

Disease activity and stress are linked in a subpopulation of chronic spontaneous urticaria patients

To the Editor,

Chronic spontaneous urticaria (CSU) is a condition characterized by the development of itchy wheals (hives), angioedema, or both, with reoccurring symptoms for more than 6 weeks. CSU is often fluctuating and unpredictable in its course,¹ which is a great burden to the patients, especially when no underlying causes are found. Psychosomatic and psychiatric comorbidities are often reported and an association between CSU and stress was proposed, in which psychosocial strain may initiate a vicious cycle of stress-induced worsening of the disease causing a higher psychosocial burden, which in turn amplifies the stress influence on the disease.²⁻⁵

At present, systematic studies in support of a stress- and disease-relationship in CSU are largely missing, rendering the stress-contribution to CSU unclear. Comprehensive studies of the association between stress and urticaria are needed to answers to the following questions: Do CSU patients report relevant stress levels? Are stress levels higher when no underlying cause can be identified (CSU- CSU+ patients)? Do CSU- patients suffer from higher disease activity compared to CSU+ patients? And finally, are stress levels in CSU- and CSU+ patients linked to disease activity? To address these knowledge gaps, we studied stress perception and resilience and their association with disease severity, assessed by use of the urticaria activity

score (UAS7) in an explorative manner. In addition, selected routinely assessed immune outcomes that have been discussed to play a role in stress effects in urticaria (IgE, basophils, eosinophils) were studied.

The exploratory study was approved by the ethics committee of the Charité - Universitätsmedizin Berlin, Germany. A total of 303 CSU patients that provided informed written consent were assessed for mental distress, resilience, and immune outcomes (ELISA, complete blood count), and then, for potentially relevant underlying conditions, the results of which were disclosed to the patient after completion of the comprehensive workup of the etiologic tests by a team of experienced dermatologists (EMP, MM, MM). The scales "worries," "tension," and "demands" of the Perceived Stress Questionnaire (PSQ) were used to assess stress perception, "joy" and the Self-efficacy, Optimism and Pessimism (SWOP) questionnaire to assess resilience to stress.^{6,7} PSQ "summary score" values above 50 are one SD (=17) higher, values below 16 are one SD lower than the mean (=33) in a German reference population,⁶ and were set as cut-offs for severe, medium and low stress, respectively. Additional data obtained included age, sex, body mass index, previous steroid- and anti-histamine intake. Investigated potentially relevant underlying clinical and laboratory conditions included autoreactivity, chronic viral, bacterial, fungal, and parasitic infections, intolerance to food

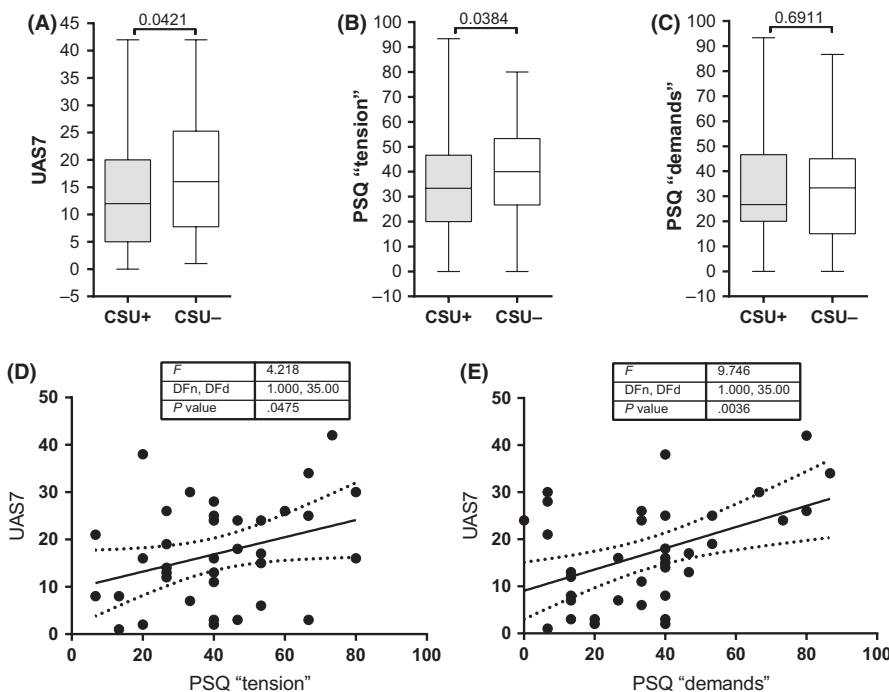


FIGURE 1 A, B, C, CSU+ and CSU- differ significantly in UAS7 and PSQ "tension". Median and minimum to maximum are shown. D, E, Linear regression analyses showed that the urticaria activity during the 7 d prior to enrollment in the diagnostic workup (UAS7) could be predicted by "tension" and "demands" (adjusted $R^2 = .082$ and $.195$, respectively) in patients with CSU-

TABLE 1 Spearman Rank correlations between urticaria disease activity and immunological measures with self-rated psychological stress and resilience

		PSQ "worries"		PSQ "demands"		PSQ "tension"	
		<i>q</i>	<i>P</i>	<i>q</i>	<i>P</i>	<i>q</i>	<i>P</i>
UAS7	Total group	0.043	.494	0.102	.106	0.065	.309
	CSU+	0.022	.744	0.050	.468	0.021	.762
	CSU-	0.188	.265	0.362	.028	0.292	.079
Total IgE	Total group	0.070	.250	0.074	.223	0.055	.362
	CSU+	0.052	.437	0.059	.378	0.056	.226
	CSU-	0.162	.261	0.184	.200	0.067	.645
Basophils	Total group	0.026	.673	-0.065	.285	-0.009	.883
	CSU+	0.066	.320	-0.065	.333	0.023	.734
	CSU-	-0.196	.178	-0.064	.661	-0.196	.177
Eosinophils	Total group	0.072	.229	0.019	.752	0.020	.742
	CSU+	0.084	.209	0.024	.715	0.034	.608
	CSU-	0.044	.762	-0.025	.863	-0.034	.814

The UAS7 is the gold standard and guideline-recommended instrument to assess CSU activity.⁹ UAS7 values are calculated based on the daily recordings of wheal numbers (none; <20; 20-50; >50) and itch intensity (none, mild, moderate, severe). Spearman rank correlations were calculated and given as $\rho = q$. Associations were considered as weak if $-0.3 < q < 0.3$, medium if $0.3 < q < 0.49$ or $-0.3 > q > -0.49$ and strong if $q > 0.5$ or $q < -0.5$.¹⁰ *P*-values are indicated as *P*. Bold are significances below 0.05, italic trends below 0.1.

components, intolerance to physical provocation and chronic inflammatory diseases including autoimmune disorders and allergies.

In 249 CSU patients, potentially relevant underlying conditions were identified (CSU+) as opposed to 54 patients without potentially relevant underlying conditions (CSU-). Only a minority received oral medication prior to the assessment (antihistamines 20%, steroids 6%) and no medication or demographic differences were found between CSU+ and CSU- patients (Table S1). Levels of self-reported stress perception and resilience in CSU patients showed a wide range of mental distress levels, with low, moderate, and high PSQ scores in 21%, 64%, and 15% of patients, respectively. The mean PSQ "summary score" in women (32.05 ± 17.04 , 72% of all patients) was slightly but not significantly higher than in men (29.82 ± 15.06). Patients younger than 45 years (55% of all patients) had slightly but not significantly higher PSQ "summary score" levels (33.12 ± 16.20) than older patients (29.55 ± 16.73).

Chronic spontaneous urticaria- patients had significantly higher disease activity than CSU+ patients (Figure 1A). In CSU- patients, 52.6%, 31.6%, and 15.8% had UAS7 levels indicative of mild, moderate, and severe CSU, respectively, as compared to 64.2%, 25.8%, and 10% in CSU+ patients. CSU- patients reported higher PSQ "worries," "tension," and "demands," with statistically increased values for the scale "tension" (Figure 1B,C, Table S2). In contrast, stress resilience in CSU- and CSU+ patients was similar. No group differences with respect to selected immunological measures such as total serum IgE, blood basophil and eosinophil counts were found (Table S3).

Correlation analyses revealed that in CSU- patients, UAS7 scores showed a moderate positive correlation with the results of the PSQ-scales "demands" ($r = .362$; $P = .028$) and a trend for "tension" ($r = .292$; $P = .0791$) (Table 1). A regression analysis (including the confounders age, gender, and body mass index) confirmed these links

in CSU- patients (adjusted R^2 "demands" = 0.195; $F(1/35) = 9.746$; $P = .004$, Figure 1D; adjusted R^2 "tension" = 0.082; $F(1/35) = 4.218$; $P = .048$, Figure 1E). The explained variance of 19.5% expresses a medium effect of $f^2 = 0.24$ and of 8.2% a low effect of $f^2 = 0.09$, respectively. By contrast, the common confounders age, gender, and body mass index were not significant predictors of the UAS7 in this group.

Our comprehensive analyses of stress in patients with CSU are the first to demonstrate that most CSU patients report stress, but also that mean levels of mental distress are comparable to the general population.⁸ More importantly, our findings confirm that in CSU- perceived stress and disease activity are linked in the absence of demographic group differences and even before CSU- patients know that no underlying cause for their urticaria will be found. These observations are relevant and may help to destigmatize CSU patients, who often feel that their doctors and peers do not take their disease-burden seriously and attribute their suffering to the seemingly minor mental problem of having too much stress.

In conclusion, our findings suggest a possible causal link between CSU and mental distress and encourage further research to confirm whether the increased levels of stress in the CSU- subpopulation are the reason or the result of their high disease levels. Clearly, in some CSU patients, the signs and symptoms of urticaria and stress are linked, which confirms the need to assess both the clinical symptoms and stress, ideally by daily diary-assessments and during patient visits, and also to address both by therapy and research, for example by the implementation of psychological interventions.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

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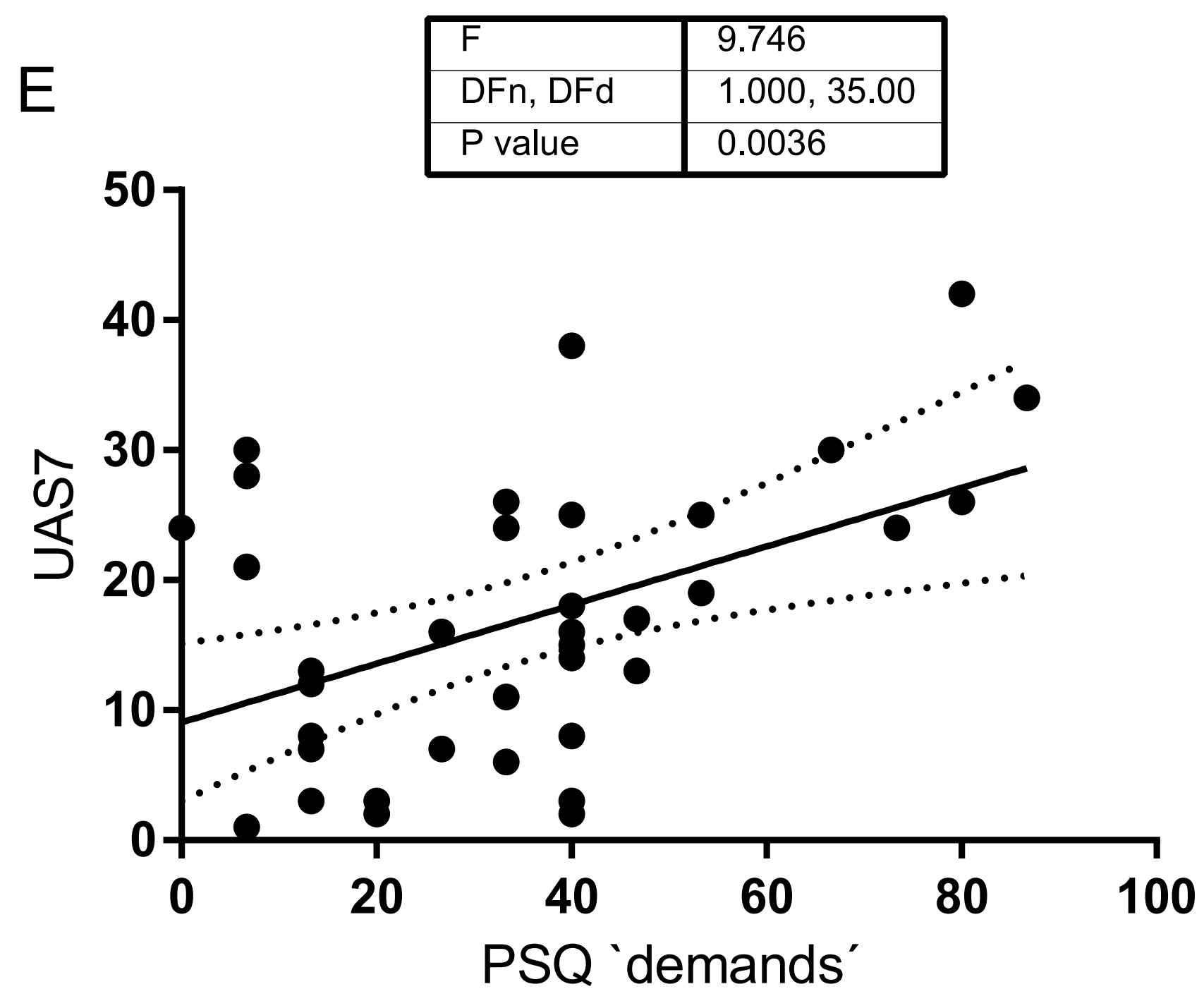
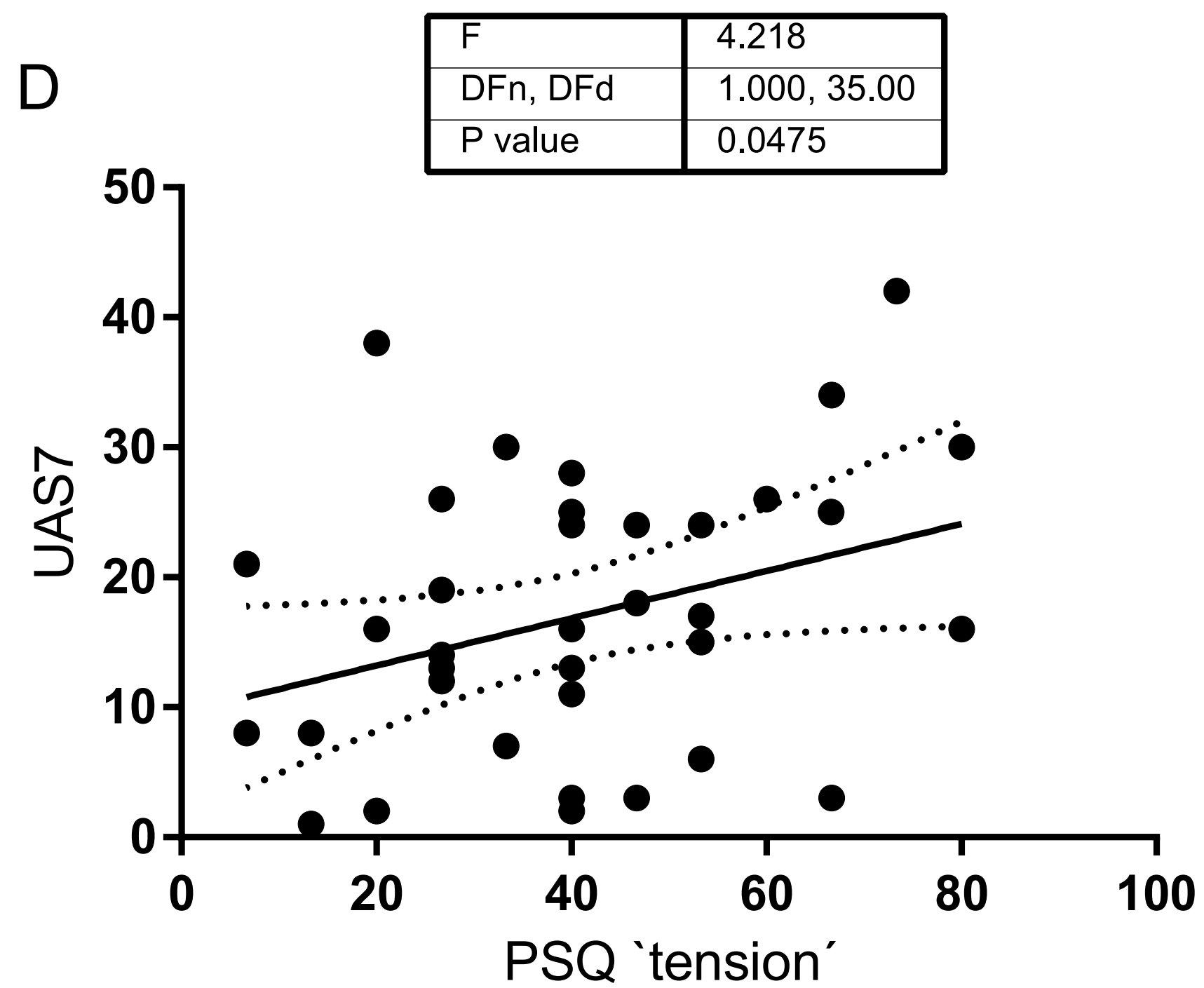
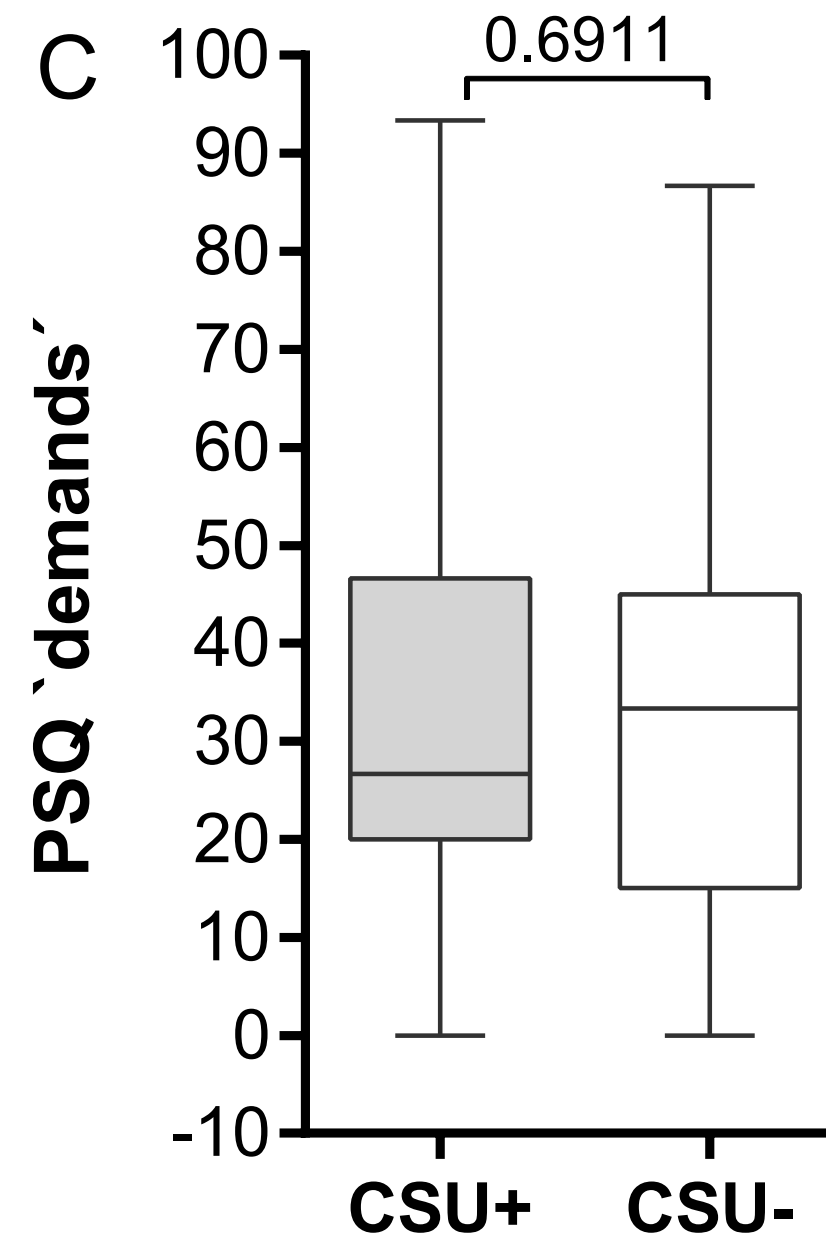
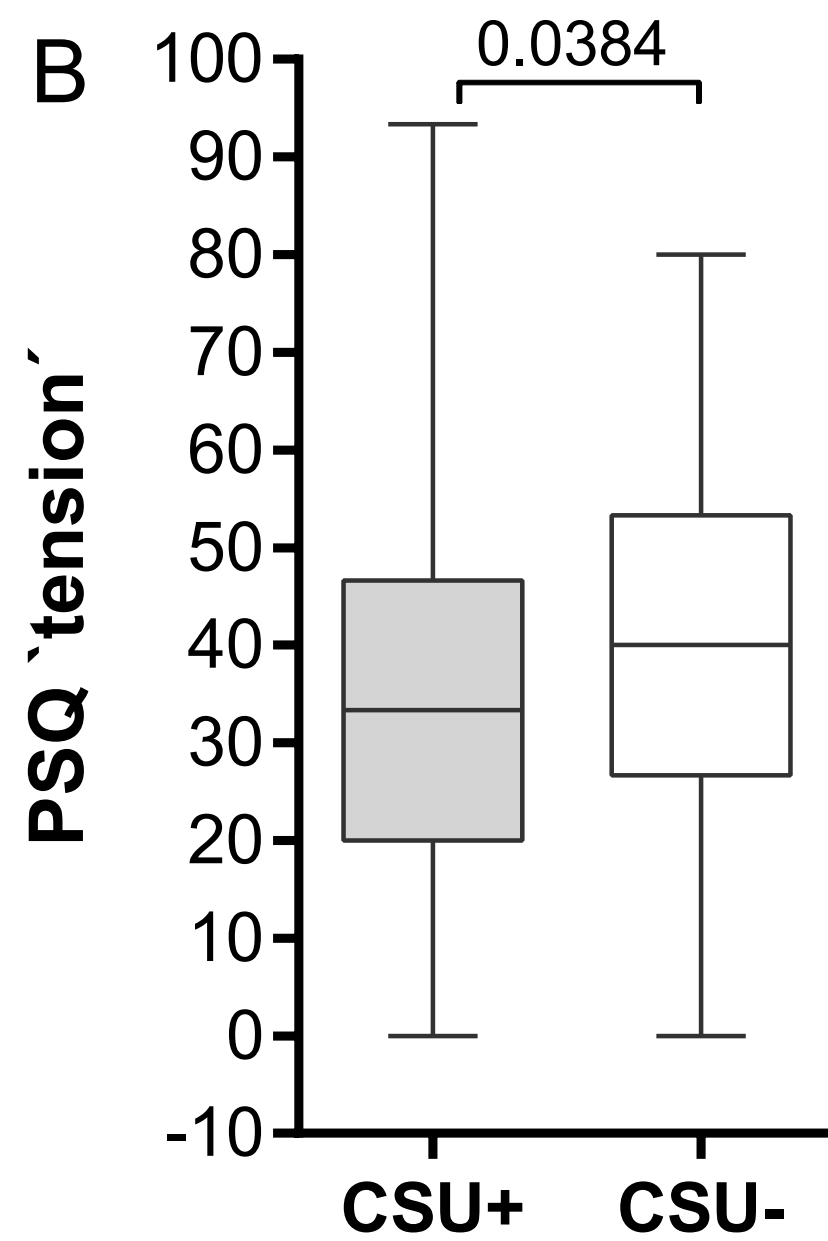
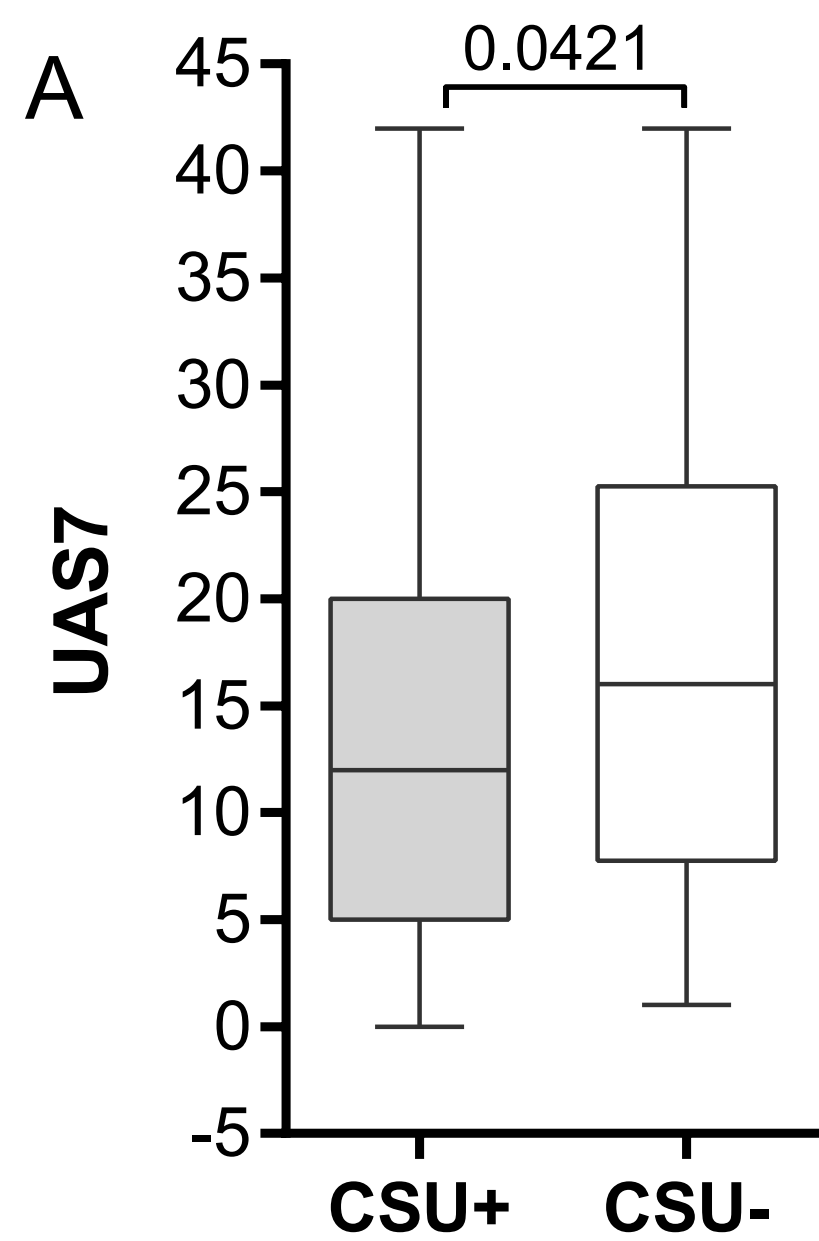
DOI: 10.1111/all.13986

IgE reactivity against herpes simplex virus 1 in patients with atopic dermatitis complicated by eczema herpeticum

To the Editor,

Eczema herpeticum (EH) is a severe and widespread viral skin infection caused by herpes simplex virus 1 (HSV-1), which particularly affects patients with atopic dermatitis (AD) who have a more severe course of the disease, higher allergen sensitization, and greater Th2 polarization.^{1,2} The condition has been named ADEH (AD complicated by EH). The pronounced shift to a Th2 immune response in ADEH has been proposed as a cause of an ineffective immune response against microorganisms.³ Th2 cell predominance goes along with overproduction of cytokines such as IL-4 and IL-13 which are key for IgE induction and may prevent the development

of cellular immunity against microorganisms. Specific IgE can be produced against microorganisms such as bacteria and yeasts in a subgroup of patients with AD with a potential contribution to AD severity.^{4,5} Evidence also exists that IgE can be produced against viruses.^{6,7,51-53} Although the role of specific IgE in viral infections is still unknown, this might be associated with exacerbation of atopic diseases.^{8,9,54-55} In humans, specific IgE against different viruses has been linked with poorer prognosis.^{52,53,56} In that respect, it has been suggested that virus-specific IgE should be analyzed due to its possible association with atopic diseases.⁵⁴ Currently, there is only sparse information about IgE-mediated mechanisms against viruses



Online supporting information for the Letter to the editor entitled: Disease activity and stress are linked in a subpopulation of chronic spontaneous urticaria patients

In depth introduction of stress response systems malfunctioning in CSU

Since CSU is a mast cell driven disease and mast cells have been identified as prime immune-targets of mal-adaptive stress responses in skin (1-5), the interaction between stress-activated neuroendocrine response systems and mast cell activation can be expected to play a relevant functional role in the stress-promotion of CSU flare-ups. The activation of mast cells in response to stress was studied extensively by euthanizing experimental animals after a defined stress exposure such as to noise or restraint (2, 5). These studies revealed an increase of mast cell activation by stress through a direct interaction between peptidergic nerve fibers in skin and the there residing mast cells. The resulting mast cell hyperactivation depended on the release of neuropeptides such as Substance P or Corticotrophin Releasing Factor (5, 6). Interestingly, one of the most potent mast cell degranulators, IgE, which plays a key role in acute urticaria, was demonstrated to have a much more dramatic effect on murine mast cells in the presence of sensory nerve fibers or neuropeptides acutely released from such fibers in response to stress (5, 7, 8). In the wake of this interaction higher numbers of basophils and eosinophils were found to be recruited into the skin contributing to chronification of inflammatory processes (3). In the presence of stress mediators, lower levels of IgE may therefor be required to occasion a flare-up of urticaria.

In humans, this thight interaction between mast cells and neuropeptides in skin may also be one of the mechanism through which stress can trigger a flare-up in CSU. However, this interaction is technically challenging to study as the detection of neuromediators released in skin or of mast cell activation in response to stress requires invasive in vivo sampling likely to cause stress. To demonstrate increased neuropeptidergic nerve contacts with mast cells or the release of neuropeptides in skin during stress exposure would require multiple skin biopsies or skin dialysis, which in themselves are highly stressfull procedures and ethically problematic. Since stress-released neuropeptids enhance IgE sensitivity and increase translocation of basophils and eosinophils into the skin of mice, the interaction of these clinical routine measures with stress perception in humans may be of interest.

In addition to nerve fiber derived neuropeptides, classical stress mediators such as cortisol moderate the interaction between stress and mast cell activation. This seems to be a complex interaction. Stress exposures that lead to a release of high levels of cortisol, i.e. acute stresses, can be expected to improve urticaria associated inflammation. However, severe stress exposures such as traumatic life events are known to decrease the capacity of the hypothalamus pituitary axis (HPA) to release cortisol while they increase inflammatory markers such as CRP and IL-18. A study including 54 CSU patients is instructive in this context. In this study, low cortisol was present together with high CRP and IL-18 in the serum of patients compared to controls (9). The CSU patients with lowest cortisol also reported the highest number of life events and life events correlated with disease activity. This suggestes that a relative lack of cortisol contributes to mast cell hyperactivation in severely stressed CSU individuals. However, not all studies in this vein confirm this notion and the exact relationship between different stress intensities and urticaria driving immune-pathologies remain to be defined.

Supplemental Table 1: CSU- and CSU+ patients are similar in demographic characteristics. For statistical analysis, SPSS 24 (IBM, Ehningen, Germany) was used. The category "does not apply" and item non-response were coded as missing values. For all calculations, a p-value of ≤ 0.05 was considered as statistically significant. We did not find differences in the gender ratio, weight, height or BMI between CSU- and CSU+ patients (all $p > 0.05$). All data is shown as means $\pm$ SDs with exception of sex, which is shown as %. $p = p$ values are given for the comparison of CSU- versus CSU+. n for CSU+ = 54 (none missing) for gender, and 53 (1 missing) for age, height, weight and BMI; n for CSU- = 249 (none missing) for gender, and 249 (2 missing) for age, height, weight and BMI. Of note, to be designated as CSU-, patients had to be negative for all tests performed to identify these potentially underlying conditions including an elimination diet, autologous serum skin test, screening for infections, e.g. with *Helicobacter pylori*, tooth infections, tests for systemic inflammation including C-reactive protein, and tests for autoimmune disease and allergies. 48 patients had comorbid physical or cholinergic urticaria as shown by respective tests (dermographism, cold baths, thermal testing, pressure testing, exercise testing, light testing with UVA and UVB), and 3 had comorbid urticaria vasculitis.

Variable	CSU-	CSU+	p
Gender (♀)	70.4 %	72.7 %	0.739
Age (in years)	44.6 $\pm$ 15.6	45.4 $\pm$ 15.0	0.734
Height (in cm)	168.53 $\pm$ 8.8	169.4 $\pm$ 8.7	0.527
Weight (in kg)	70.5 $\pm$ 15.1	72.7 $\pm$ 14.5	0.334
BMI	24.7 $\pm$ 4.2	25.3 $\pm$ 4.8	0.375

Supplemental Table II. CSU- patients show higher levels of perceived stress than CSU+ patients. Ordinal items were transformed to a scale ranging from 0 to 100 points. Stress perception was assessed by use of the three PSQ factors “worries”, “demands”, and “tension”. The factor tension contains the following PSQ items: “you feel tense”, “you don’t feel rested”, “you feel mentally exhausted”, “you have trouble relaxing”, “you don’t feel calm”, “you feel tired”, and “you feel irritable or grouchy” (10). Stress resilience was assessed by the use of the PSQ factors “joy” and the SWOP factors “optimism”, “pessimism”, and “self-efficacy”. PSQ CSU- versus CSU+: n = 233 (16 missing), CSU-: 52 (2 missing). SWOP CSU- versus CSU+: n for CSU+ = 246 (3 missing), CSU-: 54 (0 missing). Data shown as means $\pm$ SDs. Data shown as means $\pm$ SDs.

Variable	CSU+	CSU-	p
Worries (PSQ)	24.1 $\pm$ 18.4	27.4 $\pm$ 16.9	0.117
Tension (PSQ)	34.0 $\pm$ 20.8	40.5 $\pm$ 20.2	0.039
Demands (PSQ)	32.4 $\pm$ 21.4	34.4 $\pm$ 22.6	0.690
Joy (PSQ)	65.3 $\pm$ 21.8	60.3 $\pm$ 19.9	0.114
Optimism (SWOP)	69.8 $\pm$ 23.8	64.5 $\pm$ 22.4	0.115
Pessimism (SWOP)	28.5 $\pm$ 24.3	33.3 $\pm$ 22.7	0.183
Self-efficacy (SWOP)	67.6 $\pm$ 19.4	65.9 $\pm$ 17.4	0.385

Supplemental Table III: CSU- and CSU+ patients are similar in immunological characteristics. All data shown as means $\pm$ SDs. p = p values are given for the comparison of CSU- versus CSU+. Total serum IgE: n for CSU+ = 52 (7 missing), CSU-: 241 (8 missing). Blood basophil numbers: n for CSU+ = 51 (8 missing), CSU- = 243 (6 missing). Blood eosinophil numbers: n for CSU+ = 52 (7 missing), CSU- = 244 (5 missing).

Variable	CSU-	CSU+	p
Total serum IgE in kU/l	195.19 $\pm$ 308.78	172.06 $\pm$ 280.85	0.428
Blood basophil numbers/nl	0.02 $\pm$ 0.02	0.02 $\pm$ 0.06	0.468
Blood eosinophil numbers/nl	0.17 $\pm$ 0.11	0.19 $\pm$ 0.17	0.754

In depth discussion

Our study shows that CSU patients investigated for potentially underlying conditions without success have higher levels of stress than successfully investigated CSU patients. This difference is present even before the patients come to know about the outcome of these investigations. The only difference we found, which can explain this, is that disease activity in patients without a potentially underlying cause was higher and linked to their stress levels.

In many CSU patients who are subjected to clinical investigations that aim to find conditions (summarized in 29) that are relevant to their disease (11, 12), the search is not successful. This is commonly thought to result in a vicious cycle. It is reasonable to assume that CSU-leads to excess mental distress, which in turn worsens the disease. This notion may need to be corrected though. That CSU-patients, i.e. patients who are investigated for relevant somatic conditions without success, are more stressed than CSU+ patients before the patients even know whether a potentially relevant underlying cause for their CSU will be found, is intriguing. It argues for the mental distress to start the vicious cycle in CSU- patients. However, it does not exclude the possibility that learning about the negative outcome of investigations for potentially relevant conditions further enhances stress levels in CSU- patients. In the present study, we did not investigate this.

We did not find any differences in selected demographic features or routine immunological markers in CSU- and CSU+ patients. We also did not find differences in their resilience to stress. The only difference we found between CSU+ and CSU- patients was that the latter had higher levels of disease activity and that disease activity in CSU- patients was correlated with stress levels. Thus, it can be hypothesized that, at least in part, the higher disease activity is the reason for the increased levels of stress in CSU-.

Our study is not suited to answer this question, but it is interesting to note that in CSU- patients PSQ 'demands' partially explained urticaria activity in regression analysis. In support of acute stress as a cause for flare-ups of CSU, one case control study with many daily measurements in a patient in stationary psychosomatic therapy for his CSU exists. In this study, decreased perception of tension occurred prior to CSU improvement (13). Also, in patients with cholinergic urticaria brief emotional arousal provoked flare-ups (14) and patients often report stressful life events and trauma preceding CSU (15, 16). Moreover, they reported to experience less support from their families, more intense sleeping problems and were younger at diagnosis (17). Hence, acute stress may lower the threshold for urticaria triggers and lead to higher disease activity.

Again, our study is not suited to answer this question but acute stress is known to trigger the release of neuropeptides in the skin (18-20). An important cellular target of cutaneous neuropeptides are mast cells. Their response to IgE is enhanced in the presence of the neuropeptidergic stress-mediator substance P. This inflammatory circuit is known as neurogenic inflammation and sporadic experimental reports suggest it's stress sensitivity in urticaria. Dermographism, which gives some evidence of neurogenic inflammation, occurred together with psychological stress (14). One case report showed activated mast cells after stress-experience in a patient with cutaneous mastocytosis (21).

In addition, acute stress activates the classical stress response systems and releases stress mediators such as cortisol and adrenaline (36). Occasionally, patients respond to the subcutaneous injection of adrenaline with flare and wheal (22)). Also, stress-reduction was shown to improve morning cortisol levels and urticaria symptoms simultaneously (13). However, in one study performed in patients with chronic urticaria, 12 patients subjected to an acute stress test failed to show enhanced urticaria responses (23).

Consequently, the exact mechanism through which stress mediators interact with disease activity in inflammation in general and CSU in particular remains a matter of debate as both worsening and improving stress paradims and inflammatory responses have been described in men and mice in a number of mast cell activation settings including allergy and cancer immune surveillance (3, 19, 24-27).

Nevertheless, it can be argued that acute distress can worsen urticaria via the release of stress mediators affecting target cell populations and functions in urticaria such as mast cells and their cytokine release. However, this was not addressed in the assessment of potentially relevant underlying causes for CSU in our study and there are findings that challenge this concept. With respect to IgE levels as well as basophil and eosinophil counts we found no difference between CSU- and CSU+ in the present study. These routine immune markers appear to be rather stable despite stress experience and are hence not instructive with respect to pathways involved in stress-associated CSU disease activity.

Finally, our study has several strengths and limitations. On the plus side, we assessed a large patient population for demographic, immunological, and clinical features as well as for stress levels and resilience to stress. Also, we investigated patients for a broad spectrum of somatic conditions that are potentially relevant for CSU. The results of these investigations were used to compare patients who were informed that no potentially relevant underlying cause had been found with those that were informed they had a cause after being investigated. However, some potentially relevant conditions, which were only described recently, were not tested in more detail such as neurogenic inflammation, flare and wheal response to stress mediators or type I autoimmunity. Present concepts of CSU identify IgG against IgE and its corresponding *FcεRI* receptor as well as mal-adaptive intracellular signaling pathways involving Syk, SHIP-1, or SHIP-2 in basophils and mast cells as CSU's main driving pathomechanisms. It will be a challenging task for future stress studies, to investigate possible links between these mechanisms and neuroendocrine stress responses. Finally, as described above, our study was not designed to conclusively show if stress drives CSU disease activity or vice versa and hence to clarify the direction of the interaction between stress and CSU, which may well be bidirectional. Since stress was linked to CSU only in the CSU- but not the CSU+ group, while the former had both higher stress and disease activity, it may be argued that disease activity does not result in emotional distress per se and that stress plays either an aggravating role or results from more severe disease in individuals not knowing the cause of their disease. That this was only disclosed after completion of the assessment, suggests the possibility that stress as a trigger of disease aggravation is the missing cause in the CSU- group, though the design of the study only revealed the relation. In any case, both stress and CSU are treatable and better therapeutic results may be obtained when addressed simultaneously. To study this, further randomized controlled studies are needed.

Authors contributions

1) Substantial contributions to conception and design: McM, MR, UG, EMJP; or substantial contributions to acquisition, analysis and interpretation of data: CS, Mkm, TH, JK, EMJP; 2) drafting the article or revising it critically for important intellectual content: CS, Mkm, TH, JK, MR, UG, McM, EMJP; and 3) final approval of the version to be published: CS, Mkm, TH, JK, MR, UG, McM, EMJP; 4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: CS, Mkm, TH, JK, MR, UG, McM, EMJP.

Supplemental literature

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