


## ORIGINAL ARTICLE

# Depression, anxiety and quality of life in subjects with atopic eczema in a population-based cross-sectional study in Germany

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## Abstract

**Background** Atopic eczema (AE) may be associated with several mental health problems. In Germany, existing data from selected patient cohorts may lead to misestimation of the problem.

**Objectives** We aimed to cross-sectionally determine associations of AE with depression, anxiety, quality of life (QoL) and social interactions in subjects from the population-based LIFE-Adult-Study.

**Methods** Subjects underwent standardized interviews (medical history) and answered standardized questionnaires [Centre of Epidemiologic studies-Depression scale (CES-D), Generalized Anxiety Disorder (GAD-7), Lubben Social Network Scale (LSNS), Short Form Health Survey (SF-8)]. We compared data from subjects with AE with those from subjects with selected other chronic/disabling diseases (cardiovascular, diabetes, cancer) and adjusted for selected sociodemographic parameters. Multivariate binary logistic regression was used for categorical variables, linear regression for continuous variables.

**Results** Out of 9104 adults included (57% female, median age 54 years), 372 (4.1%) had a history of AE. Compared with controls, subjects with AE showed higher scores for depressive symptoms (9.3% vs. 6.3%;  $P < 0.001$ ) and anxiety (8.4% vs. 5.6%,  $P < 0.001$ ). Odds ratio (OR) was 1.5 [CI 1.0; 2.3] ( $P = 0.031$ ) for depression, which was comparable to OR in patients with a history of cancer (OR 1.6 [1–2.3],  $P = 0.001$ ). OR for anxiety in AE was 1.5 [1.0; 2.2],  $P < 0.049$ , which was slightly higher than in diabetes mellitus (OR 1.2) and stroke (OR 1.4). Other than in diabetes and/or stroke, we did not find a significant association between AE and social isolation. QoL scores were lower in AE than in controls (mean 46.9 vs. 48.0,  $P < 0.001$  for physical and 50.6 vs. 52.5,  $P < 0.001$  for mental components).

**Conclusions** Subjects with AE showed higher values for depression and anxiety as well as lower QoL scores compared to controls. With regard to depression, odds in AE and cancer were hardly different. Medical care of AE patients should therefore include mental health evaluation and treatment if indicated.

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## Conflicts of interest

RT has received lecture fees and honoraria for advisory boards as well as a non-restricted scientific grant from Sanofi Genzyme, Berlin, Germany, lecture fees and honoraria for advisory boards from Novartis, Erlangen, Germany, Takeda, Berlin, Germany, and ALK-Abello, Hamburg, Germany, and congress support from Takeda, Berlin, Germany. JCS has received lecture fees and honoraria for advisory boards as well as a non-restricted scientific grant from Sanofi Genzyme, Berlin, Germany, lecture fees and honoraria for advisory boards from Novartis, Erlangen, Germany and congress support from ALK-Abello, Hamburg, Germany. PK has received travel grants from ALK-Abello and Sanofi Genzyme. All other authors have no COI to declare.

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## Introduction

Atopic eczema (AE, atopic dermatitis) is an inflammatory skin disease that affects between 10% and 35% of children while the prevalence in adults is estimated to be around 3–5% in the general population.<sup>1–5</sup>

Over the last years, there was increasing awareness on non-atopic comorbidities in patients with AE.<sup>2</sup> Data on comorbidities were shown to differ between geographical regions, that is with regard to cardiovascular comorbidities registered in US but not in European subjects with AE.<sup>5–7</sup> These differences may be due to divergent diagnostic criteria, severity and history of the disease,<sup>6</sup> therapeutic options available in different countries, age of patients, lifestyle factors (i.e. nutrition, smoking) and/or other comorbidities in study groups.<sup>5</sup>

While depression and anxiety are known to be associated with several somatic diseases, especially those of chronic and/or disabling character,<sup>7–9</sup> psychosocial comorbidities in AE only recently gained strong attention.<sup>10</sup> AE was reported to be associated with increased odds of clinical depression, depressive symptoms, antidepressant use and suicidality.<sup>11</sup> Eczema was also associated with social isolation in a sample of 54 adults from the United Kingdom.<sup>12</sup>

The majority of data on mental health or psychosocial burden in AE comes from the United States and from Asian adult populations<sup>13–25</sup>; only a few data exist from continental Europe<sup>1,26–28</sup> and even less from Germany. Currently available data on adults with AE from Germany rely on selected cohorts of patients,<sup>1,28–31</sup> including health insurance data.<sup>29</sup> 22.5% of 181 subjects with AE, sampled from a psychodermatological department, from dermatological practices and from an internet forum in Germany, reported on mental disorders.<sup>32</sup> When compared to controls, significantly more of these patients reached values indicating depression (8.8% vs. 1.6%;  $P = 0.049$ ) and anxiety (26.0% vs. 12.5%;  $P = 0.026$ ) and suicidal ideation was high (21.3%).<sup>32</sup> Data from the TREAT registry (TREATment of ATopic eczema), investigating 241 patients in Germany, revealed significantly reduced quality of life (QoL).<sup>30</sup> Another paper investigated health insurance data, showing about 15% of subjects with AE being also diagnosed (ICD-10 code) with depression (prevalence rate 1.41 [CI 1.38; 1.45]).<sup>29</sup> Only recently, reports from a large European study on 1189 adult patients with AE showed scores indicating depression in 10% of patients, and 55% reported to suffer from effects of AE on health-related QoL.<sup>1</sup> About 15% of them were from Germany.<sup>1</sup> Suicidal ideation was reported to occur as a consequence of depression and anxiety.<sup>13,32</sup>

Available data from Germany are limited by the fact that they only rely on selected patient cohorts. These patients either went to see their medical doctor (health insurance data) and/or suffered from moderate-to-severe disease within clinical trials. As the severity of the skin disease is expected to interfere with the

prevalence of mental health and psychosocial burden, existing data might lead to misestimation of the problem.

Our study investigated associations between AE and depression, anxiety, QoL as well as social isolation in subjects from the cross-sectional population-based Leipzig Research Centre for Civilization Diseases (LIFE) cohort, Germany. The study included a random sample of residents.<sup>33</sup> Subjects with AE were investigated for signs of depression, anxiety, reduced health-related QoL and/or social isolation. For data adjustment, we included sociodemographic parameters and selected somatic diseases possibly being associated with main mental health and/or social outcome parameters.

Data are expected to be closer to the real life than in previous observations as the study also includes subjects (i) who suffer from milder forms of AE, (ii) who do not see a medical doctor and/or who seek help in alternative medicine and/or (iii) who are not a member of a compulsory health insurance company. In parallel, we had the opportunity to investigate any associations of main outcome parameters with sociodemographic factors and to compare the degree of mental health abnormalities in AE with those in other selected diseases.

## Methods

### Study design

Data analysis was based on the LIFE-Health Adult Study, a large cross-sectional population-based study investigating prevalence, early onset markers, genetic predispositions and the role of lifestyle factors of major civilization diseases in inhabitants of the city of Leipzig in Germany. The LIFE-Health Adult Study was conducted conforming to the principles embodied in the Declaration of Helsinki and was approved by the ethics committee of the Medical Faculty of the University of Leipzig (263/09-ff). The details of the study are described elsewhere.<sup>33</sup> Briefly, the residents' registry office provided a random age- and sex-stratified sample of residents of the city of Leipzig aged 40–79 years old. In addition, a subsample of 400 individuals aged 18–39 years old was recruited. Recruitment was carried out until the intended age- and sex-stratified sample size, and a total of 10 000 participants were reached. The total response rate was 33%. The only exclusion criterion was being pregnant. All participants signed written consent prior to participation. The assessments took place between August 2011 and November 2014 at the LIFE study centre located on the premises of the University Hospital of Leipzig. Every participant followed a standardized study protocol that was administered by trained study assistants and monitored by experienced scientists.

### Assessment programme

The assessment programme comprised, among others, several physical examinations, computer-assisted personal interviews

and computer- or paper-based self-administered questionnaires. Within the present investigation, we included sociodemographic data [age, sex, socioeconomic status (SES)], smoking history and body mass index (BMI) as well as data from the general medical history with regard to selected physician diagnosed diseases of chronic and/or disabling character (myocardial infarction, stroke, diabetes mellitus and cancer), which also may show an association with depression, anxiety, QoL or social isolation.

For investigation of main psychosocial outcome parameters, validated questionnaires were used. Data of subjects with history of physician diagnosed AE were compared to those without history of AE and also to those with myocardial infarction, stroke, diabetes mellitus and cancer. Only subjects in whom data of all relevant items were fully available were included.

### Depression

The Centre for Epidemiologic Studies-Depression Scale (CES-D) is a commonly used 20-item self-rating scale designed to measure depressive symptomatology,<sup>34</sup> which was shown to be a reliable and valid instrument for detecting depressive symptoms.<sup>35,36</sup> Subjects reported on their symptoms by using a 4-grade scale ranging from 0 (rarely/none) to 3 (frequently). Maximum sum score is 60, the recall period is 1 week. In Germany, a sum score of  $\geq 23$  is regarded as cut-off of value for the presence of depression.<sup>35,36</sup>

### Anxiety

We used a German version of the established self-report questionnaire Generalized Anxiety Disorder-7 (GAD-7)<sup>37,38</sup> to screen for anxiety. The GAD-7 (covering symptoms of generalized anxiety disorder, panic disorder, social anxiety disorder and post-traumatic stress disorder) consists of seven items asking patients how often, during the last 4 weeks, they were bothered by each symptom. The answer options were 'not at all', 'several days', 'more than half the days' and 'nearly every day' scored from 0 to 3 points. Maximum score is 21. A total score of  $\geq 10$  indicate the presence of an anxiety symptomatology.

### Social isolation

Social isolation was assessed via the short form of the Lubben Social Network Scale (LSNS-6),<sup>39</sup> an 6-item questionnaire measuring social engagement including family and friends. Scores reach from 0 (none) to 5 (nine or more relatives/friends). Maximum score is 30. A higher score indicates more social engagement. Individuals who scored 11 or less are considered to be socially isolated.<sup>39</sup>

### Quality of life

Quality of life was measured with the Short Form Health Survey-8 (SF-8).<sup>40</sup> It is a short form of the commonly used SF-36, which measures eight dimensions of health-related QoL. The

recall period is 4 weeks. This questionnaire comprises eight-one-item dimensions: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. Two factors of second order can be calculated: the Physical Component Score (PCS) and the Mental Component Score (MCS). Interpretation relies on comparison with norm based scores,<sup>41</sup> whereas higher values indicate better physical/mental health.

### Statistics

Mann-Whitney *U*-test was used for continuous variables, chi-squared or Fisher's exact test for categorical data. We used models adjusted for selected parameters [age, sex, SES, BMI, history of myocardial infarction (MI), stroke, diabetes mellitus, cancer] to investigate associations of depression, anxiety, social network, QoL and AE. Multivariate binary logistic regression was used for categorical variables CES-D, LSNS-6 and GAD-7. Since there are no cut-off scores for the SF-8 scales, linear regression was used for the continuous variables of the SF-8.

### Results

Of the 10 000 participants, 9481 (94.8%) were included in this investigation. 372 (4.1%) had a history of AE. Patients with AE were significantly younger than those without AE. There were no significant differences between AE and non-AE subjects with regard to BMI, smoking status, SES or history of myocardial infarction, stroke, diabetes mellitus and cancer (Table 1).

### Association between depression and AE

Univariate analysis showed CES-D scores indicating depression to be significantly increased in subjects with AE (Table 1). Binary logistic regression showed odds ratio (OR) 1.5 [Confidence interval 1.0; 2.3],  $P = 0.031$ , in subjects with AE, being comparable to odds in patients with a history of cancer (OR 1.6 [1–2.3],  $P = 0.001$ , Table 2). Significantly increased OR for depression was also noted in older patients, females, subjects with low/middle SES as well as in subjects with history of stroke or diabetes (Table 2).

### Association between anxiety and AE

In subjects with AE, there was a significant increase in GAD-7 values indicating anxiety (8.4 vs. 5.6,  $P < 0.001$ ; Table 1). Logistic binary regression showed OR 1.5 [1.0; 2.2],  $P < 0.049$  for anxiety in AE which was decreased compared with subjects with history of cancer (OR 1.9) but slightly increased compared with subjects with history of diabetes mellitus (OR 1.2) and stroke (OR 1.4; Table 2). Older age, female sex, low/middle SES and history of cancer, but not history of myocardial infarction or stroke, were also significantly associated with anxiety (Table 2).

**Table 1** Baseline data, comorbidities and univariate analysis of Centre for Epidemiologic Studies-Depression Scale, Generalized Anxiety Disorder Scale and Lubben Social Network Scale from subjects with Atopic Eczema and from Controls

	Atopic eczema	Controls	P value
n	372 (4.1%)	9109 (95.9%)	
Sex female	57.0%	51.9%	0.053
Age			
Median (Range) in years	52 (21–79)	58 (19–80)	<b>&lt;0.0001</b>
Body mass index			
<25 kg/m <sup>2</sup>	37.4%	34.5%	
≥25 to < 30 kg/m <sup>2</sup>	39.2%	40.4%	0.490
≥30 kg/m <sup>2</sup>	23.4%	25.1%	
Smoking			
Never	48.9%	49.0%	
Former	29.1%	29.7%	0.940
Current	22.0%	21.3%	
Socioeconomic status			
Low	20.1%	18.1%	
Middle	60.1%	58.6%	0.240
High	19.8%	23.2%	
Myocardial infarction	1.1%	2.6%	0.076
Stroke	1.9%	2.2%	0.707
Diabetes mellitus	9.3%	10.7%	0.411
Cancer	9.5%	10.4%	0.559
Depression			
CES-D ≥ 23	9.3%	6.3%	<b>0.027</b>
Anxiety			
GAD-7 ≥ 10	8.4%	5.6%	<b>0.029</b>
Social isolation			
LSNS ≤ 11	13.6%	17.7%	<b>0.047</b>

Significant P values are marked in bold. CES-D, Centre of Epidemiologic studies-Depression scale; GAD-7, generalized anxiety disorder 7; LSNS, Lubben Social Network Scale.

**Association between social isolation and AE**

Lubben Social Network Scale-6 score indicated significantly less often social isolation in subjects with AE (13.6% with values below 11) compared with controls (17.7%, P < 0.001). Even after adjustment of LSNS-6 scores with age, SES and other selected parameters, AE was not shown to be associated with social isolation. In contrast, increased age, lower/middle SES and history of diabetes mellitus, stroke or cancer showed significantly increased odds for social isolation (Table 2).

**QoL in subjects with AE**

Physical Component Score and MCS were significantly lower in subjects with AE compared with controls (mean 46.9 vs. 48.0 and 50.6 vs. 52.5, P < 0.001, respectively). Linear regression showed regression coefficients of -1.7 (PCS; P < 0.001) and -1.5 (MCS; P < 0.001) which points out reduced QoL with regard to physical and mental parameters in subjects with AE (Table 3).

**Table 2** Regression of depression, anxiety and social isolation on sociodemographic and clinical variables (binary logistic regression)

	Depression		Anxiety		Social isolation		P value					
	Odds ratio	95% confidence interval		Odds ratio	95% confidence interval							
		Lower value	Upper value		Lower value	Upper value						
Atopic eczema	1.5	1.0	2.3	1.5	1.0	2.2	0.049	0.9	0.6	1.2	0.331	
Age	0.976	0.968	0.984	<b>&lt;0.001</b>	0.981	0.974	0.989	<b>&lt;0.001</b>	1.022	1.017	1.027	<b>&lt;0.001</b>
Sex female	2.8	2.3	3.5	<b>&lt;0.001</b>	1.9	1.6	2.3	<b>&lt;0.001</b>	0.7	0.7	0.8	<b>&lt;0.001</b>
BMI ≥ 25 kg/m <sup>2</sup>	1.2	1.0	1.5	0.095	1.1	0.9	1.4	0.268	1.0	0.9	1.2	0.581
SES (low vs. middle)	2.9	2.1	3.9	<b>&lt;0.001</b>	2.4	1.8	2.3	<b>&lt;0.001</b>	2.1	1.8	2.3	<b>&lt;0.001</b>
SES (middle vs. high)	1.4	1.0	1.8	0.024	1.3	1.0	1.7	<b>0.038</b>	1.8	1.5	2.1	<b>&lt;0.001</b>
Myocardial infarction†	1.6	0.9	2.9	0.088	1.2	0.6	2.1	0.650	1.0	0.7	1.3	0.818
Stroke†	2.2	1.3	3.6	<b>0.003</b>	1.4	0.8	2.5	0.251	1.5	1.1	2.1	<b>0.011</b>
Diabetes mellitus†	1.3	1.0	1.8	<b>0.048</b>	1.2	0.9	1.7	0.158	1.2	1.0	1.4	<b>0.048</b>
Cancer†	1.6	1.0	2.3	<b>0.001</b>	1.9	1.4	2.4	<b>0.001</b>	0.9	0.8	1.1	0.323

†Self-reported. Significant P values are marked in bold. BMI, body mass index; SES, socioeconomic status.

**Table 3** Associations between Atopic eczema and quality of life

		Atopic eczema	Controls	P value
PCS	Mean ( $\pm$ SD)	46.9 $\pm$ 8.7	48.0 $\pm$ 8.5	<b>0.010</b>
	Median (quartile)	48.4 (42.0, 53.8)	49.9 (43.1, 54.8)	
MCS	Mean ( $\pm$ SD)	50.6 $\pm$ 8.8	52.5 $\pm$ 8.2	<b>&lt;0.001</b>
	Median (quartile)	52.5 (46.6, 57.4)	55.1 (49.5, 57.8)	

Significant *P* values are marked in bold.

MCS, mental component score of Short Form Health Survey-8; PCS, physical component score of Short Form Health Survey-8; SD, standard deviation.

## Discussion

A total of 4.2% of subjects from the LIFE cohort reported on history of physician diagnosed AE, which was within a comparable range of previous data or estimations.<sup>1,2,5,42</sup> However, in a Swedish population-based questionnaire study with 34 313 participants the self-reported prevalence of AE was as high as 14% and adults with AE had an increased risk for severe depression and anxiety.<sup>26</sup>

Depression may have long-term consequences including reduced QoL, risk of suicide, increased rates of hospital admission, increased risk for chronic medical conditions and stigmatization.<sup>43</sup> A lower stress resilience, as recently shown in Swedish men who underwent military conscription,<sup>44</sup> may be one favoring factor for depression in AE.

Within LIFE cohort, significantly more of subjects with AE than controls reached scores indicating depression. The frequency in our study group (9.3%) was within the range of other studies, reporting on prevalences between 9% and 15% of depressive disorders in subjects with AE.<sup>13,28,29,32</sup>

In our study, the odds for depression in subjects with AE were remarkably close to values from subjects with history of cancer. A recently published meta-analysis showed an association of AE with depression with pooled odd ratios of 2.19.<sup>13</sup> We suppose that the lower odds in our study (OR 1.5) are due to broader spectrum of disease severity in our subjects, while studies included within the meta-analysis were mainly those with moderate–severe type of the disease.<sup>13</sup>

Scores indicating anxiety in our study again were higher in adults with AE than in controls (8.4% vs. 5.6%). In selected groups from Germany, even up to 26% of AE patients showed scores indicating anxiety.<sup>32</sup> In our study group, the odds for anxiety in AE were not as high as in subjects with history of cancer (OR 1.5 vs. 1.9) but higher than in those with history of myocardial infarction, stroke or diabetes mellitus. Pooled odds ratios from international studies for anxiety in AE were 2.19.<sup>13</sup> It was shown that increased anxiety scores were associated with AE severity,<sup>45</sup> which, however, could not be assessed in our study.

Overall, one has to recognize that abnormal values in depression and anxiety questionnaires do not necessarily mean ‘psychiatric’ conditions, but rather psychosomatic involvement in the disease process.

We also examined social relationships, which may be complicated for individuals with skin diseases<sup>28</sup> and in depression.<sup>46</sup> Within the LIFE cohort, in univariate analysis, subjects with AE showed significantly less social isolation than controls (13.6% vs. 17.7%). This may be explained by the fact that subjects with AE tended to be more often female and were significantly younger than controls. These two factors may have reduced the risk for social isolation as, within the whole LIFE cohort, a population-weighted prevalence of social isolation was reported to be higher in men, older and less educated population groups.<sup>47</sup> Overall, depression and anxiety do not seem to negatively impact on social relationships in subjects with AE from LIFE cohort. This confirms a recent observation of partnership satisfaction not being severely impaired in subjects with AE.<sup>48</sup>

Finally, when investigating QoL, we noted an association between AE and physical (i.e. physical functioning, physical role, bodily pain, general health, vitality) as well as mental aspects (social functioning, emotional role, mental health).

A strength of our investigation was the large set of general population data, which makes the results more generalizable than in previous reports from selected groups from Germany. Also, the LIFE cohort allowed to compare and adjust data from subjects with AE with those from subjects with selected other diseases. We want to point out that depression in AE reaches odds being comparable to those measured in subjects with history of cancer. A limiting factor in our study was the lack of information on severity of the diseases. Also, univariate analysis has to be interpreted with caution as there are significant age differences between subjects with AE and controls.

Overall, there is increasing evidence that AE is more than a skin disease and may be associated with several, non-atopic comorbidities. One might speculate that itch, skin pain and sleep disturbances in combination with typical AE skin lesions, cause psychologic distress which may result in development of depression, anxiety<sup>13,49</sup> and/or impaired QoL.<sup>50,51</sup> There is still debate whether the depressive and anxious symptoms result from physical discomfort and psychosocial burden of the skin disease or whether these disorders are based on shared inflammatory pathomechanisms.<sup>10,52,53</sup>

Further investigations are needed to investigate therapeutical effects of new or upcoming treatment options for AE on mental health in AE patients.<sup>54</sup> Trial results from phase 3 dupilumab, a monoclonal antibody against interleukin 4, showed that the proportion of patients with moderate-to-severe AE who reported depression and anxiety was significantly reduced in the active arm compared to the placebo arm.<sup>55</sup> There may also be an effect of antidepressants on skin signs and symptoms in AE.<sup>56,57</sup>

In conclusion, our data show that AE in adults is associated with depression, anxiety and reduced QoL in a population-based cohort in Germany. When treating patients with AE, clinicians should be aware of potentially associated mental health

abnormalities. It remains to be investigated if these conditions rely on similar inflammatory processes as in the skin or if they arise secondary, that is from itching, sleeplessness and other stress factors.

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### Author contributions

RT, SZ and JCS generated the concept of the present investigation; RT, JCS, SZ, SRH, AH, HG and ML contributed to concept of LIFE study; RT, SZ, SRH and AH contributed to acquisition; and RT, SZ, PK, SRH, AZ, SR and AH contributed to analysis and interpretation of data. All authors revised and approved the final manuscript.

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