Atopic dermatitis is associated with an increased risk for rheumatoid arthritis and inflammatory bowel disease, and a decreased risk for type 1 diabetes

Jochen Schmitt, MD, MPH,[a,b] Kristin Schwarz, MSc,[a] Hansjörg Baurecht, MSc,[c] Melanie Hotze, MSc,[c] Regina Fölster-Holst, MD,[c] Elke Rodríguez, PhD,[c] Young A. E. Lee, MD,[d,e] Andre Franke, PhD,[f] Frauke Degenhardt, MSc,[c,f] Wolfgang Lieb, PhD,[g] Christian Gieger, PhD,[h] Michael Kabesch, MD,[i] Markus M. Nöthen, MD,[j,k] Alan D. Irvine, MD,[l,m,n] W. H. Irwin McLean, PhD,[o] Stefanie Deckert, MPH,[a] Victoria Stephan,[a] Peter Schwarz, MD,[p] Martin Aringer, MD,[p] Natalija Novak, MD,[q] and Stephan Weidinger, MD, MaHM[c]

Dresden, Kiel, Berlin, Neuherberg, Regensburg, and Bonn, Germany, Dublin, Ireland, and Dundee, United Kingdom

Background: Atopic dermatitis (AD) is characterized by epidermal barrier failure and immune-mediated inflammation. Evidence on AD as a potential risk factor for inflammatory comorbidities is scarce.

Objectives: We sought to test the hypothesis that prevalent AD is a risk factor for incident rheumatoid arthritis (RA) and inflammatory bowel disease (IBD; Crohn disease [CD], ulcerative colitis [UC]) and is inversely related to type 1 diabetes (T1D) and to investigate established RA, IBD, and T1D susceptibility loci in AD.

Methods: This cohort study used data from German National Health Insurance beneficiaries aged 40 years or younger (n = 655,815) from 2005 through 2011. Prevalent AD in the period 2005 to 2006 was defined as *primary exposure*, and incident RA, IBD, and T1D in the period 2007 to 2011 were defined as *primary outcomes*. Risk ratios were calculated with generalized linear models. Established RA, IBD, and T1D loci were explored in high-density genotyping data from 2,425 cases with AD and 5,449 controls.

Results: Patients with AD (n = 49,847) were at increased risk for incident RA (risk ratio [RR], 1.72; 95% CI, 1.25-2.37) and/or IBD (CD: RR, 1.34; 95% CI, 1.11-1.61; UC: RR, 1.25; 95% CI, 1.03-1.53). After adjusting for health care utilization, there was a nominally significant inverse effect on T1D risk (RR, 0.72; 95% CI, 0.53-0.998). There was no disproportionate occurrence of known RA, CD, UC, or T1D risk alleles in AD.

Conclusions: AD is a risk factor for the development of RA and IBD. This excess comorbidity cannot be attributed to major known IBD and RA genetic risk factors. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Atopic dermatitis, cohort study, epidemiology, inflammatory bowel disease, rheumatoid arthritis, type 1 diabetes*

Atopic dermatitis (AD) is among the most prevalent chronic-inflammatory disorders, characterized by intense pruritus and recurrent eczematous skin lesions[1] that arise as a consequence of skin barrier deficiency and immune-mediated inflammation,[2] and has major genetic contributions.[3] AD has a strong impact on health, as demonstrated in the World Health Organization 2010 Global Burden of Disease survey, in which it was ranked first among common skin diseases.[4] Aside from the disease *per se*, comorbidities and associated psychosocial impairments further add to the burden of the disease. It is firmly established that patients with AD often coexpress asthma and allergic rhinitis, although

From [a]the Center for Evidence-based Healthcare, Medizinische Fakultät Carl Gustav Carus, TU Dresden, Dresden; [b]the University Allergy Center, TU Dresden, Dresden; [c]the Department of Dermatology, Venereology and Allergy, University Hospital Schleswig-Holstein, Campus Kiel, Kiel; [d]the Max-Delbrück-Centrum for Molecular Medicine, Berlin-Buch, Berlin; [e]the Pediatric Allergy, Experimental and Clinical Research Center, Universitätsmedizin Berlin, Berlin; [f]the Institute of Clinical Molecular Biology, Christian-Albrechts-University of Kiel, Kiel; [g]the Institute of Epidemiology and PopGen Biobank, University Hospital Schleswig-Holstein, Kiel; [h]the Institute of Genetic Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg; [i]the Department of Pediatric Pneumology and Allergy, University Children's Hospital Regensburg (KUNO), Regensburg; [j]the Institute of Human Genetics, University of Bonn, Bonn; [k]the Department of Genomics, Life & Brain Center, University of Bonn, Bonn; [l]the Department of Paediatric Dermatology, Our Lady's Children's Hospital, Crumlin, Dublin; [m]National Children's Research Centre, Dublin; [n]the Department of Clinical Medicine, Trinity College Dublin, Dublin; [o]the Dermatology and Genetic Medicine, Division of Molecular Medicine, College of Life Sciences and College of Medicine, Dentistry and Nursing, University of Dundee, Dundee; [p]the Department of Medicine III, Medizinische Fakultät Carl Gustav Carus, TU Dresden, Dresden; and [q]the Department of Dermatology and Allergy, University of Bonn Medical Center, Bonn.

The project received infrastructure support through the DFG Clusters of Excellence "Inflammation at Interfaces" (grant nos EXC306 and EXC306/2), and was supported by the German Federal Ministry of Education and Research (BMBF) within the framework of the e:Med research and funding concept (sysINFLAME, grant no. 01ZX1306A), and the PopGen 2.0 network (grant no. 01EY1103). N.N. was supported by the German National Research Council (DFG) through SFB704, the Cluster of Excellence "ImmunoSensation," and the Christine Kühne Stiftung Center for Allergy Research and Education.

Disclosure of potential conflict of interest: J. Schmitt has received research support from Sanofi, Novartis, and Pfizer. M. Kabesch has received research support from the European Union, the German Ministry of Education and Research, and the German Research Foundation and has received payment for lectures from the European Respiratory Society, the European Academy of Allergy and Clinical Immunology, the American Thoracic Society, Novartis, and GlaxoSmithKline. A. D. Irvine has consultant arrangements with Regeneron. N. Novak has received research support from the German Research Council, Bonfor, Christine Kühne Stiftung Center for Allergy Research and Education, and ALK Abello; has consultant arrangements with Leti Pharma and HAL Allergy; and has received payment for lectures from Astella, Bencard Allergy Therapeutics, MSD, GlaxoSmithKline, HAL Allergy, Astellas, Leo, and Jenapharm. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication February 21, 2015; revised April 20, 2015; accepted for publication June 12, 2015.

Corresponding author: Jochen Schmitt, MD, MPH, Center for Evidence-based Healthcare, Medizinische Fakultät Carl Gustav Carus, TU Dresden, Fetscherstr. 74, D-01307 Dresden, Germany. E-mail: jochen.schmitt@uniklinikum-dresden.de.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2015.06.029

Abbreviations used
AD: Atopic dermatitis
CD: Crohn disease
IBD: Inflammatory bowel disease
ICD-10: International Classification of Diseases, Tenth Revision
IMID: Immune-mediated inflammatory diseases
RA: Rheumatoid arthritis
RR: Risk ratio
SNP: Single nucleotide polymorphism
T1D: Type 1 diabetes
UC: Ulcerative colitis

the risk appears to be smaller than previously thought.[5,6] Furthermore, several studies have found an association of AD with mental health disorders.[7-9]

Gene mapping studies have established a total of 13 European and 10 Asian AD loci, which, with the exception of the dominant risk gene *FLG*, which is involved in skin barrier function, are mostly implicated in immune dysregulation.[10-15] Most of these loci are not specific for AD, but rather shared with several other immune-mediated inflammatory diseases (IMIDs), including seemingly unrelated diseases that are thought to be T_H1/T_H17-mediated such as inflammatory bowel disease (IBD), rheumatoid arthritis (RA),[10] and type 1 diabetes (T1D).[16] However, the effects of shared genetic susceptibility loci between different IMIDs are complex, and the effects of these loci might be agonistic or opposing.[17,18] Furthermore, potential epidemiological relationships with other IMIDs have received little attention so far.[19]

To date, only small cross-sectional studies and case-control studies have been published on the relationship between AD and IBD,[20-22] RA,[23,24] and T1D.[25-27] These studies provided preliminary evidence for an association between AD and Crohn disease (CD) or ulcerative colitis (UC),[20-22,28] whereas results on the relationship between AD and RA[23,24] and on that between AD and T1D[25-27] are conflicting.

We set out to examine the relationship of AD with IBD, RA, and T1D in a large cohort study, hypothesizing that prevalent AD increases the risk of incident IBD and incident RA and lowers the risk of incident T1D. Furthermore, we evaluated established RA, IBD, and T1D susceptibility loci for association with AD.

METHODS

Epidemiological analyses

Study design and participants. This retrospective cohort study used the Allgemeine Ortskrankenkasse Saxony database,[7,29,30] a pseudonymized population-based administrative health care database that holds complete information on outpatient health care (diagnoses according to the International Statistical Classification of Diseases, Tenth Revision [ICD-10]), treatments according to Anatomical Therapeutic Chemical (ATC) Classification code and sociodemographic characteristics (age, sex, area ZIP code) of 2.4 million individuals from Germany from 2005 until 2011. All individuals aged 40 years or younger in 2005 who were consistently insured from 2005 to 2011 were included in the study.

Exposure and confounding variables. *Primary exposure* was defined as prevalent AD in 2005 and/or 2006. To minimize misclassification, we defined *a priori* that the ICD-10 code for AD (L20) had to be documented at least twice to classify patients having AD.[29] We attempted to deal with unmeasured disease severity by stratification by AD-specific medication to differentiate participants with AD into those with no anti-inflammatory treatment prescribed, those with topical anti-inflammatory therapy (ATC codes D07 [topical corticosteroids], D11AX14 [topical tacrolimus], and D11AX15 [topical pimecrolimus]), and those with both topical and systemic anti-inflammatory therapy (L04AA01 [ciclosporin] and H02AB [systemic corticosteroids]) prescribed in 2005 and/or 2006. The role of AD-specific health care utilization behavior was assessed by modeling the number of physician visits due to AD (as a continuous variable).

As confounders, we primarily considered age (continuously) and sex. Data on the socioeconomic status and the distance to qualified health care providers may not be directly inferred from the administrative database used. Therefore, we used the area ZIP code to visualize socioeconomic characteristics of the living environment and access to health care based on a comprehensive nationwide database (INKAR 2012).[31] Factors used to describe the socioeconomic characteristics of the neighborhood include unemployment rate (%), average income tax (euro per head of population), and percentage of graduates with higher education entrance qualification. Access to health care was calculated as the number of inhabitants per physician in the area. Following the recommendations of the German National Public Health Institute (The Robert-Koch Institute), these factors were classified into 3 groups encasing bottom and top 20% and a center of 60% of the population.[32]

To explore the effect of general health care utilization behavior and overall morbidity, the total number of physician contacts due to reasons other than AD graded into 4 equally sized groups was modeled as a confounder as part of the sensitivity analyses.

Primary outcomes. Outcomes of interest were IBD, RA, or T1D incident between January 1, 2007, and December 31, 2011. *Incident IBD* was defined as no documentation of IBD, that is, CD (ICD-10 code K50) or UC (ICD-10 code K51) in 2005 and 2006 *plus* at least 2 documented physician contacts due to IBD in the period 2007 to 2011. *Incident RA* was defined as no documentation of seropositive RA (ICD-10 code M05) in 2005 and 2006 *plus* at least 2 documented physician contacts due to seropositive RA in the period 2007 to 2011. *Incident T1D* was defined as no visit due to T1D (ICD-10 code E10) in 2005 and 2006 *plus* at least 2 visits due to T1D and at least 1 prescription for insulin (ATC code A10A) in the period 2007 to 2011. In accordance with the German good practice of secondary data analysis,[33] we excluded patients who had more documentations of diabetes type 2 (ICD-10 code E11) than T1D.

Patients with only 1 physician contact due to IBD or RA within the 5 years were not considered in the corresponding analyses because their disease status has to be classified as unclear.[34]

Statistical analysis

Counts and percentages were calculated for each confounding, outcome, and exposure variable and for each severity group. Outcome and confounding variables were tabulated against different AD categories.

Risk ratios (RRs) were calculated with the help of generalized linear models using a Poisson link function with robust error variance as suggested by Zou.[35] The primary model adjusted for age and sex. Sensitivity analyses included extended models additionally adjusting for socioeconomic characteristics of the living environment and access to health care and for the total number of physician contacts as an indicator of health care utilization behavior and overall morbidity. Data were analyzed using STATA version 12 (STATA Corp, College Station, Tex).

Genetic analysis

A composite list of variants associated with RA, CD, UC, and T1D with genome-wide significance ($P < 5 \times 10^{-8}$) was compiled using the Catalogue of Published genome-wide association studies.[36] A total of 556 single nucleotide polymorphisms (SNPs) (189 CD, 117 UC, 187 RA, and 96 T1D) were then evaluated for association with AD in ImmunoChip data on 2425 patients with AD and 5449 controls[10] and genome-wide association studies data on 2262 cases with AD and 4093 controls.[18] The ImmunoChip was designed to cover all the major autoimmune diseases, in particular, RA, CD, and UC. SNPTEST[37] was used to associate the imputed dosage for each SNP with AD status separately in each study sample with adjustment for the first 3 principal components from a multidimensional scaling analysis of population

stratification. The association test results of those SNPs with relatively high confidence (PROPER_Info > 0.4) were then meta-analyzed with METAL[38] using the inverse-variance method based on a fixed-effect model. For ImmunoChip data, adjusted association tests were carried out by means of logistic regression using PLINK.[39]

Furthermore, the proportion of CD, UC, RA, and T1D risk-increasing alleles with a positive association with AD (odds ratio [OR] > 1) was assessed, and it was tested whether these proportions differed from 0.5 (proportion of SNPs with an OR of >1 for, e.g., CD by chance) using an exact binomial test as proposed elsewhere.[40]

All participating centers were approved by their institutional review boards, and all participants (or their parents or guardians) gave written informed consent.

RESULTS

Study population and follow-up

The initial cohort consisted of all insured persons of the AOK-Plus Saxony from 2005 to 2011 who were 40 years or younger in 2005 and consistently insured from 2005 to 2011 (n = 655,815; 49.5% women; mean age, 23 years). A total of 49,847 individuals (7.6%) were classified as having prevalent AD in the period 2005 to 2006. Most of the patients with AD received topical anti-inflammatory treatment in the period 2005 to 2006 (n = 29,359; 58.9%). Topical corticosteroids were prescribed to 27,330 patients with AD (54.8%), topical pimecrolimus to 5203 patients with AD (10.4%), and topical tacrolimus to 1781 patients with AD (3.6%). Systemic anti-inflammatory treatment was prescribed to 6357 patients with AD (12.8%). Oral steroids were by far the most frequently used systemic medications. A total of 6349 patients with AD (12.7%) received oral steroids. Ciclosporin was prescribed to 20 patients with AD (<0.1%). Participants' characteristics are summarized in Table I.

A total of 1408 (0.2%) patients with prevalent CD, 1440 (0.2%) patients with prevalent UC, 313 (0.1%) patients with prevalent RA, and 1779 (0.3%) patients with prevalent T1D in the period 2005 to 2006 were excluded from subsequent analyses. Patients with prevalent AD were more likely to have prevalent CD ($P = .009$) and less likely to have prevalent T1D ($P = .001$), whereas prevalent AD was unrelated to prevalent UC ($P = .34$) and prevalent RA ($P = .55$) (Table I).

In 2059 patients (0.3%) from the follow-up cohort, only 1 single physician contact due to CD was documented in the follow-up period (2007-2011). Because their disease state was considered as unclear, these patients were excluded from the following analyses. The corresponding numbers of patients excluded because of only a single, nonconfirmed diagnosis of UC, RA, and T1D were 1936 (0.3%), 493 (0.1%), and 1543 (0.2%), respectively.

The incidence of IBD and RA was higher among women than among men. In contrast, the incidence of T1D was lower among women than among men. Incidence rates of IBD, RA, and T1D among patients with AD and individuals without AD are provided in Table II.

Relationship of prevalent AD and incident IBD

Adjusting for age and sex (primary model), patients with prevalent AD in the period 2005 to 2006 had an approximately 34% increased risk of incident CD than did patients without AD (RR, 1.34; 95% CI, 1.11-1.61) (Table III). The likelihood of incident CD increased with each physician visit due to AD (RR, 1.07; 95% CI, 1.04-1.11 per visit).

TABLE I. Characteristics of study base stratified by prevalent AD in 2005 and 2006

Characteristic	Total (n = 655,815)		Prevalent AD 2005-2006 (n = 49,847)		No prevalent AD 2005-2006 (n = 605,968)	
	n	%	n	%	n	%
Sex: female	324,741	49.52	29,231	58.64	295,510	48.77
Age in 2005 (y)						
0-10	110,757	16.89	20,689	41.51	90,068	14.86
11-20	167,761	25.58	13,928	27.94	153,833	25.39
21-30	174,860	26.66	7,834	15.72	167,026	27.56
31-40	202,437	30.87	7,396	14.84	195,041	32.19
CD (K50) in 2005-2006	1,408	0.21	133	0.27	1,275	0.21
UC (K51) in 2005-2006	1,440	0.22	119	0.24	1,321	0.22
RA (M05) in 2005-2006	313	0.05	21	0.04	292	0.05
T1D (E10) in 2005-2006	1,779	0.27	96	0.19	1,683	0.28
SES unemployment*						
Low	117,277	17.88	8,910	17.87	108,367	17.89
Middle	452,405	68.99	34,835	69.88	417,570	68.92
High	86,051	13.12	6,102	12.24	79,949	13.20
SES income tax†						
Low	85,061	12.97	7,041	14.13	78,020	12.88
Middle	385,905	58.85	29,527	59.24	356,378	58.82
High	184,762	28.18	13,278	26.64	171,484	28.30
SES education†						
Low	122,638	18.70	9,341	18.74	113,297	18.70
Middle	289,676	44.18	23,114	46.37	266,562	44.00
High	243,419	37.12	17,392	34.89	226,027	37.31
Access to health care*						
Low	108,573	16.56	9,022	18.10	99,551	16.43
Middle	273,658	41.73	19,993	40.11	253,665	41.87
High	273,502	41.71	20,832	41.79	252,670	41.70
Health care utilization behavior						
<25%	158,944	24.24	8,280	16.61	150,664	24.86
25%-<50%	168,096	25.63	12,953	25.99	155,143	25.60
50%-<75%	160,426	24.46	13,833	27.75	146,593	24.19
75%	168,349	25.67	14,781	29.65	153,568	25.34

SES, Socioeconomic status.
*Access to health care measured by number of inhabitants per physician in neighborhood.
†Socioeconomic status measured by rate of unemployment, income tax in euro per inhabitant, and graduates with higher education entrance in neighborhood classified into 3 groups encasing bottom and top 20% and a center of 60% of the population as suggested by the Robert Koch Institute for primary data.[41]

TABLE II. Incidence outcome in the period 2007 to 2011 stratified by prevalent AD in the period 2005 to 2006 and by sex

Outcome of interest (present)	Total		AD in 2005-2006				Sex			
			Present		Absent		Male		Female	
	n	%	n	%	n	%	n	%	n	%
CD (K50)	1391	0.21	130	0.26	1261	0.21	556	0.17	835	0.26
UC (K51)	1427	0.22	112	0.23	1315	0.22	644	0.19	783	0.24
RA (M05)	489	0.07	43	0.09	446	0.07	122	0.04	367	0.11
T1D (E10)	593	0.09	40	0.08	553	0.09	368	0.11	225	0.07

Considering UC, the primary model yielded a 1.25-fold increased risk in patients with AD than in patients without AD (RR, 1.25; 95% CI, 1.03-1.53) (Table III).

Subsequent analyses demonstrated that only patients with AD receiving topical anti-inflammatory treatment were at increased

TABLE III. RR of outcome in the period 2007 to 2011 of patients with vs patients without AD in the period 2005 to 2006

	Primary model		Sensitivity analyses			
	Multivariate analysis (adjusted for age and sex)		Multivariate analysis (adjusted for age, sex, socioeconomic status,* and access to health care†)		Multivariate analysis (adjusted for age, sex, socioeconomic status,* access to health care,† and health care utilization behavior)	
Exposure variable	**RR (95% CI)**	***P* value**	**RR (95% CI)**	***P* value**	**RR (95% CI)**	***P* value**
CD (K50) in 2007-2011						
AD (primary exposure, reference no AD)	1.34 (1.11-1.61)	.002	1.35 (1.12-1.63)	.002	1.20 (1.00-1.44)	.049
Health care utilization due to AD per visit (no. of physician contacts)	1.07 (1.04-1.11)	<.001	1.07 (1.04-1.11)	<.001	1.06 (1.03-1.10)	<.001
Treatment of AD (reference no AD)						
No anti-inflammatory treatment	1.03 (0.74-1.43)	.870	1.04 (0.75-1.44)	.828	1.02 (0.73-1.41)	.920
Topical anti-inflammatory treatment	1.59 (1.26-2.00)	<.001	1.60 (1.27-2.01)	<.001	1.40 (1.12-1.77)	.004
Topical and systemic anti-inflammatory treatment	1.26 (0.67-2.36)	.467	1.28 (0.69-2.40)	.433	0.92 (0.49-1.73)	.805
UC (K51) in 2007-2011						
AD (primary exposure, reference no AD)	1.25 (1.03-1.53)	.025	1.26 (1.03-1.53)	.022	1.11 (0.92-1.35)	.283
Health care utilization due to AD per visit (no. of physician contacts)	1.05 (1.01-1.09)	.014	1.05 (1.01-1.09)	.012	1.03 (0.99-1.08)	.106
Treatment of AD (reference no AD)						
No anti-inflammatory treatment	1.18 (0.85-1.62)	.322	1.18 (0.86-1.63)	.316	1.13 (0.83-1.56)	.443
Topical anti-inflammatory treatment	1.40 (1.08-1.80)	.010	1.40 (1.09-1.80)	.009	1.22 (0.95-1.57)	.115
Topical and systemic anti-inflammatory treatment	0.70 (0.28-1.68)	.424	0.70 (0.29-1.69)	.432	0.51 (0.21-1.23)	.134
RA (M05) in 2007-2011						
AD (primary exposure, reference no AD)	1.72 (1.25-2.37)	.001	1.73 (1.26-2.38)	.001	1.45 (1.06-1.99)	.021
Health care utilization due to AD per visit (no. of physician contacts)	1.09 (1.03-1.15)	.002	1.09 (1.03-1.15)	.002	1.06 (1.00-1.13)	.043
Treatment of AD (reference no AD)						
No anti-inflammatory treatment	1.63 (0.97-2.73)	.067	1.62 (0.97-2.72)	.068	1.47 (0.88-2.46)	.144
Topical anti-inflammatory treatment	1.61 (1.04-2.51)	.034	1.62 (1.04-2.52)	.032	1.34 (0.86-2.08)	.192
Topical and systemic anti-inflammatory treatment	1.55 (0.50-4.82)	.449	1.58 (0.51-4.94)	.426	1.11 (0.36-3.45)	.857
T1D (E10) in 2007-2011						
AD (primary exposure, reference no AD)	0.80 (0.58-1.11)	.189	0.81 (0.59-1.12)	.202	0.72 (0.53-0.998)	.049
Health care utilization due to AD per visit (no. of physician contacts)	0.94 (0.87-1.01)	.111	0.94 (0.87-1.02)	.119	0.92 (0.85-1.01)	.066
Treatment of AD (reference no AD)						
No anti-inflammatory treatment	0.49 (0.25-0.95)	.036	0.50 (0.26-0.96)	.037	0.50 (0.26-0.97)	.040
Topical anti-inflammatory treatment	0.86 (0.56-1.33)	.503	0.87 (0.56-1.34)	.516	0.77 (0.50-1.18)	.229
Topical and systemic anti-inflammatory treatment	1.51 (0.71-3.19)	.283	1.53 (0.72-3.24)	.267	1.06 (0.50-2.23)	.884

*Socioeconomic status measured by rate of unemployment, income tax in euro per inhabitant, and graduates with higher education entrance in neighborhood classified into 3 groups encasing bottom and top 20% and a center of 60% of the population as suggested by the Robert Koch Institute for primary data.[41]
†Access to health care measured by number of inhabitants per physician in neighborhood.

risk of developing CD (RR, 1.59; 95% CI, 1.26-2.00) and UC (RR, 1.40; 95% CI, 1.08-1.80), whereas patients with AD not receiving anti-inflammatory treatment did not differ from patients without AD. Patients with AD receiving systemic anti-inflammatory treatment (mainly oral steroids) were not at increased risk for incident IBD. The association between AD and IBD was independent of local health care and socioeconomic status (Table III).

Relationship of prevalent AD and incident RA

After adjustment for age and sex, the risk of incident RA was 72% higher for patients with AD than for patients without AD (RR, 1.72; 95% CI, 1.25-2.37) (Table III). The likelihood of incident RA increased with each physician contact due to AD (RR per visit, 1.09; 95% CI, 1.03-1.15) and was independent of anti-inflammatory treatment of AD.

The adjustment for socioeconomic status and local health care had negligible effects on the relationship between AD and RA (RR, 1.73; 95% CI, 1.26-2.38) and decreased slightly after adjustment for health care utilization behavior (RR, 1.45; 95% CI, 1.06-1.99).

Relationship of prevalent AD and incident T1D

The primary model did not indicate a significantly decreased risk of incident T1D for patients with AD compared with patients without AD (RR, 0.80; 95% CI, 0.58-1.11) (Table III).

The inverse relationship reached statistical significance after adjustment for health care utilization behavior (RR, 0.72; 95% CI, 0.53-0.998; $P = .049$).

Sensitivity analyses indicated that patients with AD not receiving anti-inflammatory treatment had an approximately 50% reduced risk to develop incident T1D compared with patients without AD (RR, 0.49; 95% CI, 0.25-0.95). Patients with AD receiving systemic anti-inflammatory treatment tended to be at increased risk for incident T1D, but this association was not statistically significant (Table III).

Association analysis of established CD, UC, T1D, and RA risk loci with AD. Established risk variants in 4 CD (2q12.1, 11q13.5, 17q21.2, and 20q13.33), 3 UC (4q27, 11q13.5, and 20q13.33), 1 RA (1q21.3), and 2 T1D (4q27 and 6p21.32) susceptibility loci were significantly associated with AD after correction for multiple testing (Table IV; see Tables E1-E4 in this article's Online Repository at www.jacionline.org). Apart from rs2228145 in *IL6R* (1q21.3; RA), rs9268645 in *HLA-DRA*

TABLE IV. AD-associated known CD, UC, RA, and T1D SNPs

Location	Candidate gene	SNP	CHR	POS	AD			RiA	OR	Trait	Direction
					EA/OA	OR (95% CI)	*P* value				
1q21.3	IL6R	rs2228145	1	154426970	A/C	0.856 (0.787-0.931)	2.61×10^{-4}	A	1.08	RA	Antagonistic
2q12.1	IL1RL1, IL18R1, IL18RAP	rs2058660	2	103054449	C/T	1.191 (1.104-1.284)	6.56×10^{-6}	C	1.19	CD	Agonistic
4q27	ADAD1, KIAA1109, IL2, IL21	rs17388568	4	123329362	T/C	1.176 (1.094-1.264)	1.07×10^{-5}	T	1.12	UC	Agonistic
					T/C	1.176 (1.094-1.264)	1.07×10^{-5}	T	1.26	T1D	Agonistic
6p21.32	HLA-DRA	rs9268645	6	32408527	C/G	1.149 (1.073-1.231)	6.80×10^{-5}	G	1.91*	T1D	Antagonistic
11q13.5	C11orf30, LRRC32	rs2155219†	11	76299194	G/T	0.808 (0.755-0.864)	6.85×10^{-10}	T	1.13	UC	Agonistic
		rs7927894†		76301316	T/C	1.154 (1.076-1.236)	5.10×10^{-5}	T	1.16	CD	Agonistic
17q21.2	STAT3	rs9891119	17	40507980	C/A	1.153 (1.075-1.237)	6.63×10^{-5}	A	1.37	CD	Antagonistic
20q13.33	RTEL1, TNFRSF6B, ZGPAT	rs2297441‡	20	62327582	G/A	0.766 (0.703-0.834)	9.09×10^{-10}	A	1.09	UC	Agonistic
		rs4809330‡		62349586	T/C	0.812 (0.753-0.876)	7.53×10^{-8}	C	1.12	CD	Agonistic

EA/OA, Effect allele/other allele; *RiA*, risk allele.
*OR and risk allele derived from Bradfield et al.[42]
†Linkage disequilibrium (LD) between rs2155219 and rs7927894: $r^2 = 0.733$.
‡Moderate LD between rs2297441 and rs4809330: $r^2 = 0.484$.

(6p21.32, T1D), and rs9891119 in *STAT3* (17q21.2; CD), all risk SNPs showed agonistic effects with AD.

A total of 23 additional risk SNPs for CD, 11 for UC, 23 for RA, and 13 for T1D showed suggestive association with AD ($P < .05$) (see Tables E1-E4). Of these, 11 (47.8%), 2 (18.2%), 13 (56.5%), and 4 (30.8%) had effect directionalities consistent with findings from the epidemiological analysis, that is, ORs of more than 1 for CD, UC, and RA SNPs and OR of less than 1 for T1D risk SNPs.

Proportion of CD, UC, RA, and T1D risk alleles associated with AD

In 53.6%, 52.4%, and 48.6% of all risk SNPs for CD, UC, and RA, the same risk alleles showed a positive association (OR > 1) and 54.7% of the T1D SNPs showed a negative association with AD, which is in the range of expectation by chance ($P > .39$). Restricting to those SNPs showing nominal association with AD ($P < .05$), the proportions of risk allele with agonistic association were 53.6%, 35.7%, and 54.2% for CD, UC, and RA and with antagonistic association was 33.3% for T1D, which is also within the range of expectation by chance ($P > .18$).

DISCUSSION

Main findings

This large cohort study extends previous findings indicating that patients with prevalent AD are at a significantly increased risk to develop IBD and RA than are patients without AD. In this cohort, patients with prevalent AD also had a slightly decreased risk for incident T1D, which, however, was significant only when considering health care utilization behavior as confounder. The associations between AD and IBD, RA, and T1D were independent of local health care and socioeconomic status. The risk of incident IBD and RA increased with each physician visit due to AD, and was increased in patients who received topical anti-inflammatory treatment for AD, suggesting a possible "dose-response" relationship. As previously reported,[43] a substantial proportion of patients with AD received systemic steroids, whereas other systemic agents such as ciclosporin were rarely used. In the present study, the RR of incident comorbidities differed between patients with AD receiving topical anti-inflammatory treatments and patients additionally receiving systemic anti-inflammatory agents (>99% oral steroids). Although none of these subgroup analyses reached statistical significance, our sensitivity analysis suggest that the risk of incident T1D may be increased in patients with AD receiving systemic steroids, whereas the chance of detection/manifestation of comorbidities such as IBD and RA may be decreased as compared with patients with AD receiving topical treatment only.

We did not find a higher proportion of established risk alleles for IBD and RA nor was T1D associated with AD in a consistent directionality more frequently than the 50% expected by chance, indicating that, for the most part, these diseases do not have a shared genetic background. However, 4 CD risk loci and 1 UC locus, which comprise genes important for adaptive immune regulation (*IL1RL1/IL18R1/IL18RAP*, *RTEL1/TNFRSF6B*, *STAT3*, and *IL2/IL21*) and tissue response (*LRRC32*), were significantly associated with AD. Four of these loci showed a concordant effect directionality (Tables E1 and E2) and could contribute to the excess comorbidity in that they confer a higher risk for disease coexpression. To test this hypothesis, however, large cohorts with phenotype information on both diseases would be needed.

Possible explanations

AD, IBD, and RA are characterized by T-cell–mediated chronic inflammation.[1,44-46] Prominent T_H1 and T_H17 responses promoting autoimmunity are well known to contribute to the chronicity of RA and IBD.[47] More recently, they have also been implicated in the transition to chronic inflammation in AD.[2,48] Furthermore, a recent systematic review provided evidence for autoreactivity in up to one third of the patients with AD, in particular those with severe and persistent disease.[49] Interestingly, our data suggest that the strongest association with IBD and RA is seen for such patients with AD. Although our data do not allow conclusions on causality, it is tempting to speculate that the development of RA and IBD in subgroups of patients with AD is precipitated by a sustained skin inflammation with increased T_H1/T_H17 signaling and secretion of proinflammatory cytokines

including TNF-α, similar to what has been postulated for a subgroup of patients with psoriasis.[50] Epigenetic changes secondary to prolonged systemic inflammation might be another mechanism linking chronic-inflammatory diseases.[51,52]

The immune abnormalities observed in AD are in part genetically predetermined, as evidenced by established AD susceptibility genes that regulate T-cell differentiation and effector function, or encode components of the innate immune system.[53] Interestingly, previous disease-by-disease gene mapping studies indicated that many of these AD risk genes are also implicated in other IMIDs, including IBD and RA.[10] In some cases, the direction of genetic effects is clearly divergent, for example, for a functional polymorphism in *IL6R*, which was shown to increase the risk for AD and asthma,[54,55] while exerting a protective effect on RA,[56] and for common polymorphisms in *IL2/IL21*.[10,57,58] In contrast, the same effect directions were observed for variants at *C11orf30/LRRC32* and *TNFRSF6B*[10,11,59,60] and AD/IBD, or *IL18R1* and AD/IBD/RA.[10,59,60] Our comprehensive *in silico* analysis including both large-scale genome-wide association studies and high-density genotyping data for IMID candidate loci confirms these observations, but beyond this they do not indicate a disproportionate occurrence of CD, UC, RA, or T1D risk alleles in AD. Although we cannot exclude that there are as yet undetermined genetic determinants that specifically confer risk to coexpression of AD with CD, UC, and RA or protection to T1D in certain AD subtypes, known susceptibility loci of these IMIDs cannot explain the excess comorbidities. Current knowledge of risk factors and biological mechanisms involved in these diseases does not allow a coherent explanation. Analyses based on systematic reviews concerning environmental risk factors of AD resulted in, for example, an increased risk of AD in children with antibiotics in the first years of life,[61] a favorable or inconsistent effect of exposure to pets,[62-64] and an inverse association between AD and endotoxin as well as early day care.[64] None of these risk factors was investigated in systematic reviews on IBD, T1D, and RA. Much of this uncertainty may be related to their phenotypic heterogeneity, which may well reflect different mechanisms and risk factors. Large cohort studies with detailed clinical information, for example, on disease subphenotypes and courses, will be needed to work out determinants of subtle disease corelationships.

Study strengths and limitations

To our knowledge, this is the first study that used routine data to assess the association between AD on the one hand and IBD, T1D, and RA on the other hand. A major strength of our study is the design, allowing us to capture a comprehensive and complete picture of the course of AD and comorbidities in a large and relatively unselected population of approximately 650,000 patients, with low risks for selection and recall bias. In addition, we adjusted for *a priori* defined confounders, including age and sex. Because of the inadequate documentation of socioeconomic status and missing documentation of local health care access within administrative health care data in Germany, we used an innovative way to adjust for both confounders through a linkage of the AOK Saxony database and a comprehensive nationwide database of socioeconomic and other characteristics for every ZIP-code area in Germany.[31] A limitation of our study is possible residual confounding and ecological bias due to aggregated socioeconomic data for neighborhood instead of individual data. Furthermore, in our secondary data, false classification bias or incomplete documentation cannot be ruled out. However, the sensitivity analyses performed suggest that the observed findings are robust. From patients with prevalent autoimmune disease in the period 2005 to 2006 who were excluded from the analysis, AD was disproportionally more prevalent in patients with CD and less prevalent in patients with T1D, indicating that the present analysis might actually underestimate the risk for patients with AD to develop those diseases.

Implications for future research

Overall, this study indicated a modest increase in the risk of incident IBD and RA in patients with AD. Further research is needed to identify the subset of patients with AD at highest risk for the development of RA and/or IBD and the underlying determinants. This may (1) lead to a better understanding of the pathophysiology of AD and the comorbidities investigated and (2) may eventually induce the development, evaluation, and implementation of targeted comprehensive care models.

Further research is also needed to disentangle the effects of AD and AD treatment on the risk of incident comorbidities. In our cohort, oral steroids were used in a substantial proportion of patients with AD, whereas other systemic anti-inflammatory agents were rarely prescribed. The introduction of new biological agents will offer the chance to better understand the effects of targeted AD treatment as a potential modifier of the observed risk for comorbidities.

We thank the Saxony Compulsory Health Insurance AOK-PLUS for cooperation in data utilization and for providing technical support.

Clinical implication: Patients with prevalent AD are at an increased risk for RA and IBD.

REFERENCES

1. Bieber T. Atopic dermatitis. N Engl J Med 2008;358:1483-94.
2. Gittler JK, Shemer A, Suarez-Farinas M, Fuentes-Duculan J, Gulewicz KJ, Wang CQ, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. J Allergy Clin Immunol 2012;130:1344-54.
3. Williams HC. Clinical practice. Atopic dermatitis. N Engl J Med 2005;352:2314-24.
4. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2197-223.
5. Williams H, Flohr C. How epidemiology has challenged 3 prevailing concepts about atopic dermatitis. J Allergy Clin Immunol 2006;118:209-13.
6. van der Hulst AE, Klip H, Brand PL. Risk of developing asthma in young children with atopic eczema: a systematic review. J Allergy Clin Immunol 2007;120:565-9.
7. Schmitt J, Romanos M, Pfennig A, Leopold K, Meurer M. Psychiatric comorbidity in adult eczema. Br J Dermatol 2009;161:878-83.
8. Schmitt J, Chen CM, Apfelbacher C, Romanos M, Lehmann I, Herbarth O, et al. Infant eczema, infant sleeping problems, and mental health at 10 years of age: the prospective birth cohort study LISAplus. Allergy 2011;66:404-11.
9. Yaghmaie P, Koudelka CW, Simpson EL. Mental health comorbidity in patients with atopic dermatitis. J Allergy Clin Immunol 2013;131:428-33.
10. Ellinghaus D, Baurecht H, Esparza-Gordillo J, Rodriguez E, Matanovic A, Marenholz I, et al. High-density genotyping study identifies four new susceptibility loci for atopic dermatitis. Nat Genet 2013;45:808-12.
11. Esparza-Gordillo J, Weidinger S, Folster-Holst R, Bauerfeind A, Ruschendorf F, Patone G, et al. A common variant on chromosome 11q13 is associated with atopic dermatitis. Nat Genet 2009;41:596-601.
12. Weidinger S, Willis-Owen SA, Kamatani Y, Baurecht H, Morar N, Liang L, et al. A genome-wide association study of atopic dermatitis identifies loci with overlapping effects on asthma and psoriasis. Hum Mol Genet 2013;22:4841-56.

13. Paternoster L, Standl M, Chen CM, Ramasamy A, Bonnelykke K, Duijts L, et al. Meta-analysis of genome-wide association studies identifies three new risk loci for atopic dermatitis. Nat Genet 2012;44:187-92.
14. Sun LD, Xiao FL, Li Y, Zhou WM, Tang HY, Tang XF, et al. Genome-wide association study identifies two new susceptibility loci for atopic dermatitis in the Chinese Han population. Nat Genet 2011;43:690-4.
15. Hirota T, Takahashi A, Kubo M, Tsunoda T, Tomita K, Sakashita M, et al. Genome-wide association study identifies eight new susceptibility loci for atopic dermatitis in the Japanese population. Nat Genet 2012;44:1222-6.
16. Saleh NM, Raj SM, Smyth DJ, Wallace C, Howson JM, Bell L, et al. Genetic association analyses of atopic illness and proinflammatory cytokine genes with type 1 diabetes. Diabetes Metab Res Rev 2011;27:838-43.
17. Parkes M, Cortes A, van Heel DA, Brown MA. Genetic insights into common pathways and complex relationships among immune-mediated diseases. Nat Rev Genet 2013;14:661-73.
18. Baurecht H, Hotze M, Brand S, Buning C, Cormican P, Corvin A, et al. Genome-wide comparative analysis of atopic dermatitis and psoriasis gives insight into opposing genetic mechanisms. Am J Hum Genet 2015;96:104-20.
19. Deckert S, Kopkow C, Schmitt J. Nonallergic comorbidities of atopic eczema: an overview of systematic reviews. Allergy 2014;69:37-45.
20. Baron S, Turck D, Leplat C, Merle V, Gower-Rousseau C, Marti R, et al. Environmental risk factors in paediatric inflammatory bowel diseases: a population based case control study. Gut 2005;54:357-63.
21. Feeney MA, Murphy F, Clegg AJ, Trebble TM, Sharer NM, Snook JA. A case-control study of childhood environmental risk factors for the development of inflammatory bowel disease. Eur J Gastroenterol Hepatol 2002;14:529-34.
22. Jakobsen C, Paerregaard A, Munkholm P, Wewer V. Environmental factors and risk of developing paediatric inflammatory bowel disease – a population based study 2007-2009. J Crohns Colitis 2013;7:79-88.
23. Rudwaleit M, Andermann B, Alten R, Sorensen H, Listing J, Zink A, et al. Atopic disorders in ankylosing spondylitis and rheumatoid arthritis. Ann Rheum Dis 2002;61:968-74.
24. Karatay S, Yildirim K, Ugur M, Senel K, Erdal A, Durmus B, et al. Prevalence of atopic disorders in rheumatic diseases. Mod Rheumatol 2013;23:351-6.
25. Olesen AB, Juul S, Birkebaek N, Thestrup-Pedersen K. Association between atopic dermatitis and insulin-dependent diabetes mellitus: a case-control study. Lancet 2001;357:1749-52.
26. Meerwaldt R, Odink RJ, Landaeta R, Aarts F, Brunekreef B, Gerritsen J, et al. A lower prevalence of atopy symptoms in children with type 1 diabetes mellitus. Clin Exp Allergy 2002;32:254-5.
27. Fsadni P, Fsadni C, Fava S, Montefort S. Correlation of worldwide incidence of type 1 diabetes (DiaMond) with prevalence of asthma and atopic eczema (ISAAC). Clin Respir J 2012;6:18-25.
28. Niwa Y, Sumi H, Akamatsu H. An association between ulcerative colitis and atopic dermatitis, diseases of impaired superficial barriers. J Invest Dermatol 2004;123:999-1000.
29. Schmitt J, Romanos M, Schmitt NM, Meurer M, Kirch W. Atopic eczema and attention-deficit/hyperactivity disorder in a population-based sample of children and adolescents. JAMA 2009;301:724-6.
30. Schmitt J, Maywald U, Schmitt N, Meurer M, Kirch W. Cardiovascular comorbidity in patients with chronic inflammatory skin diseases: a case-control study utilising a population-based administrative database. Ital J Public Health 2008;5:187-93.
31. Augurzky B, Kopetsch T, Schmitz H. What accounts for the regional differences in the utilisation of hospitals in Germany? Eur J Health Econ 2013;14:615-27.
32. Lampert T, Kroll LE, von der Lippe E, Muters S, Stolzenberg H. Socioeconomic status and health: results of the German Health Interview and Examination Survey for Adults (DEGS1) [in German]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2013;56:814-21.
33. Arbeitsgruppe Erhebung und Nutzung von Sekundardaten der Deutschen Gesellschaft fur Sozialmedizin und P, Arbeitsgruppe Epidemiologische Methoden der Deutschen Gesellschaft fur Epid e m, Deutschen Gesellschaft fur Medizinische Informatik BuE, Deutschen Gesellschaft fur Sozialmedizin und P. [Good practice of secondary data analysis, first revision]. Gesundheitswesen 2008;70:54-60.
34. Swart E, Ihle P, Geyer S, Grobe T, Hofmann W; German Society for Social Medicine and Prevention. GPS–good practice secondary data analysis. Working Group for the Survey and Utilization of Secondary Data (AGENS) of the German Society for Social Medicine and Prevention (DGSMP) [in German]. Gesundheitswesen 2005;67:416-21.
35. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004;159:702-6.
36. Welter D, MacArthur J, Morales J, Burdett T, Hall P, Junkins H, et al. The NHGRI GWAS Catalog, a curated resource of SNP-trait associations. Nucleic Acids Res 2014;42:D1001-6.
37. Marchini J, Howie B, Myers S, McVean G, Donnelly P. A new multipoint method for genome-wide association studies by imputation of genotypes. Nat Genet 2007;39:906-13.
38. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics 2010;26:2190-1.
39. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 2007;81:559-75.
40. Lieb W, Jansen H, Loley C, Pencina MJ, Nelson CP, Newton-Cheh C, et al. Genetic predisposition to higher blood pressure increases coronary artery disease risk. Hypertension 2013;61:995-1001.
41. Lampert T, Kroll L, Müters S, Stolzenberg H. Measurement of socioeconomic status in the German Health Interview and Examination Survey for Adults (DEGS1) [in German]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2013;56:631-6.
42. Bradfield JP, Qu HQ, Wang K, Zhang H, Sleiman PM, Kim CE, et al. A genome-wide meta-analysis of six type 1 diabetes cohorts identifies multiple associated loci. PLoS Genet 2011;7:e1002293.
43. Schmitt J, Schmitt NM, Kirch W, Meurer M. Outpatient care and medical treatment of children and adults with atopic eczema. J Dtsch Dermatol Ges 2009;7:345-51.
44. Ordas I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. Lancet 2012;380:1606-19.
45. Baumgart DC, Sandborn WJ. Crohn's disease. Lancet 2012;380:1590-605.
46. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010;376:1094-108.
47. Wilke CM, Bishop K, Fox D, Zou W. Deciphering the role of Th17 cells in human disease. Trends Immunol 2011;32:603-11.
48. Koga C, Kabashima K, Shiraishi N, Kobayashi M, Tokura Y. Possible pathogenic role of Th17 cells for atopic dermatitis. J Invest Dermatol 2008;128:2625-30.
49. Tang TS, Bieber T, Williams HC. Does "autoreactivity" play a role in atopic dermatitis? J Allergy Clin Immunol 2012;129:1209-15.e2.
50. Davidovici BB, Sattar N, Prinz J, Puig L, Emery P, Barker JN, et al. Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and co-morbid conditions. J Invest Dermatol 2010;130:1785-96.
51. Rodriguez E, Baurecht H, Wahn AF, Kretschmer A, Hotze M, Zeilinger S, et al. An integrated epigenetic and transcriptomic analysis reveals distinct tissue-specific patterns of DNA methylation associated with atopic dermatitis. J Invest Dermatol 2014;134:1873-83.
52. Roberson ED, Liu Y, Ryan C, Joyce CE, Duan S, Cao L, et al. A subset of methylated CpG sites differentiate psoriatic from normal skin. J invest Dermatol 2012;132:583-92.
53. Barnes KC. An update on the genetics of atopic dermatitis: scratching the surface in 2009. J Allergy Clin Immunol 2010;125:16-29, e1-11; quiz 30-1.
54. Esparza-Gordillo J, Schaarschmidt H, Liang L, Cookson W, Bauerfeind A, Lee-Kirsch MA, et al. A functional IL-6 receptor (IL6R) variant is a risk factor for persistent atopic dermatitis. J Allergy Clin Immunol 2013;132:371-7.
55. Ferreira MA, Matheson MC, Duffy DL, Marks GB, Hui J, Le Souef P, et al. Identification of IL6R and chromosome 11q13.5 as risk loci for asthma. Lancet 2011;378:1006-14.
56. Okada Y, Wu D, Trynka G, Raj T, Terao C, Ikari K, et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. Nature 2014;506:376-81.
57. Festen EA, Goyette P, Green T, Boucher G, Beauchamp C, Trynka G, et al. A meta-analysis of genome-wide association scans identifies IL18RAP, PTPN2, TAGAP, and PUS10 as shared risk loci for Crohn's disease and celiac disease. PLoS Genet 2011;7:e1001283.
58. Daha NA, Kurreeman FA, Marques RB, Stoeken-Rijsbergen G, Verduijn W, Huizinga TW, et al. Confirmation of STAT4, IL2/IL21, and CTLA4 polymorphisms in rheumatoid arthritis. Arthritis Rheum 2009;60:1255-60.
59. Franke A, Balschun T, Sina C, Ellinghaus D, Hasler R, Mayr G, et al. Genome-wide association study for ulcerative colitis identifies risk loci at 7q22 and 22q13 (IL17REL). Nat Genet 2010;42:292-4.
60. Franke A, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. Nat Genet 2010;42:1118-25.
61. Tsakok T, McKeever TM, Yeo L, Flohr C. Does early life exposure to antibiotics increase the risk of eczema? A systematic review. Br J Dermatol 2013;169:983-91.
62. Pelucchi C, Galeone C, Bach JF, La Vecchia C, Chatenoud L. Pet exposure and risk of atopic dermatitis at the pediatric age: a meta-analysis of birth cohort studies. J Allergy Clin Immunol 2013;132:616-22.e7.
63. Langan SM, Flohr C, Williams HC. The role of furry pets in eczema: a systematic review. Arch Dermatol 2007;143:1570-7.
64. Flohr C, Yeo L. Atopic dermatitis and the hygiene hypothesis revisited. Curr Probl Dermatol 2011;41:1-34.