

Original article

The German version of the chronic urticaria quality-of-life questionnaire: factor analysis, validation, and initial clinical findings

Background: Chronic urticaria (CU) is a common skin disorder that causes a substantial burden on patients' quality-of-life (QoL). The aim of this work was to generate and validate a German version of the Chronic Urticaria Quality of Life Questionnaire (CU-Q₂oL) and to provide reference assessments of QoL.

Methods: The Italian CU-Q₂oL was translated into German and administered to 157 CU patients. They also completed two well-established general dermatology QoL questionnaires, the Dermatology Life Quality Index (DLQI) and Skindex-29. Factor analysis was used to identify scales of the German CU-Q₂oL. Correlation to the DLQI and Skindex-29 was used for validation. Multiple linear regression was used to determine which patient characteristics were associated with which dimensions of QoL.

Results: The factor analysis identified six scales of the German CU-Q₂oL: functioning, sleep, itching/embarrassment, mental status, swelling/eating, and limits looks, which accounted for 70% of the data variance. Five of these six scales showed good internal consistency, and another five demonstrated convergent validity. On a percentile scale, they had these median CU-Q₂oL scores: 29 functioning, 44 sleep, 50 itching/embarrassment, 50 mental status, 31 swelling/eating, 31 limits looks. Disease severity significantly predicted scores on all scales. Age predicted functioning, sleep, itching/embarrassment, and swelling/eating. Sex predicted itching/embarrassment and limits looks.

Conclusion: This study yielded a robust validation of the German version of the CU-Q₂oL. It confirmed previous studies that CU has a clinically meaningful burden on QoL, especially for sleep and mental health, and that women are more severely affected by pruritus. The German CU-Q₂oL should be widely adopted in clinical research on the treatment of CU.

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Chronic urticaria (CU) is a common skin disorder. It is characterized by spontaneously arising itchy wheals and/or angioedema, occurring on a regular basis for longer than 6 weeks (1–5). In the majority of cases, the cause remains unidentified and patients report insufficient symptom control (4, 5). Consequently, many CU patients remain afflicted by the condition, often for years, and it has repeatedly been found that CU has a substantial impact on patient quality-of-life (QoL) (6–8).

A better understanding of CU patients' QoL is necessary for both clinical research and routine patient care. In clinical research, QoL measurements provide a rich evaluation of the benefits of a treatment, as experienced from the patient's perspective. In routine care, QoL measures can provide physicians with a better understanding of the ways in which they can help their patients, when a definitive physical cure is unavailable. Although there are many excellent general and dermatological QoL

questionnaires, there were no questionnaires specifically designed for CU patients and addressing the aspects of QoL most relevant to their condition. But recently Baiardini et al. (9) developed a new questionnaire for measuring QoL specifically in CU patients, the Chronic Urticaria Quality-of-Life Questionnaire (CU-Q₂oL), which promises to be a great benefit to both clinical research and routine patient care. Our research network has just developed a German version of the CU-Q₂oL.

Translated questionnaires always need to be revalidated in the new language/culture/setting (10), but unfortunately, this is not always adequately performed. The translated and culturally adapted questionnaire must always be backtranslated into the original language, and the original and backtranslation must be compared for discrepancies. Then after collecting data, a new factor analysis should be performed if possible, to determine the proper construction of the questionnaire into subscales and the appropriate assignment of individual items to those subscales (11). The face validity and clinical utility of these subscales should be examined. Even if a new factor analysis is not performed, the newly translated questionnaire should be briefly revalidated by assessing its convergence with other relevant established instruments. Finally, it is helpful to provide initial results with the translated questionnaire.

The aim of this study is to present the factor analysis and validation of the German version of the CU-Q₂oL, as well as our initial findings on QoL among German CU patients. The CU-Q₂oL was translated into German and administered to 157 CU patients at our clinic. The CU-Q₂oL is a relatively new questionnaire that had only been tested in one modest sized sample (9), so factor analysis was performed a new to identify the underlying dimensions of the German version of the questionnaire and appropriately group the questionnaire items onto their correct scales. Then the scores on the CU-Q₂oL scales were correlated with other QoL instruments, to confirm the accuracy of this new questionnaire. Finally, we analyzed the QoL results found in this German clinical population sample.

Methods

Translation of the questionnaire

The original Italian version of the CU-Q₂oL was translated into German by a native, professional German translator. It was then reviewed by several medical experts and several patients at our department for the comprehensibility of the items. After mild revision for clarity, it was then backtranslated into Italian by a native, professional Italian translator. The original and backtranslated Italian versions were then reviewed in a consensus conference with the original Italian author and our team. The German translation was then approved and used without further modification. The German version of the questionnaire (including an unofficial English translation) is presented in Table 1.

Patient sample and data acquisition

Data were collected from March 2007 until January 2008 at the urticaria clinic of our university hospital department. To be seen at our specialized clinic, a patient must be referred by either a dermatologist or an allergist. All consecutive patients who came to our clinic and had a diagnosis of CU were given the questionnaire pack for this study. The questionnaires were given to the patients at the hospital but filled out by them at home and mailed back to us. A written informed consent form was included with the questionnaires, so all patients who returned the questionnaires also read and signed the written informed consent form. The target sample size was 100 completed questionnaire packs. When we received 100 completed questionnaires, we stopped distributing them but continued accepting them.

Measurements

The clinical severity of CU was assessed by the UAS-7 (12), a validated patient clinical diary system that scores the quantity of wheals and intensity of itch, daily for 1 week, yielding a total score of 0–42. On the 7th day, the subject also filled out the CU-Q₂oL (which includes questions on sex, age, and CU duration), the Dermatology Life Quality Index (DLQI) (13–15), and Skindex-29 (16–18). The DLQI and Skindex-29 are instruments to measure QoL for any dermatology patient. The DLQI was designed to provide a quick, simple assessment of QoL for routine clinical use (10, 14). Skindex-29 is widely used in research and assesses three domains of QoL: symptoms, functioning, and emotions (17). The need for a disease-specific QoL questionnaire for CU has been explained previously (9).

Statistical analysis

The preliminary stage of validation of the German version revolved around determining the appropriate scales, based on the data from the German clinical population sample. Because the CU-Q₂oL is a new questionnaire and because we did not make any presumptions about the questionnaire's construction, exploratory factor analysis was used to discover the correct scales of the German version (11). As the goal of our exploratory factor analysis was data reduction into summary scores more than identification of underlying causal variables (11), the approach employed was a principal component analysis with Varimax rotation with Kaiser normalization. The criterion chosen to retain factors was an eigenvalue ≥ 1.0 for that factor. Individual items loading onto a factor with a factor loading ≥ 0.5 were assigned to that factor. The face validity of the resulting scales was examined, both in terms of the scales' global meaning and in terms of the appropriateness of each individual item to that scale. Furthermore, consideration was given to the utility of the scales for further clinical research.

After identifying the scales, Cronbach's correlation coefficient was calculated for each scale, to test its internal consistency. The theoretical range of Cronbach's α is 0–1. Suggested guidelines for interpretation are: <0.60 unacceptable, 0.60 – 0.65 undesirable, 0.65 – 0.70 minimally acceptable, 0.70 – 0.80 respectable, 0.80 – 0.90 excellent, >0.90 excessive consistency, implying item redundancy. Cronbach's alpha was also used to aid in the final assignment of items that loaded onto more than one factor.

After finalizing the German scales, their convergent validity was assessed by calculating their correlation coefficients to scales or items from two other established dermatology QoL questionnaires, Skindex and DLQI, using Pearson's r .

Table 1. The German translation of the CU-Q2oL questionnaire

Item no.	Item name	Statement	Translation
1	Pruritus	Juckreiz	Itching
2	Wheals	Quaddeln	Wheals
3	Eyes swell	Schwellung der Augen	Swelling of your eyes
4	Lips swell	Schwellung der Lippen	Swelling of your lips
5	Work	Arbeit	Work
6	Physical activities	Körperliche Betätigung	Physical activities
7	Sleep	Schlaf	Sleep
8	Free time	Freizeit	Free time
9	Social relationships	Soziale Beziehungen	Social relationships
10	Eating	Ernährung	Eating
11	Fall asleep	Haben Sie Schwierigkeiten, einzuschlafen?	Do you have difficulties falling asleep?
12	Wake up	Wachen Sie nachts auf?	Do you wake up at night?
13	Tired	Sind Sie tagsüber müde, da Sie nachts nicht richtig schlafen?	Are you tired during the day, because you didn't sleep well at night?
14	Concentration	Haben Sie Schwierigkeiten, sich zu konzentrieren?	Do you have difficulties concentrating?
15	Nervousness	Fühlen Sie sich nervös?	Do you feel nervous?
16	Bad mood	Fühlen Sie sich niederschlagen?	Do you feel miserable?
17	Limit food	Müssen Sie sich bei der Auswahl an Speisen einschränken?	Do you have to limit your food choices?
18	Bothered by signs	Belasten Sie die Krankheitszeichen, die durch die Nesselsucht (Urtikaria) auf Ihrem Körper erscheinen?	Are you bothered by the symptoms of hives (urticaria) that appear on your body?
19	Embarrassed in public	Schämen Sie sich öffentliche Orte aufzusuchen?	Are you embarrassed to go to public places?
20	Cosmetics	Stellt die Anwendung von Kosmetika ein Problem für Sie dar (z.B. Parfums, Cremes, Lotionen, Badeschaum, Schminke)?	Is it a problem for you to use cosmetics (e.g. perfumes, creams, lotions, bubblebath, make up)?
21	Limits clothes	Sind Sie bei der Wahl Ihrer Kleidung eingeschränkt?	Do you have to limit your clothing choices?
22	Sports	Schränken Sie ihre sportlichen Aktivitäten aufgrund der Nesselsucht (Urtikaria) ein?	Are your sports activities limited because of your hives (urticaria)?
23	Medication side-effects	Leiden Sie unter den Nebenwirkungen der Medikamente, die Sie gegen die Nesselsucht (Urtikaria) einnehmen?	Do you suffer side-effects from the medications you take for hives (urticaria)?

This shows the items of the German translation, in the order they appear on the questionnaire, along with an English equivalent and a shorthand name. Each statement or question is scored on a 5-point scale as explained. Items 1–4 are preceded by the question, 'Wie sehr wurden Sie in den letzten 14 Tagen von folgenden Symptomen geplagt?' (In the past 14 days, how much were you troubled by the following symptoms?) The five choices presented are: 'gar nicht, wenig, ziemlich, viel, sehr viel' (not at all, a little, rather, a lot, very much). Items 5–10 are preceded by the statement 'Geben Sie an, ob Sie in den letzten 14 Tagen in den nachfolgend aufgeführten Bereichen des täglichen Lebens von Ihrer Nesselsucht (Urtikaria) eingeschränkt wurden'. (Indicate how often you were limited by your hives (urticaria) in the past 14 days in the following areas of daily life). Items 11–23 were preceded by the statement, 'Mit den nachfolgenden Fragen möchten wir näher auf die Schwierigkeiten und Probleme eingehen, die mit Ihrer Nesselsucht (Urtikaria) verbunden sein können (bezüglich der letzten 14 Tage)'. [In the following questions, we would like to know more about the difficulties and problems that could be related to your hives (urticaria) (regarding the past 14 days)]. Items 5–23 presented five possible answers: 'nie, selten, gelegentlich, oft, sehr oft' (never, rarely, sometimes, often, very often).

Descriptive statistics were used to characterize the study sample and their QoL scores. Multiple linear regression was used to assess significant predictors of the CU-Q2oL scores. Sex, age, disease severity, and disease duration were used as independent/control variables, while the CU-Q2oL scores were the dependent variables. The data met all the necessary assumptions for this regression analysis.

Statistical analyses were performed with SPSS version 15.0 (SPSS; Chicago, IL, USA). Statistical graphing was performed with SPSS version 15.0, STATA 10.0 (Stata, College Station, TX, USA), R version 2.6.2 (R Foundation for Statistical Computing, Vienna, Austria), and ADOBE ILLUSTRATOR 10 (Adobe, San Jose, CA, USA).

Results

Subject characteristics

There were 157 subjects in this study. The sex and age of the study sample are shown in Fig. 1A. Consistent with the reported prevalence of CU (19), there were twice as many women as men in the study sample, and the ages

were spread mostly over the broad range of 31–75. The severity and duration of the study sample's CU is shown in Fig. 1B. As can be seen, the study sample mostly had CU for less than 5 years, but many patients had had CU for decades. As also can be seen, the sample was spread out over a range of severity. Statistical analysis of the correlation between severity and duration showed that it is highly likely that the two are correlated ($P = 0.006$), yet the (inverse) correlation between them is weak (Spearman's $\rho = -0.23$). The mean DLQI score of this study sample was 6.8, and the distribution of DLQI scores is shown in Fig. 1C. Although seemingly low, these scores are somewhat comparable to the mean DLQI score of 9.9 reported in a literature review covering 518 CU patients from four studies (14), the mean of 8.0 from a very recent two-center German study on 111 CU patients (12), and the mean of 9.7 calculable from a validation study of the DLQI on 857 CU patients from two multicenter studies (15). The Skindex scores of this study sample are shown in Fig. 1D. Although many subjects

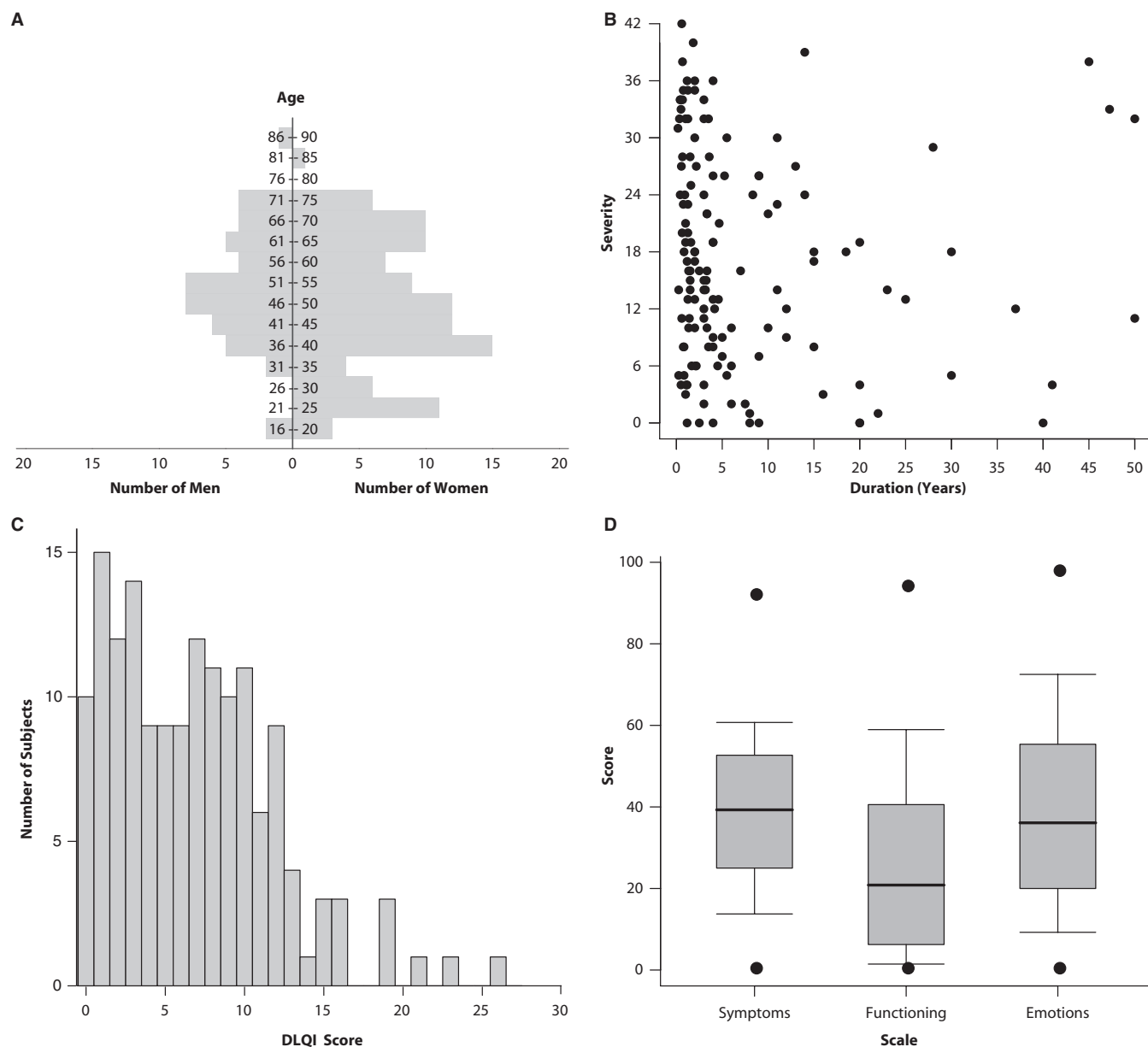


Figure 1. Patient characteristics. (A) The population pyramid shows the distribution of subjects by sex and age. (B) The scatter plot shows the distribution of chronic urticaria (CU) severity and duration in the study population, whereby each dot represents one subject. (C) The histogram shows the number of subjects with each DLQI score. (D) The box-and-whisker plot shows the Skindex scores of the study population. The thick middle line of each box-and-whisker plot represents the median score on that scale. The ends of each box represent scores of the 25th and 75th quartiles. The whisker ends represent the scores of the 10th and 90th percentiles. The dots represent the minimum and maximum scores.

show only mild functional impairment, most subjects show a moderate burden on the symptoms and emotions scales.

Identification and validation of German scales

Guidelines recommend a minimum sample size of 5 subjects per variable for factor analysis (11). As the CU-Q₂oL has 23 items, this study needed a minimum of 115

subjects. Thus, the sample size was adequate for the factor analysis.

Only 11 of 3611 (0.3%) intended data entries were missing, which is negligibly little. These data were missing at random according to Little's MCAR test. This missing data were not rectified in the analysis.

The factor analysis yielded a six-factor solution for the German data. The results of the six-factor solution are shown in Table 2A. As can be seen, this six-factor

Table 2. Determination of the structure of scales of the German version of the CU-Q₂oL Questionnaire

Factor	Initial eigenvalues			Rotation sums of squared loadings		
	Total	% of variance	Cumulative %	Total	% of variance	Cumulative %
(A) Results of the Varimax rotation						
I	8.340	36.3	36.3	3.823	16.6	16.6
II	2.431	10.6	46.8	3.088	13.4	30.0
III	1.752	7.6	54.4	2.661	11.6	41.6
IV	1.386	6.0	60.5	2.582	11.2	52.8
V	1.195	5.2	65.7	2.326	10.1	63.0
VI	1.132	4.9	70.6	1.756	7.6	70.6

		Factors					
Item no.	Item name	I	II	III	IV	V	VI
(B) Component matrix for six factor solution.							
1	Pruritus	0.323	0.236	0.709	−0.016	0.213	0.085
2	Wheals	0.282	0.183	0.825	−0.012	0.196	0.098
3	Eyes swell	0.192	0.114	0.070	0.124	0.671	0.014
4	Lips swell	0.077	0.049	0.255	0.147	0.745	−0.142
5	Work	0.731	0.162	0.144	0.157	0.343	0.055
6	Physical activities	0.876	0.124	0.140	0.124	0.097	0.053
7	Sleep	0.238	0.766	0.326	−0.093	0.217	0.020
8	Spare time	0.783	0.061	0.350	0.150	0.238	−0.031
9	Social relations	0.692	0.018	0.309	0.312	0.247	0.105
10	Eating	0.176	0.212	0.017	−0.002	0.648	0.498
11	Falling asleep	0.070	0.781	0.027	0.182	0.030	0.074
12	Waking up at night	0.067	0.826	0.046	0.219	0.201	0.080
13	Tired	0.084	0.731	0.103	0.449	0.071	0.162
14	Concentration	0.322	0.222	−0.064	0.724	0.094	0.145
15	Nervous	0.120	0.314	0.122	0.739	0.082	0.173
16	Bad mood	0.273	0.379	0.162	0.665	0.208	−0.022
17	Limit food	0.021	0.265	0.005	−0.018	0.631	0.572
18	Embarrassed by signs	0.318	0.101	0.698	0.343	0.013	0.143
19	Embarrassed in public	0.175	−0.153	0.538	0.567	0.056	0.144
20	Cosmetics	−0.005	−0.015	0.107	0.224	0.059	0.770
21	Limits clothes	0.366	0.195	0.264	0.116	−0.076	0.514
22	Sports	0.601	0.007	0.346	0.279	−0.057	0.021
23	Medication side-effects	0.529	0.218	0.079	0.025	−0.075	0.371

This shows how well each item loaded onto each of the six factors, whereby higher numbers show higher loading. The threshold for assigning an item to a factor had been pre-set to 0.5. Bold values indicate item loadings that met this threshold.

Scale	Item no.	Cronbach's α
(C) Internal consistency of the German scales		
I	5, 6, 8, 9, 22, 23	0.87
II	7, 11, 12, 13	0.86
III	1, 2, 18, 19	0.82
IV	14, 15, 16	0.82
V	3, 4, 10, 17	0.75
VI	20, 21	0.52

solution explains over 70% of the variance, giving it a strong validity. For comparative reference, the Italian six-factor solution explained 59.97% of the variance of the Italian data (9), and the three factors of Skindex accounted for 63.3% of the variance in the German version of Skindex (18).

The principal component analysis with a minimum factor loading of 0.5 assigned all 23 items to a factor and assigned only two items to two factors each (Table 2B). This was quite satisfying, because it allowed

retention of all 23 items, and the data made it clear which scales they belong to. For the two factors that loaded onto two scales each, the calculation of Cronbach's correlation coefficient for each of the two possible assignments made it clear which of the two scales was more appropriate.

The internal consistency of these six scales, as calculated by Cronbach's correlation coefficient, is shown in Table 2C. Thus, scales I-IV all have excellent consistency, and scale V has respectable consistency. Scale VI,

unfortunately, does not show consistency according to our interpretive schema. Two possible partial explanations for the low alpha on scale VI are: (i) there are only two items, and Cronbach's alpha is known to decrease with fewer items; and (ii) item 20 (use of cosmetics) does not apply well to men, so the low alpha may reflect suboptimal item construction in the German translation. Baiardini et al. (9) took the position that a Cronbach's α of 0.50 or higher would be acceptable, so we have retained this scale despite its poor consistency.

Altogether, our analysis of the data from the German clinical population sample yielded the set of scales for the German version shown in Table 3.

We then correlated the scores of these scales with the scores from scales or item-bundles of Skindex and DLQI. CU-Q₂oL scale I, Functioning, was correlated with the Skindex Functioning scale and also with the mean score of DLQI items 3 (shopping/home/garden), 5 (social/leisure), 6 (sports), and 7/7a (work/studying). CU-Q₂oL scale II, Sleep, was correlated with the mean of Skindex items 2 (sleep) and 30 (tired). CU-Q₂oL scale III, itching/embarrassment, was correlated with the mean of Skindex items 10 (itches) and 21 (embarrassed), and also with the mean score of DLQI items 1 (itching/soreness/pain/stinging) and 2 (embarrassment/self-consciousness). CU-Q₂oL scale IV, mental status, was correlated with the Skindex emotions scale. CU-Q₂oL scale V, swelling/eating, was not correlated to any other questionnaire scale or item, because there are no analogous items in Skindex or DLQI. CU-Q₂oL scale VI, limits looks, was correlated with DLQI item 4 (clothes), using Spearman's ρ in addition to Pearson's r , because the DLQI data was not normally distributed. All of these two-tailed correlations were highly significant at $P < 0.001$, confirming that five of the six German scales of the CU-Q₂oL have strong convergent validity with other established QoL questionnaires. The other scale, swelling/eating, measures a novel area of QoL.

Quality-of-life scores

The CU-Q₂oL scores for this German patient population are presented in Fig. 2. Functioning, swelling/eating, and limits looks were less affected, whereas sleep, itching/embarrassment, and mental status were more affected. As can be seen, the median scores were: functioning 29, sleep 44, itching/embarrassment 50, mental status 50, swelling/eating 31, limits looks 31. As also can be seen, the

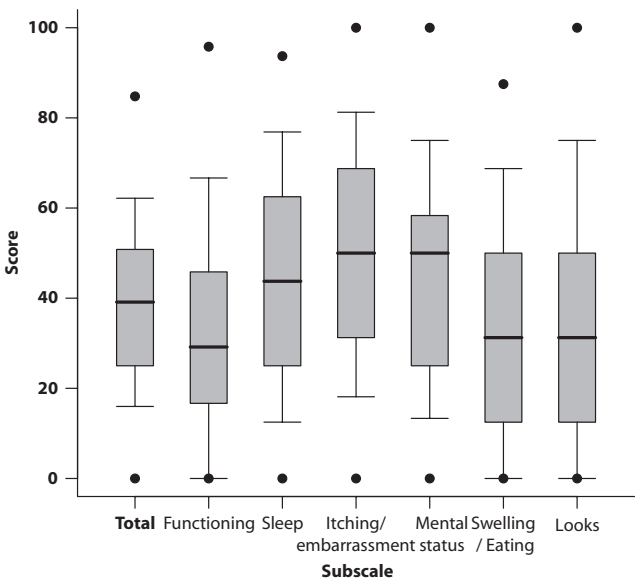


Figure 2. CU-Q₂oL scores. The box-and-whisker plots present the distribution of CU-Q₂oL scores. The thick middle line of each box-and-whisker plot represents the median score on that scale. The ends of each box represent the scores of the 25th and 75th quartiles. The whisker ends represent the scores of the 10th and 90th percentiles. The dots represent the minimum and maximum scores.

interquartile range, 10th/90th percentile range, and the min/max range all spanned wide spectrums of scores, implying an even and broad distribution of patient QoL.

Factors driving quality-of-life scores

Not surprisingly, disease severity was highly significantly ($P \leq 0.001$) predictive of the CU-Q₂oL score on all scales. Age significantly predicted functioning ($P = 0.004$), sleep ($P = 0.009$), itching/embarrassment ($P = 0.003$), and swelling/eating ($P = 0.009$), whereby younger subjects were more affected on functioning and itching/embarrassment, while older patients were more severely affected on sleep and swelling/eating. Sex significantly predicted itching/embarrassment ($P = 0.048$), and limits looks ($P < 0.001$), whereby women were more severely affected on both scales. Disease duration did not significantly predict any CU-Q₂oL score. The correlations

Table 3. Scales of the German CU-Q₂oL

Scale no.	Scale name	Questionnaire item no.	Questionnaire item names
I	Functioning	5,6,8,9,22,23	work, physical activities, free time, social relations, sports, medication side-effects
II	Sleep	7,11,12,13	sleep, fall asleep, wake up, tired
III	Itching/Embarrassment	1,2,18,19	pruritus, wheals, bothered by signs, embarrassed in public
IV	Mental Status	14,15,16	concentration, nervous, bad mood
V	Swelling/Eating	3,4,10,17	eyes swell, lips swell, eating, limit food
VI	Limits Looks	20,21	cosmetics, limit clothes

between sex, age, and CU severity on one hand and CU-Q₂oL scores on the other are shown in Fig. 3.

Discussion

Chronic urticaria has a substantial impact on patients' QoL. Validated QoL questionnaires are needed to assess better the effectiveness of possible treatments. The statistical analysis here strongly supports the structure and validity of the German version of CU-Q₂oL. This study also provides a reference assessment of the QoL of CU patients, as assessed by the German CU-Q₂oL, and an initial analysis of the patient characteristics associated with QoL impairment.

The factor analysis yielded six scales with highly satisfying face validity. Factor I, functioning, groups together all the items related to daily activities, and removes everything else. [medication side-effects (item 23) can be understood as disrupting daily activities, not sleep or mental status or something else]. Factor II, sleep, groups together all the items explicitly referring to sleep and no others. Factor III was one of the surprising yet insightful results of this factor analysis. It combines the two physical symptom items on hives with the two psychosocial items on feeling embarrassment/bothered. What this implies is that patients' embarrassment is directly tied to the physical symptoms of pruritus and wheals; not to swelling; not to limitations on their appearance; not to mood, personality, or other psychological factors; not to some other factors independent of the physical symptoms of pruritus and wheals. This kind of complex factor was obviously not anticipated by the Italians or by us but has insightful sensibleness. It even suggests that patients' experience of the intensity of their pruritus may in part be influenced by the degree of embarrassment they are feeling, and vice versa. Factor IV, mental status, groups together the three items related to the patient's psychiatric and physiological state. Factor V was another one of the surprising yet insightful results of this factor analysis. It combines the two physical symptom items on angioedema with the two behavioral items on difficult eating. Again, this combination was not anticipated either by the Italians or by us, but it makes perfect sense clinically. Moreover, it suggests that the main problem patients experience as a consequence of swelling is not embarrassment about their appearance or something else, but the difficulties they have eating. Conversely, eating and food choices are not really disrupted in the absence of swelling. Factor VI, limits looks, groups the remaining two items related to how a person makes himself or herself appear. Altogether this factor structure has very satisfying face validity, because each of the scales has a clearly comprehensible coherence and because none of the items seems misplaced onto the wrong scale. The loading of each variable onto a factor (Table 2B) is well saturated for most variables (above 0.60 and sometimes even above 0.80), and thus it can be anticipated

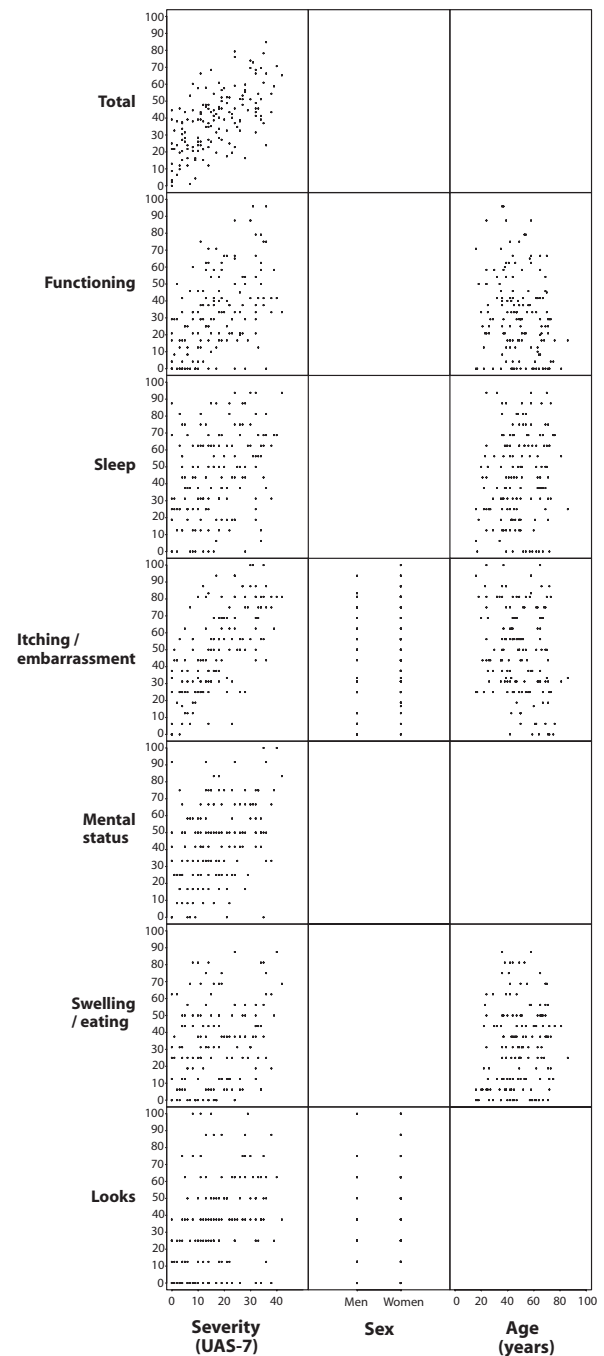


Figure 3. Patient characteristics predicting CU-Q₂oL scores. The scatter matrix shows the correlation between chronic urticaria (CU) severity, sex, or age on the one hand and the CU-Q₂oL scores on the other hand. Each dot represents one subject. Boxes have been left blank where there is no significant correlation between the two variables. In many instances, the pattern of correlation between the two variables is only weakly visible, indicating that other factors or random change account for a large portion of the variance in the data. It should be noted that, unlike the multiple linear regression, the figure cannot control for co-variables, and the significance of the bivariate association would be different and less valid than the *P*-values of the multiple linear regression presented in the main text.

that this factor solution, given the sample size of 157 subjects, will be stable across other samples (11). Moreover, these scales emerge from an almost purely mathematical analysis of the data, with truly minimal input, choices, or revision from us. Finally, virtually all of the statistical analysis for construction and validation yielded very robust numbers.

These six scales in the German version have high utility for further clinical research. Scale I (functioning) is a workhorse scale of QoL, comparable to the functioning scale of Skindex. Scale II (sleep) has obvious clinical usefulness, especially in light of our findings from a nationwide internet survey in Germany and France that sleep disturbances are widespread and not mild among people with CU (20). Scale III (itching/embarrassment) fuses together measurement of clinical symptoms with their personal impact on the patient, thus providing richer information than a simple physical examination could. Scale IV (mental status) provides a valuable, albeit brief, indication in the psychological domain, known to be an important factor among CU patients (21–23) and an important component of QoL generally. Scale V (swelling/eating) again provides a compound assessment of clinical symptoms and their immediate impact on the patient's life, in an area not assessed by other QoL questionnaires. Scale VI (limits looks) may be less useful for research, but it reflects items identified by CU patients in the original construction of the instrument, so it must have some importance for them.

It is important to note that the CU-Q₂oL, like Skindex-29, does not provide a 'total' score. The original generation and selection of the 23 items for the Italian CU-Q₂oL made it clear that patients assign different weights of importance to the various items and that many other items not retained in the CU-Q₂oL have some importance for some patients (9). Therefore, merely calculating the score of all 23 items together would not accurately reflect any patient's global QoL. Moreover, such a 'total' score has not been validated in either the Italian version (9) or the German version.

It is also important to remark that the German and Italian versions of the CU-Q₂oL have different scales. Briefly, the Italian version uses these six scales: (i) pruritus; (ii) swelling; (iii) impact on life activities; (iv) sleep problems; (v) limits; (vi) looks (9). Although both the German and Italian version have the same 23 items, as well as some scales using similar names, the 23 items are assigned differently, thus creating six different scales in each version. This difference was to be expected, because the respective factor analyses were conducted on two different study populations and because the CU-Q₂oL is still a relatively new instrument. Unfortunately, this effectively rules out direct comparisons between future clinical results from the German and the Italian CU-Q₂oL at this time. Nonetheless, some indirect comparisons – or juxtapositions – will still be entirely possible, with appropriate caution to their interpretation. The Italian scale

'impact on life activities' is quite close to the German 'functioning' scale, and the Italian 'sleep problems' scale is comparable to the combination of the German 'sleep' and 'mental status' scales. Also, the Italian scales 'pruritus' and 'swelling' are like purely symptomatic versions of the German scales 'itching/embarrassment' and 'swelling/eating'. Yet, the item-bundles on the Italian scales 'limits' and 'looks' are too different from the item bundles on any of the German scales for even indirect comparison, and are best understood independently on their own terms. We believe that future studies with new larger data samples and rigorous in-depth analysis will eventually consolidate the CU-Q₂oL into a uniform set of scales across many languages/cultures. In the meanwhile, there is actually one way rigorous direct comparisons can be made between datasets from the Italian and German versions: the scores on the 23 individual items can be compared, one-by-one.

The CU-Q₂oL should become one of the main outcome measurements in research on therapy for CU. As CU is a chronic condition yet does not represent a threat to the patient's further health or life, patient-rated outcomes, such as the CU-Q₂oL scores, are somewhat more sensible than a traditional clinical evaluation for evaluating the efficacy of treatment of CU. Currently, the cause and 'cure' for CU remain unidentified in most patients (24). There is insufficient evidence on most medications other than second-generation antihistamines (25) and scant information on any non-pharmacological approaches to CU treatment/management. Yet, CU imposes a long-lasting burden on patients' QoL. Thus, there is a need for many further clinical trials of various treatments for CU. Clinical trials cannot limit themselves to assessing physical symptoms; they must assess the patient's QoL, to understand the larger picture of their effect on the patient's experience (26, 27). The CU-Q₂oL should be a valuable way to measure the benefits of these treatments, as experienced from the patient's perspective. It would be important, however, to assess first its responsiveness and minimally important difference.

The fact that the DLQI scores (Fig. 1C) of this CU sample appear quite low for many subjects probably reflects the inadequacy of the DLQI for CU more than it reflects a lack of QoL problems for these patients. It has been determined that DLQI scores of 0–1 mean that the skin condition has 'no effect at all' on the patient's life, and scores of 2–5 mean that the skin condition has only 'a small effect' on the patient's life (28). As can be seen, nearly half the subjects of this study fell into this range. But the DLQI is a short questionnaire that focuses predominantly on a patient's functional ability to perform daily activities. It makes no assessment of sleep, mental status, or eating, all of which are often affected by CU. By capturing these other dimensions, the CU-Q₂oL, in contrast to the DLQI, made it clear that only very few subjects had no QoL issues at all. The DLQI is very well suited for its purposes (10, 14), but this study confirms the need for a disease-specific QoL questionnaire for research (9).

There are four minor areas where further research and refinement of the German CU-Q₂oL would be beneficial. First, the responsiveness of the German CU-Q₂oL should be assessed by administering it in the same clinical population twice – before and after a month of beneficial treatment. The amount of objective clinical improvement should then be correlated to their improvement in the CU-Q₂oL scores, as was performed in the Italian version (9). Secondly, the minimally relevant difference of CU-Q₂oL scores should be determined, similar to its determination for the DLQI (29). This would enable a better understanding of when improvements in CU-Q₂oL scores are actually meaningful improvements in the patient's real life and not merely minor numerical improvements on paper. Thirdly, the swelling/eating scale of the CU-Q₂oL should be better validated by correlating it with objective clinical assessments of swelling and validated questionnaires that measure eating difficulties. The DLQI and Skindex-29 do not assess swelling or eating, and we did not anticipate the emergence of this scale from the factor analysis. Strictly speaking, we cannot prove that scale V is a valid assessment of swelling/eating, but practically there are, to our awareness, no other validated QoL instruments to use instead for assessing swelling/eating. Finally, the limits looks subscale could benefit from further in-depth study. The items on this scale were provided by the original Italian study sample and met their criteria for retention, so these items must have some importance for many CU patients. In the German version, however, this factor was the last one to meet the criteria for retention and explained the least amount of data variance. Only two items loaded onto only this factor; a third item (limits food) that loaded onto two factors was better suited to the other factor (swelling/eating). The consistency of this scale, as determined by Cronbach's alpha, was barely permissible. In-depth qualitative research with CU patients scoring relatively worse on the CU-Q₂oL limits looks scale than on the other scales would provide better insight and permit refined use of this small section of the CU-Q₂oL. It should be kept in mind that the scale name, 'limits looks', is our own designation; in-depth research (or a new factor analysis on new datasets) might reveal that the commonality of these two questionnaire items may relate to something else (e.g. only 'looks' or only 'behavioral prevention' or something else entirely).

Alternately, it might make more sense to just eliminate scale VI and its two items from the instrument, as one of two revisions in the list of items on the CU-Q₂oL. This scale explained the least amount of data variance in the factor analysis and had very weak internal consistency, so the other scales and the instrument as a whole would probably gain robustness if unburdened of these two items. Both of these items barely cleared the Italian authors' criteria for retention from the original list of 37 items and were actually the lowest two retained items in 'overall impact' in their item selection process (9). The cosmetics item (#20) is poorly applicable to men and to

any women who do not normally use cosmetics. The instrument would also be easier to administer, score, and report if this scale was dropped. The second of two separate revisions we would suggest for the items on the CU-Q₂oL would be inclusion of another item in the psychophysiological realm. The original Italian study identified an item, which regrettably was not retained past their development phase: 'I feel anxious about my health condition' (9). Psychological problems generally and anxiety specifically are known to play an important role in CU patients (21, 22) and fall into the sphere of health care more than other QoL issues, such as fashion. This item would certainly have fit well with the mental status scale of the German factor structure and provided more items for that short scale. This item on anxiety was experienced by 38% of the 80 Italian subjects involved in item reduction, and they assigned it a mean importance of 3.12 on a 0–4 scale! The criterion for item retention in the Italian study was 'arbitrary' (9) and inadvertently favored items that were widespread over items that were highly important to those who had them. If the 'overall impact' cut-off level for retention had been set at 1.0 rather than 1.5, this is the one additional item that would have been retained. We would suggest including this item in future methodological research on the CU-Q₂oL.

With regard to the actual initial findings, it is important to note that women were more severely affected on the itching/embarrassment scale (Fig. 3). This concurs with our previous finding from a nationwide internet survey of German and French people with CU, where women had significantly higher scores on the Skindex symptoms scale (30) and were significantly more often bothered by symptoms on several body parts (20). There are three possible explanations for these consistent findings that women are more bothered by CU symptoms than men. One possible explanation is that CU has a different etiology or more severe pathogenesis in women, leading to a more severe outbreak of symptoms (31). A second possible explanation is that women's skin and/or mental perception is more sensitive to the irritation of CU symptoms. A third possible explanation is that CU manifests itself in different anatomical patterns in men and women, thereby affecting more sensitive body parts in women than men (20). In any case, this is clearly an important finding for further research, which will surely have treatment implications.

This study also found that sleep and mental status were two of the more severely affected dimensions of QoL (Fig. 2). This was consistent with our past studies showing that CU is often associated with psychological problems (21) and with sleep disturbances (20). Thus every physician caring for CU patients should ask them about their sleep and mood (nervousness, anxiety, depression) and provide treatment or advice in these areas, in addition to treating their skin symptoms.

Chronic urticaria remains poorly understood, available treatments are not always effective, and information

remains sparse on how patients experience their condition. Clearly, there is still a lot of research to be conducted on CU, to improve the treatment patients receive. The CU-Q₂oL developed by Baiardini et al. should be an essential tool for much of this future research. The German version has demonstrated robust validity and should be widely adopted in upcoming clinical studies. The CU-Q₂oL should be translated into a few more languages, and an international study with

pooled data should be conducted to arrive at a revised consensus version of the CU-Q₂oL with robust scales, item assignment, and validation.

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