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ORIGINAL ARTICLE

Itch, sleep loss, depressive symptoms, fatigue, and productivity loss in patients with moderate-to-severe atopic dermatitis: Analyses of TREATgermany registry data

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Summary

Background: TREATgermany is a multicenter registry including patients with moderate-to-severe atopic dermatitis (AD) from currently 74 study centers (university clinics, hospitals and practices) in Germany. As of August 31, 2021, 1,230 adult patients were enrolled.

Methods: In TREATgermany, patients and physicians fill in questionnaires pertaining to symptoms, disease severity, quality of life, depressiveness, and fatigue. In particular, limitations in work performance are assessed using the Work Limitations Questionnaire (WLQ). To assess associations between occupational performance/work limitations and symptoms, correlations and regression models were calculated.

Results: The examined sample of 228 employed patients reported an average of 6% at-work productivity loss within the past two weeks prior to enrolment in the registry. The WLQ productivity loss score was moderately associated with itch ($r = 0.32$) and sleep loss ($r = 0.39$) and strongly associated with depressive symptoms ($r = 0.68$) and fatigue ($r = 0.60$).

Conclusions: The analyses of the registry data show that moderate-to-severe atopic dermatitis has a negative impact on the work productivity of the patients. The analyses further point out the relevant associations between work productiv-

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ity, depressive symptoms, and fatigue highlighting the disease burden caused by the psychological components of AD.

KEYWORDS
Atopic dermatitis, productivity loss, registry, work limitations

INTRODUCTION

Atopic dermatitis (AD) affects up to 20% of children or adolescents and 5% of adults worldwide, making it one of the most common inflammatory diseases.[1,2] The prevalence in the German population was estimated at about 2% by a longitudinal data analysis of the statutory health insurance system.[3]

Itch, sleep loss, and depressive symptoms are known symptoms associated with AD.[1,4] It is conceivable that these symptoms may be further associated with limitations in work activities, including loss of productivity.[5]

Severe itch is a disease-defining symptom of AD that can severely disturb sleep, leading to a reduced quality of life. Patients describe difficulties falling and staying asleep, resulting in reduced sleep time and quality.[6] This lack of nightly rest can impair the daytime attention and negatively impact performance at school or work. The affected patients may even develop depressive symptoms or a clinically manifested depression. It is well known that patients with AD have a higher risk of developing psychological disorders such as anxiety and depression.[7–13]

As the pathophysiologic understanding of AD has improved and new therapeutic options targeting specific cytokines, receptors, or the intracellular signaling have become available, targeted therapy for itch may also improve.[9,10] If itch can be reduced then patients' sleep quality, quality of life, and depressive symptoms may also improve significantly.

With the approval of new systemic therapies for patients with moderate-to-severe AD, rapid improvement in itching, sleep loss, quality of life, and depressive symptoms compared to placebo has already been demonstrated for dupilumab, baricitinib, tralokinumab, upadacitinib, and abrocitinib.[2,14–17] Other potential treatments are currently being studied or in approval procedures in Europe and Germany.[15] In addition to the registration studies, routine care data on efficacy and safety are needed to evaluate the therapies in clinical practice, to confirm the results and to identify further research needs.

The TREATgermany registry is one of the largest AD registries for patients with moderate-to-severe AD in Europe.[18] This analysis investigated associations between occupational performance/work limitations (WLQ) and itch (Numerical Rating Scale (NRS) itch), sleep loss (NRS sleep), and depressive symptoms for a subgroup of gainfully employed patients with moderate-to-severe AD at baseline.

METHODS

Study design, registry population and data collection

TREATgermany is a non-interventional, prospective cohort study collecting routine data on diagnosis and treatment of patients with moderate-to-severe AD.[19] TREATgermany as a multicentre registry includes patients from more than 70 study centres (university clinics, hospitals and practices) in Germany. As of August 31, 2021, 1,230 adult patients were enrolled in the registry. Inclusion criteria are the diagnosis of AD according to the criteria of the UK Working Party,[20,21] an oSCORAD of more than 20[13,22–25] and/or systemic anti-inflammatory therapy for AD currently or within the past 24 months.

The TREATgermany protocol was submitted to all responsible ethics committees and received a positive vote (No. EK TUD 118032016). TREATgermany is registered in the clinicaltrials.gov database (NCT03057860) and the ENCePP Resource Database (EMA).

Measuring instruments

To assess the physician and patient reported disease severity, the following instruments were used: *"Eczema Area and Severity Index" (EASI),*[26–28] *"Patient-Oriented Eczema Measure" (POEM),*[26,29–32] and *"Dermatology Life Quality Index" (DLQI)*[33–36] as recommended by the "Harmonizing Outcome Measures for Eczema" Initiative (HOME-Initiative)[37,38] as well as *"Objective Scoring for Atopic Dermatitis" (oSCORAD),*[22–24,37] *"Investigator's Global Assessment" (IGA),*[40] and *"Patients' Global Assessment" (PGA)*. Other questionnaires utilized are the *"Work Limitations Questionnaire" (WLQ),*[41–43] *"Center for Epidemiologic Studies Depression Scale" (CES-D),*[44–46] and *"Fatigue Severity Scale" (FSS).*[47,48] Itch and sleep loss in the last three days are rated on an 11-step NRS ranging from 0 (no itch/sleep loss) to 10 (most severe itching imaginable/an unbearable sleep loss). Asthma bronchiale, allergic rhinitis and physician-reported depression are the concomitant diseases of interest for this analysis.

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The scores were categorized into severity strata as follows: EASI and oSCORAD according to *Chopra et al,*[49] FSS according to *Pfeffer A.*[50] CES-D according to *Radloff L.S.*[46] and the other scores according to their scoring manuals.

Work Limitations Questionnaire (WLQ)

The WLQ measures limitations at the workplace within the past two weeks.[42,43] Altogether four dimensions of productivity at the workplace are reported: time management, physical tasks, mental-interpersonal tasks, output tasks. Three scales use a frequency of "difficulty" response scale (i.e., time management, mental-interpersonal tasks and output tasks) and one scale uses a frequency of "able to" response scale (i.e., the physical tasks scale). A greater score indicates more self-reported difficulties at work. Computation of the scale/domain scores involves averaging over the items and transformation of the resulting average score to a score with a range from 0 to 100. The time management, mental-interpersonal tasks, output tasks, and physical tasks scale scores describe the percentage of time patients were limited in performing work activities within the past 2 weeks.[51] The WLQ index is computed by multiplying each transformed domain score by a set weight and summing the weighted average domain scores. The following formula converts the WLQ index into the WLQ At-Work Productivity Loss Score: 1 – exp(- WLQ Index). The result is multiplied by 100 to express the score as a percentage of at-work productivity loss. Note that all four scale scores are required to generate the WLQ Productivity Loss Score. The maximum attainable value for the WLQ index (with all scales at 100) is 28.6% and the maximum attainable WLQ productivity loss is 24.9%.[43,51]

Statistical analyses

Associations between occupational performance/work limitations (WLQ) and itching (NRS itch), sleep loss (NRS sleep), fatigue (FSS), and depressive symptoms (CES-D) were analyzed. Correlations and regression models involving the WLQ index/WLQ productivity loss score were analyzed for the set of patients for whom the WLQ physical task subscale score, in addition to the other three subscale scores, was available. Correlations considering the WLQ subscales individually were computed as well. When Pearson correlations were calculated a coefficient $r > 0.1$ was interpreted as a weak correlation, $r > 0.3$ as moderate correlation and $r > 0.5$ as strong correlation.[52] A line derived by local polynomial regression fit is included in the correlation plots. In case of missing data no substitution or imputation was performed. The analyses were carried out using R version 3.6.3.[53]

The following predictors were included in the multiple linear regression models for the WLQ productivity loss score: age, sex, disease severity (EASI, oSCORAD), quality of life (DLQI), systemic therapy (yes/no at enrolment), depressiveness (CES-D score), itching (NRS itch), sleep loss (NRS sleep), fatigue (FSS score), and comorbidities (asthma bronchiale, allergic rhinitis, depression). Since some of those predictors are expected to be highly correlated with each other (e.g., EASI and oSCORAD, DLQI and EASI and oSCORAD) a variable selection approach (i.e., stepwise selection based on the Akaike information criterion [AIC]) was utilized in identifying the final model. The AIC compares the quality of statistical models for a given set of data. It considers both goodness of fit (via the likelihood function) and the number of estimated parameters (by penalizing for the number of predictors).

RESULTS

This retrospective analysis used cross-sectional data obtained for 1,230 TREATgermany registry patients at the baseline visit. 927 (76.4%) of those reported that they were gainfully employed which triggered the WLQ questionnaire for them.

The WLQ was initially used in a reduced form for TREATgermany (the subscale "physical tasks" was not included), therefore a high number of missing values was observed in the total WLQ index. 228 patients out of 927 completed all subscales including "physical tasks" and hence have a value for total WLQ index. Therefore, the following analyses are primarily based on the set of n = 228. The sociodemographic data and information about clinical signs and patient reported outcomes at the baseline visit are presented in Table 1, Table 2 and Table 3. In the studied group (n = 228), 40.4% were women (n = 92). 73.3% of the patients worked full time (35 or more hours per week) and 19.5% part time (n = 43). The remaining 16 patients (7.2%) were trainees/retrainees and no patient was on leave (parental leave or similar). More than half were married/partnered (67.4%, n = 149). According to the EASI 76.4% (n = 171) were moderately to severely affected by AD, according to the oSCORAD that percentage was 83.6% (n = 189). Additionally, more than half (55.5%, n = 126) reported very large/extremely large effects of disease on their quality of life (DLQI).

In comparison to the subgroup of 228 patients with a total WLQ index, we also summarized the baseline values of the 927 gainfully employed patients as well as all 1,230 patients included in the registry at that time. No clinically relevant differences were found in clinical signs (EASI, oSCORAD), symptoms (NRS itch, NRS sleep), fatigue (FSS score), depressive symptoms (CES-D score), sex, marital status, employment status, and smoking status. The selected subgroup (n = 228) was slightly younger than the comparison groups, with a mean age of 36.8 (SD 12.7) years (n = 927: mean age 41.9 (SD 14.4); n = 1,230: mean age 40.7 [SD 14.7]). Furthermore, with regard to the socioeconomic parameters, the proportions with qualification for

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TABLE 1 Baseline characteristics for the 228 employed patients for which the WLQ work productivity loss score could be computed, in comparison to the 927 gainfully employed patients and all 1,230 patients included in the TREATgermany registry (differences in frequencies were due to missing values).

Sociodemographic		**n = 228**	**n = 927**	**n = 1,230**
		n (%)	***n (%)***	***n (%)***
Sex	Male	136 (59.6)	554 (59.8)	707 (57.5)
	Female	92 (40.4)	373 (40.2)	522 (42.4)
		228	*927*	*1,229*
Age, mean [SD]		36.6 [12.7]	39.8 [12.4]	40.7 [14.7]
Employment status	Full time (35 h and more)	162 (73.3)	665 (73.6)	681 (72.8)
	Part time or by hour	43 (19.5)	192 (21.3)	201 (21.5)
	Leave of absence (parental leave or similar)	0 (0.0)	7 (0.8)	9 (1.0)
	Trainee, retrainee	16 (7.2)	39 (4.3)	44 (4.7)
		221	*903*	*935 of 940 employed*
Marital status	Partnership (unmarried)	72 (32.6)	272 (29.6)	322 (26.7)
	Married	77 (34.8)	350 (38.1)	443 (36.7)
	Divorced	10 (4.5)	35 (3.8)	52 (4.3)
	Widowed	0 (0.0)	3 (0.3)	14 (1.2)
	Single	62 (28.1)	259 (28.2)	376 (31.2)
		221	*919*	*1,207*
Level of education	Without graduation	2 (0.9)	7 (0.8)	14 (1.2)
	Certificate of secondary education	17 (7.6)	87 (9.4)	143 (11.8)
	General certificate of secondary education	70 (31.1)	339 (36.7)	433 (35.7)
	General qualification for university entrance	70 (31.1)	247 (26.7)	327 (26.9)
	Graduate degree	66 (29.3)	244 (26.4)	297 (24.5)
		225	*924*	*1,214*
Smoking status	Smoker	49 (21.8)	227 (24.6)	303 (24.9)
	Former smoker (not smoked for less than ten years)	33 (14.7)	136 (14.7)	165 (13.6)
	Former smoker (not smoked for at least ten years)	19 (8.4)	94 (10.2)	131 (10.8)
	Never smoked	124 (55.1)	467 (50.5)	616 (50.7)
		225	*924*	*1,215*
Comorbidities				
Asthma bronchiale*	Present	94 (41.4)	409 (44.2)	528 (43.0)
	Not present	124 (54.6)	495 (53.5)	674 (54.9)
	Unclear	9 (4.0)	22 (2.4)	26 (2.1)
		227	*926*	*1,228*
Allergic rhinitis*	Present	130 (57.5)	602 (65.0)	765 (62.2)
	Not present	85 (37.4)	296 (32.0)	419 (34.1)
	Unclear	12 (5.3)	28 (3.0)	45 (3.7)
		227	*926*	*1,229*
Depression*	Present	13 (5.8)	70 (7.6)	111 (9.0)
	Not present	211 (93.0)	844 (91.1)	1,092 (88.9)
	Unclear	3 (1.3)	12 (1.3)	26 (2.1)
		227	*926*	*1,229*

*Diagnosed by a physician
Abbr.: SD, standard deviation

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TABLE 2 Distribution of systemic therapies and physician reported symptom severity at baseline for the 228 employed patients for which the WLQ work productivity loss score could be computed, in comparison to the 927 gainfully employed patients and all 1,230 patients included in the TREATgermany registry (differences in frequencies were due to missing values).

Systemic therapies	**n = 228** *n (%)*	**n = 927** *n (%)*	**n = 1,230** *n (%)*
Systemic therapies, all	64 (28.1)	274 (29.6)	357 (29.0)
Cyclosporine A	5 (2.2)	42 (4.5)	61 (5.0)
Dupilumab	48 (21.1)	148 (16.0)	192 (15.6)
Baricitinib	5 (2.2)	11 (1.2)	11 (0.9)
Tralokinumab	0 (0.0)	9 (1.0)	11 (0.9)
Upadacitinib	1 (0.4)	1 (0.1)	1 (0.1)
Systemic Glucocorticosteroide	3 (1.3)	18 (1.9)	24 (2.0)
Methotrexat	0 (0.0)	7 (0.8)	7 (0.6)
Azathioprine	0 (0.0)	3 (0.3)	5 (0.4)
Mycophenolate	0 (0.0)	1 (0.1)	1 (0.1)
Other systemic therapies	1 (0.4)	27 (2.9)	30 (2.4)
Multiple systemic therapies	1 (0.4)	7 (0.8)	14 (1.1)
No systemic therapy	164 (71.9)	653 (70.4)	873 (71.0)
Physician reported symptom severity			
EASI, mean [SD]	15.5 [12.2]	15.6 [12.7]	16.1 [12.9]
EASI, categories			
Clear (0)	6 (2.7)	14 (1.5)	19 (1.6)
Mild (0 to <6)	47 (21.0)	215 (23.3)	263 (21.6)
Moderate (6 to <23)	124 (55.4)	479 (52.0)	647 (53.1)
Severe (23 to 72)	47 (21.0)	213 (23.1)	290 (23.8)
	224	*921*	*1,219*
oSCORAD, mean [SD]	39.6 [16.4]	40.0 [16.5]	40.5 [16.3]
oSCORAD, categories			
Clear (0 to <8)	8 (3.5)	29 (3.1)	34 (2.8)
Mild (8 to <24)	29 (12.8)	117 (12.7)	147 (12.0)
Moderate (24 to <38)	69 (30.5)	282 (30.5)	354 (28.9)
Severe (38 to 83)	120 (53.1)	496 (53.7)	690 (56.3)
	226	*924*	*1,215*
IGA, categories			
Clear	4 (1.8)	13 (1.4)	20 (1.6)
Almost clear	20 (8.8)	73 (7.9)	81 (6.6)
Mild	28 (12.4)	131 (14.2)	170 (13.9)
Moderate	94 (41.6)	365 (39.5)	478 (39.0)
Severe	64 (28.3)	268 (29.0)	376 (30.7)
Very severe	16 (7.1)	75 (8.1)	100 (8.2)
	226	*925*	*1,225*

Abbr.: SD, standard deviation

university entrance or graduate degree differed slightly: 60.4% (n = 136) for the studied group of n = 228, 53.1% (n = 491) for the group of 927 patients, and 51.4% (n = 624) for the 1,230 patients. There were slightly more very large/extremely affected patients with regard to their quality of life (DLQI) in the group of n = 228 compared to the two larger sets of patients. However, there were no clinically relevant differences between the groups considered.

Work Limitations Questionnaire (WLQ)

The 228 employed patients reported on average a 6% at-work productivity loss within the past two weeks prior enrolment in the TREATgermany registry relative to a healthy benchmark sample. Considering the individual scale scores, the patients reported time management limitations 25.7% of the time at work, mental-interpersonal tasks limitations 20.0% of the time, output tasks limitations 21.2% of the time, and physical tasks restrictions 20.3% of the time at work within the past two weeks.

Associations of itch, sleep loss, depressive symptoms and productivity loss

The WLQ productivity loss score (n = 228) was moderately associated with itch (NRS itch/past three days, r = 0.32) and sleep loss (NRS sleep/past three days, r = 0.39). Strong associations were observed between the WLQ productivity loss score and depressive symptoms (CES-D score, r = 0.68) as well as fatigue (mean FSS score, r = 0.60) (Figure 1). The WLQ subscales time management, mental-interpersonal tasks, output tasks and physical tasks showed the same trends as the overall productivity loss score for all correlations examined.

Regarding correlations between scores other than the WLQ, a strong association was observed between itch and sleep loss (NRS itch/sleep in the last three days, r = 0.70) as well as between depressive symptoms (CES-D score) and fatigue (FSS score, r = 0.63). Moderate associations were found between itch and depressive symptoms (r = 0.40), fatigue and itch (r = 0.41), depressive symptoms and sleep loss (r = 0.47), and sleep loss and fatigue (r = 0.40) (Figure 2).

Regression analyses

The final regression model (selected via the Akaike information criterion) with the WLQ productivity loss score as dependent variable has statistically significant coefficients at alpha = 0.05 for depressive symptoms (CES-D score beta = 0.26, p < 0.001), fatigue (FSS score beta = 0.79, p < 0.001), clinical signs (EASI beta = 0.10, p = 0.002 and oSCORAD beta = -0.07, p = 0.003), sex (beta(female) = -1.5, p = 0.001) and quality of life (DLQI beta = 0.15, p = 0.003).

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TABLE 3 Patient reported symptom severity at baseline for the 228 employed patients for which the WLQ work productivity loss score could be computed, in comparison to the 927 gainfully employed patients and all 1,230 patients included in the TREATgermany registry (differences in frequencies were due to missing values).

Patient reported symptom severity	**n = 228**	**n = 927**	**n = 1,230**
	n (%)	***n (%)***	***n (%)***
PGA, categories			
Clear	3 (1.3)	23 (2.5)	28 (2.3)
Almost clear	18 (8.0)	77 (8.3)	99 (8.2)
Mild	43 (19.0)	194 (21.0)	245 (20.2)
Moderate	59 (26.1)	271 (29.3)	347 (28.6)
Severe	77 (34.1)	271 (29.3)	359 (29.6)
Very severe	26 (11.5)	88 (9.5)	136 (11.2)
	226	*924*	*1,214*
POEM score, mean [SD]	17.1 [7.5]	16.7 [7.5]	16.7 [7.6]
POEM score, categories			
Clear or almost clear (0 to 2)	9 (3.9)	46 (5.0)	61 (5.0)
Mild eczema (3 to 7)	23 (10.1)	81 (8.7)	110 (9.0)
Moderate eczema (8 to 16)	65 (28.5)	297 (32.0)	379 (31.1)
Severe eczema (17 to 24)	88 (38.5)	349 (37.6)	457 (37.5)
Very severe eczema (25 to 28)	43 (18.9)	154 (16.6)	211 (17.3)
	228	*927*	*1,218*
Itch last three days (NRS), mean [SD]	6.0 [2.7]	5.6 [2.8]	5.7 [2.8]
Sleep loss last three days (NRS), mean [SD]	4.8 [3.6]	4.4 [3.4]	4.6 [3.4]
	228	*926*	*1,216*
Fatigue			
FSS score, mean [SD]	3.6 [1.6]	3.6 [1.5]	3.7 [1.6]
FSS score, categories			
≤4	134 (58.8)	571 (61.8)	730 (60.1)
Increased >4 to 5	43 (18.9)	156 (16.9)	199 (16.4)
High >5	51 (22.4)	197 (21.3)	286 (23.5)
	228	*924*	*1,215*
Quality of Life			
DLQI, mean [SD]	11.7 [7.4]	11.5 [7.7]	11.8 [7.8]
DLQI, categories			
No effect at all on patients' life (0 to 1)	21 (9.3)	83 (9.0)	104 (8.6)
Small effect on patient's life (2 to 5)	39 (17.2)	165 (17.8)	213 (17.5)
Moderate effect on patients' life (6 to 10)	41 (18.1)	208 (22.5)	272 (22.4)
Very large effect on patients' life (11 to 20)	91 (40.1)	332 (35.9)	429 (35.3)
Extremely large effects on patients' life (21 to 30)	35 (15.4)	138 (14.9)	198 (16.3)
	227	*926*	*1,216*
Depressive symptoms			
CES-D score, mean [SD]	15.4 [9.2]	14.1 [9.4]	15.1 [10.2]
CES-D score, categories			
No to mild depressive symptomatology (0 to 15)	132 (57.9)	598 (64.5)	733 (60.2)
Moderate depressive symptomatology (16 to 21)	39 (17.1)	130 (14.0)	185 (15.2)
Severe depressive symptomatology (22 to 60)	57 (25.0)	199 (21.5)	300 (24.6)
	228	*927*	*1,218*

Abbr.: SD, standard deviation

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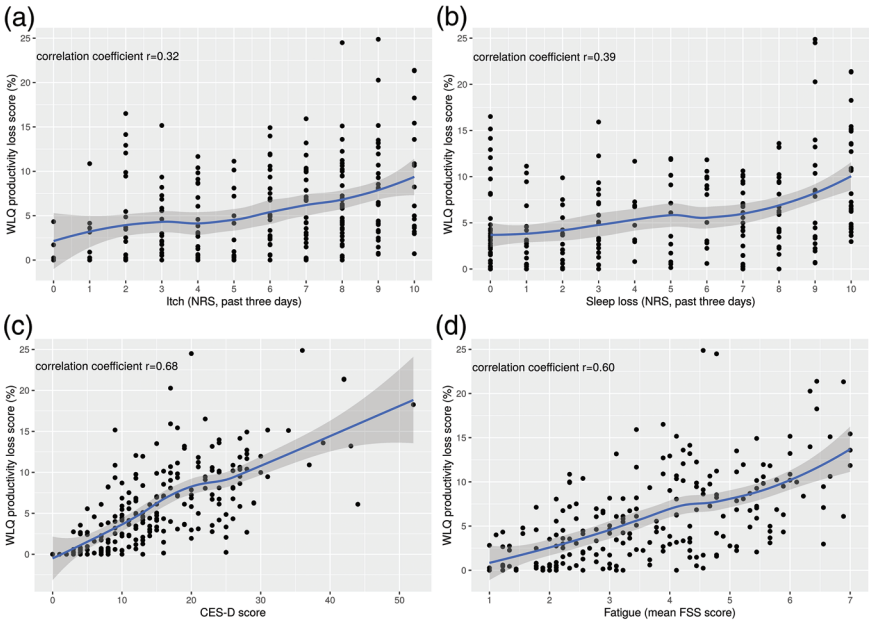

FIGURE 1 Associations of Work Limitations Questionnaire (WLQ) productivity loss score with itch (last three days, NRS), sleep loss (last three days, NRS), depressive symptoms (CES-D) and fatigue (FSS) (Scatterplots, n = 228).

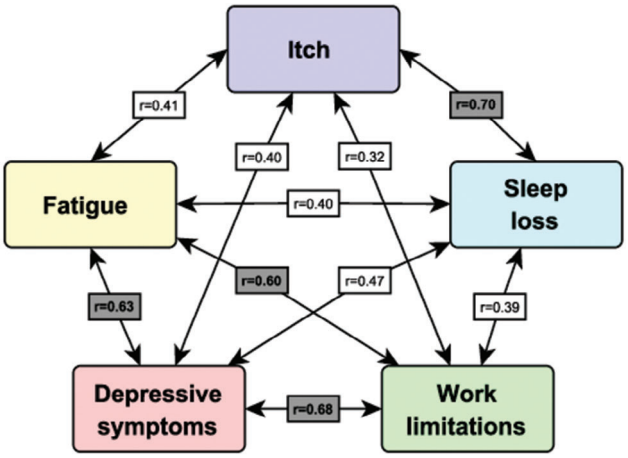

FIGURE 2 Associations of Work Limitations Questionnaire (WLQ) productivity loss score with itch (last three days, NRS), sleep loss (last three days, NRS), depressive symptoms (CES-D) and fatigue (FSS) (Pearson correlations, n = 228, gray fields: strong correlations, white fields: moderate correlations).

Itch (beta = -0.19, p = 0.11) was retained in the final model because it decreased the AIC value, despite the coefficient not being statistically significant. The estimate for the intercept is 0.30. It should be noted that the variable 'sleep loss' does not appear in the final model. The model explains 56% of the variability in the WLQ productivity loss score.

DISCUSSION

The TREATgermany subpopulation of 228 working patients exhibited the known subjective moderate-to-severe AD symptoms including itch, sleep loss, fatigue, limited quality of life and depressive symptoms at baseline visit. Further, patients reported marked limitations in work productivity, which in turn were strongly associated with depressive symptoms and fatigue.

Chronic itch is a disease-defining AD symptom, contributing to sleep loss in the affected patients.[9,54] Itch (NRS/past three days) was previously reported by 97% of TREATgermany patients at baseline with 45% reporting NRS-scores equal to or higher than 7.[55,56] The severe itching and sleep loss can lead to a reduced quality of life and lack of physical and mental recovery, which may further provoke depressive symptoms, anxiety, clinical depression, and suicidal thoughts.[57–64] In particular, the interaction of these symptoms may lead to a further exacerbation.[65] In addition, it seems plausible that more severe itching and more pronounced sleep loss increase this negative interaction. Thus, AD patients are prone to suffer from chronic fatigue.[66] These expected strong associations between itching and sleep loss were also observed in the studied patients. In addition, moderate to strong associations between itching, fatigue, depressive symptoms and work limitations were observed. Subsequently, limitations in everyday life could be triggered, for example at work or school.[5] The interaction of the patients' symptoms and disease burden may affect their work productivity.[67,68]

The TREATgermany patients included in the analyses showed this complex symptomatology with all symptoms associated with each other and additionally with respect to work limitations. Regarding the work limitations, the patients reported an average of 6% at-work productivity loss within the past two weeks (n = 228). Compared to a healthy sample incorporated as the reference group in the scoring of the WLQ by the developer, this is a substantial limitation with respect to a maximum attainable productivity loss score of 24.9%.[43,51] All four individual scales showed limitations for at least 20% of the time at work on a scale of 0 to 100, respectively. Thus, the affected AD patients reported comparably high disease-related limitations for time

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management skills, mental-interpersonal tasks, output tasks and physical tasks that resulted in a substantial loss of productivity. A similar loss of productivity was reported in patients with chronic depression (WLQ productivity loss score 6.6%).[69] The same study also showed that patients with major depression were significantly more impaired (WLQ productivity loss score of 11.4%).[69] In conclusion, it is apparent that patients affected by AD with severe symptoms are also more restricted at work compared to healthy persons.

The results confirm the strong association between itch and sleep loss, but further show a strong association between work limitations, fatigue, and depressive symptoms. The interplay of itching, sleep loss, fatigue, depressive symptoms, and work limitations is evident as the correlation analyses consistently showed at least moderate correlations.

The bivariate correlations as discussed above are confirmed and substantiated by the multivariate regression analysis. In the final model with predictors selected according to the Akaike information criterion, depressive symptoms (CES-D score) and fatigue (FSS score) also proved to be important factors influencing productivity loss. The indicated directions of the relationships are mostly intuitive (e.g., the more depressive symptoms the larger the impact on work productivity, likewise for fatigue). The same applies to the dermatological quality of life (DLQI): the lower the quality of life, the higher the productivity loss in the multivariate overall analysis. The associations of clinical severity of AD with productivity loss appear not consistent for the two measurement instruments used, EASI and oSCORAD, given the other predictors in the model. The model estimates that an increase in the EASI by one unit would lead to a 0.1 increase in the WLQ productivity loss score, whereas an increase by one unit in the oSCORAD would decrease the WLQ productivity loss score by 0.07. That estimated decrease appears counterintuitive. Potential explanations are that both clinical severity scores measure different aspects[70] and/or that the overlap in the information contained in the set of predictors (in particular EASI and oSCORAD) included in the final model leaves the oSCORAD coefficient with this small downward correction in the estimated value of the WLQ productivity loss score.

The analyses of registry data shows that moderate to severe atopic dermatitis has a significant negative health economic impact and is associated with a mean productivity loss of about 6%. They complement previous findings on the health economic relevance of this skin disease in that they show a possibility for estimating indirect costs in employed patients with moderate to severe atopic dermatitis.[68,71]

Limitations

Because the WLQ was initially used in a reduced form for TREATgermany (the subscale "physical tasks" was not included), there was a large number of missing values in the total WLQ productivity loss score. The total registry population and all patients with the incomplete questionnaires were considered for comparison to our sample to investigate potential bias. No clinically relevant differences between groups were found.

A potential limitation for the correlational analyses are the differing recall periods of the instruments: WLQ (past two weeks), NRS itch/sleep loss (past three days), and CES-D/FSS (past week).

CONCLUSIONS

The moderately to severely affected AD patients in TREATgermany exhibited moderate to strong correlations between the known AD symptoms previously reported and additionally reported a substantial loss of productivity at work. Moreover, strong associations were found between work productivity, depressive symptoms, and fatigue, highlighting the psychological component of AD. Since the pathophysiological relationship of the AD symptomatology of itch, sleep loss, fatigue, depressive symptoms, and work limitations has not been conclusively investigated, further research is needed as to which symptoms are associated or even trigger the others.

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CONFLICT OF INTEREST

S Abraham received lecture and/or consulting fees from Novartis, Sanofi, Celgene, Beiersdorf, UCB, Amgen, LEO Pharma and AbbVie.

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All other authors declare no conflicts of interest.

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REFERENCES

1. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. *Lancet*. 2020;396:345-360.
2. Siegels D, Heratizadeh A, Abraham S, et al. Systemic treatments in the management of atopic dermatitis: A systematic review and meta-analysis. *Allergy*. 2021;76:1053-1076.
3. Zietze HA, Cabral C, Theobald K, et al. Epidemiology and treatment of adult patients with atopic dermatitis : Analysis of longitudinal data of the statutory health insurance scheme. *Hautarzt*. 2021;72:963-974.
4. Gilaberte Y, Pérez-Gilaberte JB, Poblador-Plou B, et al. Prevalence and comorbidity of atopic dermatitis in children: a large-scale population study based on real-world data. *J Clin Med*. 2020;9:1632.
5. Stingeni L, Belloni Fortina A, Baiardini I, et al. Atopic dermatitis and patient perspectives: insights of bullying at school and career discrimination at work. *J Asthma Allergy* 2021;14:919-928.
6. Talamonti M, Galluzzo M, Silvaggio D, et al. Quality of life and psychological impact in patients with atopic dermatitis. *J Clin Med*. 2021;10:1298.
7. Bruin-Weller M, Pink AE, Patrizi A, et al. Disease burden and treatment history among adults with atopic dermatitis receiving systemic therapy: baseline characteristics of participants on the EUROSTAD prospective observational study. *J Dermatol Treat*. 2021;32:164-173.
8. Helmert C, Haufe E, Heinrich L, et al. Atopic dermatitis and depressive symptoms. Results of the German national AD Registry TREATgermany. *J Eur Acad Dermatol Venereol*. 2021;36:e279-e282.
9. Legat FJ. Itch in Atopic dermatitis – what is new? *Front Med* 2021;8:644-760.
10. Bonnekoh H, Butze M, Metz M. Characterization of the effects on pruritus by novel treatments for atopic dermatitis. *J Dtsch Dermatol Ges*. 2022;20:150-156.
11. Paller A, Jaworski JC, Simpson EL, et al. Major comorbidities of atopic dermatitis: beyond allergic disorders. *Am J Clin Dermatol*. 2018;19:821-838.
12. Werfel T, Heratizadeh A, Aberer W, et al. S2k guideline on diagnosis and treatment of atopic dermatitis-short version. *J Dtsch Dermatol Ges*. 2016;14:92-106.
13. Werfel T, Heratizadeh A, Aberer W, et al. Update "Systemic treatment of atopic dermatitis" of the S2k-guideline on atopic dermatitis. *J Dtsch Dermatol Ges*. 2021;19:151-168.
14. Worm M, Francuzik W, Kraft M, Alexiou A. Modern therapies in atopic dermatitis: biologics and small molecule drugs. *J Dtsch Dermatol Ges*. 2020;18:1085-1092.
15. Zhou S, Qi F, Gong Y, et al. Biological therapies for atopic dermatitis: a systematic review. *Dermatology*. 2021;237:542-552.
16. Sawangjit R, Dilokthornsakul P, Lloyd-Lavery A, et al. Systemic treatments for eczema: a network meta-analysis. *Cochrane Database Syst Rev*. 2020;9:Cd013206.
17. Drucker AM, Ellis AG, Bohdanowicz M, et al. Systemic immunomodulatory treatments for patients with atopic dermatitis: a systematic review and network meta-analysis. *JAMA Dermatol*. 2020;156:659-667.
18. Bosma AL, Musters AH, Bloem M, et al. Mapping exercise and status update of eight established registries within the TREatment of ATopic eczema (TREAT) Registry Taskforce. *J Eur Acad Dermatol Venereol*. 2022;00:1-14.
19. Heratizadeh A, Haufe E, Stölzl D, et al. Baseline characteristics, disease severity and treatment history of patients with atopic dermatitis included in the German AD Registry TREATgermany. *J Eur Acad Dermatol Venereol*. 2020;34:1263-1272.
20. Williams HC, Burney PG, Strachan D, Hay RJ. The U.K. working party's diagnostic criteria for atopic dermatitis. II. Observer variation of clinical diagnosis and signs of atopic dermatitis. *Br J Dermatol* 1994;131:397-405.
21. Williams HC, Burney PG, Hay RJ, et al. The U.K. working party's diagnostic criteria for atopic dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. *Br J Dermatol*. 1994;131:383-396.
22. Kunz B, Oranje AP, Labrèze L, et al. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology*. 1997;195:10-19.
23. Oranje AP, Glazenburg EJ, Wolkerstorfer A, de Waard-van der Spek FB. Practical issues on interpretation of scoring atopic dermatitis: the SCORAD index, objective SCORAD and the three-item severity score. *Br J Dermatol*. 2007;157:645-648.
24. Schmitt J, Langan S, Deckert S, et al. Assessment of clinical signs of atopic dermatitis: a systematic review and recommendation. *J Allergy Clin Immunol*. 2013;132:1337-1347.
25. Werfel T, Aberer W, Ahrens F, et al. Leitlinie Neurodermitis [atopisches Ekzem; atopische Dermatitis]. *J Dtsch Dermatol Ges*. 2016;14:e1-75.
26. Grinich EE, Schmitt J, Kuester D, et al. Standardized reporting of the Eczema Area and Severity Index (EASI) and the Patient-Oriented Eczema Measure (POEM): a recommendation by the Harmonising Outcome Measures for Eczema (HOME) Initiative. *Br J Dermatol*. 2018;179:540-541.

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27. Hanifin JM, Thurston M, Omoto M, et al. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp Dermatol*. 2001;10:11-18.
28. Tofte S, Graeber M, Cherill R, et al. Eczema area and severity index (EASI): A new tool to evaluate atopic dermatitis. *J Eur Acad Dermatol Venereol*. 1998;11:197.
29. Spuls PI, Gerbens LAA, Simpson E, et al. Patient-Oriented Eczema Measure (POEM), a core instrument to measure symptoms in clinical trials: a Harmonising Outcome Measures for Eczema (HOME) statement. *Br J Dermatol*. 2017;176:979-984.
30. Charman CR, Venn AJ, Ravenscroft JC, Williams HC. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. *Br J Dermatol*. 2013;169:1326-1332.
31. Schram ME, Spuls PI, Leeflang MM, et al. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. *Allergy*. 2012;67:99-106.
32. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. *Arch Dermatol* 2004;140:1513-1519.
33. Chalmers JR, Simpson E, Apfelbacher CJ, et al. Report from the fourth international consensus meeting to harmonize core outcome measures for atopic eczema/dermatitis clinical trials (HOME initiative). *Br J Dermatol*. 2016;175:69-79.
34. Lewis V, Finlay AY. 10 years experience of the Dermatology Life Quality Index (DLQI). *J Invest Dermatol Symp Proc*. 2004;9:169-180.
35. Khilji FA, Gonzalez M, Finlay AY. Clinical meaning of change in Dermatology Life Quality Index scores. *Br J Dermatol*. 2002;147: 50.
36. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)-a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19:210-216.
37. Schmitt J, Apfelbacher C, Spuls PI, et al. The Harmonizing Outcome Measures for Eczema (HOME) roadmap: a methodological framework to develop core sets of outcome measurements in dermatology. *J Invest Dermatol*. 2015;135:24-30.
38. Schmitt J, Spuls PI, Thomas KS, et al. The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. *J Allergy Clin Immunol*. 2014;134:800-807.
39. Stalder J, Taieb A, Atherton D, et al. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. *Dermatology*. 1993;186:23-31.
40. Futamura M, Leshem YA, Thomas KS, et al. A systematic review of Investigator Global Assessment (IGA) in atopic dermatitis (AD) trials: Many options, no standards. *J Am Acad Dermatol*. 2016;74: 288-294.
41. Friedli T, Villiger PM, Gantschnig BE. Workability for persons with chronic diseases. A systematic review of validity and utility of assessments in German language. *IJHP*. 2018;5:72-90.
42. Lerner D, Reed JI, Massarotti E, et al. The Work Limitations Questionnaire's validity and reliability among patients with osteoarthritis. *J Clin Epidemiol*. 2002;55:197-208.
43. Lerner D, Amick BC, 3rd, Rogers WH, et al. The Work Limitations Questionnaire. *Med Care*. 2001;39:72-85.
44. Rodríguez MR, Nuevo R, Chatterji S, Ayuso-Mateos JL. Definitions and factors associated with subthreshold depressive conditions: a systematic review. *BMC psychiatry*. 2012;12:1-7.
45. Thombs BD, Hudson M, Schieir O, et al. Reliability and validity of the center for epidemiologic studies depression scale in patients with systemic sclerosis. *Arthritis Rheum*. 2008;59:438-443.
46. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Appl Psychol Meas*. 1977;1:385-401.
47. Valko PO, Bassetti CL, Bloch KE, et al. Validation of the fatigue severity scale in a Swiss cohort. *Sleep*. 2008;31:1601-1607.
48. Reske D, Pukrop R, Scheinig K, et al. Measuring fatigue in patients with multiple sclerosis with standardized methods in German speaking areas. *Fortschritte Neurol Psychiatr*. 2006;74:497-502.
49. Chopra R, Vakharia PP, Sacotte R, et al. Severity strata for Eczema Area and Severity Index (EASI), modified EASI, Scoring Atopic Dermatitis (SCORAD), objective SCORAD, Atopic Dermatitis Severity Index and body surface area in adolescents and adults with atopic dermatitis. *Br J Dermatol*. 2017;177:1316-1321.
50. Pfeffer A. Einsatz bei Erschöpfung. *Physiopraxis* 2008;6:42-43.
51. Lerner D, Amick BC, 3rd, Lee JC, et al. Relationship of employee-reported work limitations to work productivity. *Med Care*. 2003;41:649-659.
52. Cohen J. *Statistical power analysis for the behavioral sciences*. 2. Edition. Erlbaum, 1988.
53. R Core Team (2020). *R: A language and environment for statistical computing. R Foundation for Statistical Computing*, Vienna, Austria. Available from: https://www.R-project.org/. [Last accessed April 25, 2023]
54. Weidinger S, Beck LA, Bieber T, et al. Atopic dermatitis. *Nat Rev Dis Primers*. 2018;4:1.
55. Weisshaar E, Bentz P, Apfelbacher C, et al. Itching in atopic dermatitis: patient- and physician-reported outcomes in the German atopic dermatitis registry TREATgermany. *Acta Derm-Venereo.l* 2023;103:adv00854.
56. Weisshaar E, Bentz P, Haufe E, et al. Itching and treatments in Atopic Dermatitis (AD): Results from the German AD Registry TREATgermany. *Br J Dermatol*. 2022;188:430-432.
57. Kage P, Simon JC, Treudler R. Atopische Dermatitis und psychosoziale Komorbidität. *J Dtsch Dermatol Ges*. 2020;18(2):93-102.
58. Kage P, Zarnowski J, Simon J-C, Treudler R. Atopic dermatitis and psychosocial comorbidities – What's new? *Allergologie select*. 2020;4:86-96.
59. Li JC, Fishbein A, Singam V, et al. Sleep disturbance and sleep-related impairment in adults with atopic dermatitis: A cross-sectional survey-based study. *Dermatitis*. 2018;29:270.
60. Marron S, Cebrian-Rodriguez J, Alcalde-Herrero V, et al. Psychosocial impact of atopic dermatitis in adults: a qualitative study. *Actas Dermo-Sifilogr*. 2020;111:513-517.
61. Nicholas MN, Gooderham MJ. Atopic dermatitis, depression, and suicidality. *J Cutan Med Surg*. 2017;21:237-242.
62. Ring J, Zink A, Arents BWM, et al. Atopic eczema: burden of disease and individual suffering - results from a large EU study in adults. *J Eur Acad Dermatol Venereol*. 2019;33:1331-1340.
63. Rønnstad ATM, Halling-Overgaard AS, Hamann CR, et al. Association of atopic dermatitis with depression, anxiety, and suicidal ideation in children and adults: A systematic review and meta-analysis. *J Am Acad Dermatol*. 2018;79:448-456.e430.
64. Thyssen JP, Hamann CR, Linneberg A, et al. Atopic dermatitis is associated with anxiety, depression, and suicidal ideation, but not with psychiatric hospitalization or suicide. *Allergy*. 2018;73: 214-220.
65. Silverberg JI. Comorbidities and the impact of atopic dermatitis. *Ann Allergy Asthma Immunol*. 2019;123:144-151.
66. Silverberg JI. Associations between atopic dermatitis and other disorders. *F1000Res*. 2018;7:303.
67. Ariëns LFM, van Nimwegen KJM, Shams M, et al. Economic burden of adult patients with moderate to severe atopic dermatitis indicated for systemic treatment. *Acta Derm-Venereol*. 2019;99:762-768.
68. Haufe E, Abraham S, Heratizadeh A, et al. Verminderte berufliche Leistungsfähigkeit und Lebensqualität bei Patienten mit moderater bis schwerer Neurodermitis – Ergebnisse aus dem Deutschen Neurodermitisregister TREATgermany. *Hautarzt*. 2018;69: 815-824.
69. Lerner D, Adler DA, Chang H, et al. The clinical and occupational correlates of work productivity loss among employed patients with depression. *J Occup Environ Med*. 2004;46:S46-55.

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70. Chopra R, Vakharia PP, Sacotte R, et al. Relationship between EASI and SCORAD severity assessments for atopic dermatitis. *J Allergy Clin Immunol*. 2017;140:1708-1710.e1701.
71. Haufe E, Abraham S, Heratizadeh A, et al. Verminderte berufliche Leistungsfähigkeit und Lebensqualität bei Patient/innen mit moderater bis schwerer Neurodermitis – Ergebnisse aus dem Deutschen Neurodermitisregister TREATgermany. *Allergologie*. 2019;42:266-274.

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