

Atopic dermatitis is associated with autoimmune but not with cardiovascular comorbidities in a random sample of the general population in Leipzig, Germany

Treudler R ^{1,2,3*}, Zeynalova S ^{3,4*}, Walther F ^{1,3}, Engel C ^{3,4}, Simon JC ^{1,2,3}

*contributed equally

1 Department of Dermatology, Venerology and Allergology, Universität Leipzig
2 Leipzig Interdisciplinary Allergy Center (LICA) – Comprehensive Allergy Center
3 Leipzig Research Center for Civilization Disease - LIFE
4 Institute for Medical Informatics, Statistics and Epidemiology (IMISE) Leipzig

Key words: atopic dermatitis, autoimmune, cardiovascular, comorbidity, eczema, cohort study

Correspondence:

Prof. Dr. med. Regina Treudler
Leipzig Interdisciplinary Allergy Center (LICA) – Comprehensive Allergy Center
Department of Dermatology, Venerology and Allergology
Universität Leipzig
Philipp-Rosenthal-Straße 23
04103 Leipzig
Tel.: 0341-9718690
Fax.: 0341-9718609
regina.treudler@uniklinik-leipzig.de

Atopic dermatitis (AD) was recently reported to be associated with multiple non-atopic comorbidities [1-4], especially of autoimmune or cardiovascular type. This co-occurrence was related to several immune mechanism of AD being shared with other immune-mediated diseases [2], as well as to chronic inflammation and life style factors [5].

We aimed to cross-sectionally determine any association of AD and selected comorbidities in subjects from the LIFE-Adult-Study (Leipzig Research Centre for Civilization Diseases) [6] which was approved by the ethics board of the University of Leipzig. It comprises an age and gender stratified

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jdv.14495

This article is protected by copyright. All rights reserved.

random sample of 10.000 residents of the city of Leipzig, Germany, with a target age range from 40 to 79 years and a small group of 18-39 years old. The assessment program took place between August 2011 and November 2014 and comprised physical and medical examinations, computer-assisted personal interviews, computer- or paper-based self-administered questionnaires, and laboratory analyses [6]. A follow-up investigation will start in autumn 2017.

Subjects with and without (controls) history of physician diagnosed AD (ever) were compared with regard to age, sex, body mass index (BMI), socioeconomic status (SES), history of physician diagnosed allergic rhinitis/asthma, any autoimmune (AID), rheumatic (RD), inflammatory bowel (IBD) or coronary artery disease (CAD), myocardial infarction (MI), smoking or stroke by using Mann-Whitney-, Chi-square- or Fisher's exact test.

Out of 372/9481 subjects (3.8%) with AD, 33.6% also suffered from allergic rhinitis and 19.9% from asthma. This was significantly ($p < 0.0001$) increased compared with controls (13.1% and 7.6%, respectively). Also, subjects with AD were more often female, had younger age and reported significantly more frequently history of AID and RD than controls. Other parameters investigated turned out not to be significantly different (table 1).

To evaluate any associations of AD with non-atopic comorbidities a multiple logistic regression analysis was used. Compared with controls, patients with AD were more frequently female ($p = 0.044$), were of younger age ($p \leq 0.001$) and had higher risk of associated AID ($p = 0.045$). All other parameters showed comparable frequencies in both groups (table 2). Analysis of any association of AD with IBD did not show any significant results in uni- and multivariable analysis (data not shown).

Until today, different datasets and study designs from different countries led to partly divergent findings with regard to AD and non-atopic comorbidities: AD was shown to be a risk factor for the development of RD, IBD [9], systemic lupus erythematosus [10] and – as in our observation – with AID like vitiligo and alopecia areata [11].

With regard to cardiovascular diseases (CVD) our data are in accordance with those from Standl et al. [8] from Germany, who neither could not find an increased risk for MI or stroke in patients with AD nor did those patients have any increased genetic risk factors for CVD [8].

In contrast, AD patients from the US were reported to have significantly higher odds of CAD, angina pectoris, heart attack, stroke, and/or peripheral vascular disease [9] which was suspected to be related to poor health behaviors increasing the CVD risk [5]. In a recent Danish study, patients with AD also had an increased CVD risk profile compared with the general population [6].

One plus of our study are informations upon BMI and SES which are usually lacking in health insurance data [8]. Limitations are diagnoses only relying on self-reports, lack of information about the severity of AD and the possibility that patients with severe comorbidities might not have followed the invitation to participate.

In summary, we confirmed an overall increased risk for AID in subjects with history of AD but could not find any significant independent association of AD with CVD.

Conflicts of interest: none

Legend to the tables

Table 1

Comparison between subjects with and without (controls) history of physician diagnosed atopic dermatitis with regard to sex, age, body mass index, smoking, socioeconomic status and selected non-atopic comorbidities.

Table 2

Results of logistic regression with regard to different dependent variables. Data from 4340 subjects were included, of whom 3.9% (n=168) had history of physician diagnosed atopic dermatitis (independent variable)

References:

1. Brunner PM. Silverberg JI. Guttman-Yassky E. Paller AS. Kabashima K. Amagai M. Luger TA. Deleuran M. Werfel T. Eyerich K. Stingl G; Councilors of the International Eczema Council. Increasing Comorbidities Suggest that Atopic Dermatitis Is a Systemic Disorder. *J Invest Dermatol*. 2017 Jan;137(1):18-25.
2. Radtke MA. Schäfer I. Glaeske G. Jacobi A. Augustin M. Prevalence and comorbidities in adults with psoriasis compared to atopic eczema. *J Eur Acad Dermatol Venereol*. 2017 Jan;31(1):151-157.
3. Egeberg A. Andersen YM. Gislason GH. Skov L. Thyssen JP. Prevalence of comorbidity and associated risk factors in adults with atopic dermatitis. *Allergy*. 2016 Nov 16.
4. Egeberg A. Skov L. Andersen YM. Mallbris L. Gislason GH. Silverberg JI. Wu JJ. Thyssen JP. Ten-year mortality is increased after hospitalization for atopic dermatitis compared with

the general population. but reduced compared with psoriasis. *J Am Acad Dermatol.* 2017 Jan;76(1):98-105.

5. Silverberg JI. Greenland P. Eczema and cardiovascular risk factors in 2 US adult population studies. *J Allergy Clin Immunol.* 2015 Mar;135(3):721-8.e6. doi: 10.1016/j.jaci.2014.11.023. Epub 2015 Jan 8.
6. Loeffler M. Engel C. Ahnert P. Alfermann D. Arelin K. Baber R. Beutner F. Binder H. Brähler E. Burkhardt R. Ceglarek U. Enzenbach C. Fuchs M. Glaesmer H. Girlich F. Hagendorff A. Häntzsch M. Hegerl U. Henger S. Hensch T. Hinz A. Holzendorf V. Husser D. Kersting A. Kiel A. Kirsten T. Kratzsch J. Krohn K. Luck T. Melzer S. Netto J. Nüchter M. Raschpichler M. Rauscher FG. Riedel-Heller SG. Sander C. Scholz M. Schönknecht P. Schroeter ML. Simon JC. Speer R. Stäker J. Stein R. Stöbel-Richter Y. Stumvoll M. Tarnok A. Teren A. Teupser D. Then FS. Tönjes A. Treudler R. Villringer A. Weissgerber A. Wiedemann P. Zachariae S. Wirkner K. Thiery J. The LIFE-Adult-Study: objectives and design of a population-based cohort study with 10,000 deeply phenotyped adults in Germany. *BMC Public Health.* 2015 Jul 22;15:691.
7. Standl M. Tesch F. Baurecht H. Rodríguez E. Müller-Nurasyid M. Gieger C. Peters A. Wang-Sattler R. Prehn C. Adamski J. Kronenberg F. Schulz H. Koletzko S. Schikowski T. von Berg A. Lehmann I. Berdel D. Heinrich J. Schmitt J. Weidinger S. Association of Atopic Dermatitis with Cardiovascular Risk Factors and Diseases. *J Invest Dermatol.* 2017 May;137(5):1074-1081
8. Silverberg JI. Association between adult atopic dermatitis, cardiovascular disease, and increased heart attacks in three population-based studies. *Allergy.* 2015 Oct;70(10):1300-8
9. Schmitt J. Schwarz K. Baurecht H. Hotze M. Fölster-Holst R. Rodríguez E. Lee YA. Franke A. Degenhardt F. Lieb W. Gieger C. Kabesch M. Nöthen MM. Irvine AD. McLean WH. Deckert S. Stephan V. Schwarz P. Aringer M. Novak N. Weidinger S. Atopic dermatitis is associated with an increased risk for rheumatoid arthritis and inflammatory bowel disease, and a decreased risk for type 1 diabetes. *J Allergy Clin Immunol.* 2016 Jan;137(1):130-6.
10. Wu LC. Hwang CY. Chung PI. Hua TC. Chen YD. Chu SY. Lee DD. Chang YT. Wang WJ. Liu HN. Chen CC. Autoimmune disease comorbidities in patients with atopic dermatitis: a nationwide case-control study in Taiwan. *Pediatr Allergy Immunol.* 2014 Oct;25(6):586-92
11. Mohan GC. Silverberg JI. Association of vitiligo and alopecia areata with atopic dermatitis: A systematic review and meta-analysis. *JAMA Dermatol.* 2015 May;151(5):522-8

Table 1

	History of AD	Controls	Valuable data n	P value *
	372 (3.8%)	9109	9481	
Sex female	212 (57.0 %)	4725 (51.9 %)	9481	0.053
Age (Range) in years	52 (21-79)	58 (19-80)	9481	<0.0001
Body mass index <25 kg/m ² ≥25 - <30 kg/m ² ≥30 kg/m ²	37.4 % 39.2 % 23.4 %	34.5 % 40.4 % 25.1 %	9453	0.490
smoking status never former current	48.9 % 29.1 % 22.0 %	49.0 % 29.7 % 21.3 %	9007	0.940
Socioeconomic status low middle high	20.1 % 60.1 % 19.8 %	18.1 % 58.6 % 23.2 %	9465	0.240
Autoimmune disease	5.4%	3.2%	9481	0.017
Rheumatic Disease	7.8%	5.0%	9481	0.016
Coronary artery disease	3.3%	3.5%	9244	0.850
Myocardial infarction	1.1%	2.6%	9386	0.076
Stroke	1.9%	2.2%	9405	0.707
Inflammatory bowel disease	1.9%	1.1%	9481	0.076

*Significance: p value < 0.05

Table 2

	Odds ratio	95% confidence interval		Significance Level*
		Lower value	Upper value	P value
Age	1.0**	1.0	1.0	<0.001
Sex	1.3	1.0	1.6	0.044
Rheumatic disease	1.4	0.9	2.2	0.135
Autoimmune disease	1.6	1.0	2.7	0.045
Myocardial infarction	0.5	0.2	1.6	0.268
Stroke	1.3	0.6	2.9	0.469
Coronary artery disease	1.6	0.8	3.0	0.185
SES low vs. middle	0.8	0.6	1.2	0.303
SES. middle vs. high	0.8	0.7	1.1	0.213
BMI <25 vs. 25 kg/m ² - <30 kg/m ²	0.9	0.7	1.2	0.560
BMI 25 - <30 kg/m ² vs . ≥30 kg/m ²	1.0	0.8	1.4	0.932
Smoking: never vs. previous	0.9	0.7	1.2	0.492
Smoking: previous vs. current	1.2	0.9	1.7	0.197

*Significance: p value < 0.05

**OR for age was 0.973 with 95% CI (0.964; 0.982), meaning AD prevalence decreases with age