involved in this clinical phenotype.

The combination of impaired EBV immunity and lymphoproliferation, together with the only subtle T-cell abnormalities, begs consideration of other genes potentially involved in anti-EBV defense. In our 2 patients, and apparently in the patient described

by Seidel,¹ mutations in genes known to disturb EBV immunity or cause hemophagocytic lymphohistiocytosis were not found. The latter is substantiated by our demonstration of normal cell-mediated cytotoxicity. These features suggest that absence of CD27 was the sole contributor to disturbed EBV immunity in these cases. Comparison of exome or whole-genome sequencing data of all described CD27-deficient patients would potentially support the hypothesis that CD27 is indeed solely responsible for the observed clinical phenotype.

The combined findings regarding CD27 direct the search for additional patients with CD27 deficiency toward those with disturbed EBV immunity. Because CD27 is widely used as a marker for memory B cells in patients with common variable immunodeficiency (CVID) and, thus far, absence of memory B cells but not absence of CD27 has been reported in patients with CVID, we find it unlikely that CD27 deficiency accounts for a substantial number of CVID cases. A careful re-evaluation of patients in whom memory B cells have been phenotyped, however, is warranted, especially in cases in which there has been susceptibility to EBV. More importantly, in patients with disturbed EBV immunity, CD27 is not routinely investigated, and in light of the present reports, perhaps it should be. Because CD27 is a dimer that trimerizes for proper function and serves both the role of receptor and ligand for its counterpart, CD70, it is possible that even heterozygous mutations in *CD27* can disturb proper CD27- or CD70-mediated signaling. Genotypes leading to dysfunctional CD27 might influence EBV immunity to varying degrees and thus define more subtle differences in severity and presenting clinical phenotypes.

Because the severity of clinical course in the Viennese patient was remarkable and it is unclear whether the EBV infection can be controlled, it will be important to understand EBV-specific T- and B-cell immunity in this patient. Extensive immunologic evaluation in our index patient demonstrated abnormalities in T-cell immunity, including aberrant IL-2 production by EBV-specific CD8 T cells, and severely abnormal T cell-dependent B-cell function. Reproduction of these findings in the case reported by Seidel¹ would be consistent with the clinical presentation and would solidify the importance of CD27 in human T-cell differentiation and function and T/B-cell interaction.

Joris M. van Montfrans, MD, PhD^a

Jordan S. Orange, MD, PhD^b

Kiki Tesselaar, PhD^c

From ^athe Departments of Pediatric Immunology and Infectious Diseases, Wilhelmina Children's Hospital/University Medical Center Utrecht, Utrecht, The Netherlands; ^bthe Children's Hospital of Philadelphia Research Institute, Philadelphia, Pa; and ^cthe Department of Immunology, University Medical Center Utrecht, Utrecht, The Netherlands. E-mail: j.vanmontfrans@umcutrecht.nl.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

REFERENCES

- Seidel MG. CD27: a new player in the field of common variable immunodeficiency and EBV-associated lymphoproliferative disorder? *J Allergy Clin Immunol* 2012; 129:1175.
- van Montfrans JM, Hoepelman AI, Otto S, van Gijn M, van de Corput L, de Weger RA, et al. CD27 deficiency is associated with combined immunodeficiency and persistent symptomatic EBV viremia. *J Allergy Clin Immunol* 2012;129:787-93.

Available online February 25, 2012.

doi:10.1016/j.jaci.2012.01.054

Correction

With regard to the September 2010 article "Prediction of the incidence, recurrence, and persistence of atopic dermatitis in adolescence: A prospective cohort study" (*J Allergy Clin Immunol* 2010;126:590-5.e1-3), some of the odds ratios in **Tables II and IV** are incorrect. Corrected versions of the 2 tables appear below.

TABLE II. Probabilities and adjusted ORs for incidence of AD over puberty compared with those without symptoms or AD diagnosis ever: single risk factors and all risk factors combined (final multivariate model)

AD	Probability, % (95% CI; incidence)	Adjusted OR (95% CI)
β_0 (intercept)*	0.1	
SES (high)	0.3 (0.1-0.5)	2.0 (1.0-3.7)
Sex (female)	0.2 (0.1-0.3)	1.2 (0.7-2.3)
Positive SPT response	0.3 (0.2-0.6)	2.2 (1.2-4.2)
No rhinitis symptoms at baseline	0.8 (0.1-6.0)	6.0 (0.8-45.8)
Parental history of allergic rhinitis	0.3 (0.2-0.5)	1.9 (1.1-3.4)
Risk job	0.5 (0.2-1.2)	3.2 (1.2-8.6)
All risk factors listed above present	21.4 (1.8-80.2)	195.8 (13.2-2907.2)

Items in boldface indicate a statistically significant result.

See Fig 1 for an illustration of group distribution and comparison between the groups.

OR, Odds ratio.

* $\exp(\beta_0) = 0.0014$.

TABLE IV. Probabilities and adjusted ORs for persistence of AD over puberty compared with those remitted after ISAAC II: single risk factors and all risk factors combined (final multivariate model)

AD	Probability, % (95% CI; persistence)	Adjusted OR (95% CI)
β_0 (intercept)*	28.3	
SES (high)	32.9 (24.5-42.6)	1.2 (0.8-1.9)
Sex (female)	33.9 (25.4-43.6)	1.3 (0.9-2.0)
Positive SPT response	42.0 (32.2-52.6)	1.8 (1.2-2.8)
Parental history of allergic rhinitis	35.2 (26.6-44.9)	1.4 (0.9-2.1)
Parental history of AD	39.0 (29.4-49.4)	1.6 (1.1-2.5)
Risk job	51.9 (28.4-74.6)	2.7 (1.0-7.4)
All risk factors listed above present	87.6 (63.4-96.7)	17.9 (4.4-73.0)

Items in boldface indicate a statistically significant result.

See Fig 1 for an illustration of group distribution and comparison between the groups.

* $\exp(\beta_0) = 0.3953$.