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 2016;137:130-6.)

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

Discuss this article on the JACI Journal Club blog: www.jaci-online.blogspot.com.

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.

Available online August 4, 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.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

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