

Development of a Disease-Specific Quality of Life Questionnaire in Addison's Disease

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Context: Patients with Addison's disease reproducibly self-report impairment in specific dimensions of general well-being questionnaires, suggesting particular deficiencies in health-related quality-of-life (HRQoL).

Objective: We sought to develop an Addison's disease-specific questionnaire (AddiQoL) that could better quantify altered well-being and treatment effects.

Design, Setting, Patients, Intervention, and Outcomes: We reviewed the literature to identify HRQoL issues in Addison's disease and interviewed patients and their partners in-depth to explore various symptom domains. A list of items was generated, and nine expert clinicians and five expert patients assessed the list for impact and clarity. A preliminary questionnaire was presented to 100 Addison's outpatients; the number of items was reduced after analysis of the distribution of the responses. The final questionnaire responses were assessed by Cronbach's α and Rasch analysis.

Results and Interpretation: Published studies of HRQoL in Addison's disease indicated reduced vitality and general health perception and limitations in physical and emotional functioning. In-depth interviews of 14 patients and seven partners emphasized the impact of the disease on the emotional domain. Seventy HRQoL items were generated; after the expert consultation process and pretesting in 100 patients, the number of items was reduced to 36. Eighty-six patients completed the final questionnaire; the responses showed high internal consistency with Cronbach's α 0.95 and Person Separation Index 0.94 (Rasch analysis).

Conclusions: We envisage AddiQoL having utility in trials of hormone replacement and management of patients with Addison's disease, analogous to similar questionnaires in GH deficiency (AGHDA) and acromegaly (AcroQoL). (*J Clin Endocrinol Metab* 95: 545–551, 2010)

PPrimary adrenal insufficiency (Addison's disease) is conventionally treated with glucocorticoid and mineralocorticoid replacement (1), and more recently, replacement of the adrenal androgen dehydroepiandrosterone (DHEA) has been much investigated (2–5). However, the current replacement regimens do not reproduce the normal diurnal variations of the glucocorticoid levels, with uncertain consequences for patients' health (6). Novel treatment strategies such as modified-release hy-

drocortisone tablets or continuous sc hydrocortisone infusion have been proposed (7, 8). There is no "gold-standard" for assessment of treatments, but a clinical scoring system has been proposed (9). Circulating hormone levels do not necessarily reflect the cellular effects of these hormones. Measurement of cortisol profiles can guide glucocorticoid replacement therapy (10–13), whereas mineralocorticoid therapy is monitored by measurement of biomarkers of responses such as electrolyte levels, blood

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

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doi: 10.1210/jc.2009-1711 Received August 10, 2009. Accepted November 16, 2009.

First Published Online December 16, 2009

Abbreviations: DHEA, Dehydroepiandrosterone; HRQoL, health-related quality of life.

pressure, and plasma renin activity (1). DHEA replacement therapy is assessed by measurement of DHEA sulfate and androgen levels, or possibly their metabolites (14). Even with biochemically optimal replacement regimens, patients reproducibly self-report impairment in particular dimensions of general well-being questionnaires (5, 15–17).

A multitude of general questionnaires that measure various dimensions of functioning and subjective well-being exist; they are not specific to any population or disease and are thus particularly apt for large-scale population-based observational studies, allowing comparisons across groups and conditions. Disease-specific or, more precisely, disease-sensitive questionnaires address symptom domains that are relevant to a particular disease and potentially more able to detect changes over time. Instruments that specifically measure particular symptoms are needed in endocrine disorders, as illustrated by the development of disease-specific health-related quality of life (HRQoL) questionnaires for the assessment of other endocrine disorders such as GH deficiency [Assessment of Growth Hormone Deficiency in Adults (AGHDA)] (18), acromegaly [Acromegaly Quality of Life (AcroQoL) questionnaire] (19), and Cushing's syndrome (CushingQoL) (20).

Here, we describe the development of a novel disease-specific HRQoL questionnaire (AddiQoL) for assessment of Addison's disease patients during replacement therapy.

Subjects and Methods

Design

We followed guidelines for development of disease-specific questionnaires as described by Juniper *et al.* (21), as shown in Fig. 1. The process may be divided into four stages: 1) identification of HRQoL issues, *i.e.* literature review and interview studies; 2) HRQoL item generation; 3) pretesting of the questionnaire in a patient cohort; and 4) field testing of the questionnaire.

The study was approved by the Cambridge Research Ethics Committee, and all subjects gave written informed consent before participation.

Stage 1: literature review and in-depth interviews

An extensive search of the PubMed and PsychINFO databases was undertaken with the primary search terms "Addison's disease," "adrenal insufficiency," and "quality of life." The articles thus identified were further scrutinized for relevant references. Patient surveys undertaken by Addison's disease associations in different countries were obtained via the internet or by personal contact. Surveys using validated questionnaires and surveys using nonvalidated questionnaires were analyzed separately.

Outpatients with verified Addison's disease ($n = 14$) and their partners ($n = 7$) were invited to participate in an in-depth interview aimed at identifying previously neglected HRQoL issues and to describe their relative importance. Inclusion of patients sought to represent a range of age, gender and disease duration; the inclusion stopped as successive interviews ceased to yield new information relevant to the research objective, yielding a sample size typical for in-depth interview studies. Patients with well-controlled concomitant hypothyroidism were also included. Insulin-treated diabetes mellitus or other severe comorbidities excluded participation.

The interviews began with open-ended questions like: "What is it like to live with Addison's disease?" and "Is there anything you would like to do that you cannot do because of Addison's disease?" The second part of the interview was semistructured, with questions about issues anticipated to be relevant to the patient. Their partners were interviewed in a similar way and questioned about the impact of the disease on the family. The interviews were carried out in the Wellcome Trust Clinical Research Facility at Addenbrooke's Hospital (Cambridge, UK) by an endocrinologist (K.L.) unfamiliar with the study subjects and an endocrine specialist nurse (S.C.). The interviews were taped, and transcripts were analyzed by the Atlas.ti software (Atlas.ti Scientific Software Development GmbH, Berlin, Germany) and interpreted by qualitative research methods (22).

Stage 2: HRQoL item generation

Based on the literature review and the in-depth interview data, 70 HRQoL items were generated to cover the relevant issues with both positive and negative phrasings. Thirty-six phrasings were adapted from existing questionnaires, and 34 were invented. Nine European expert endocrinologists and five expert patients recruited from the UK Addison's disease self-help group assessed each item for frequency, importance, and clarity of expression.

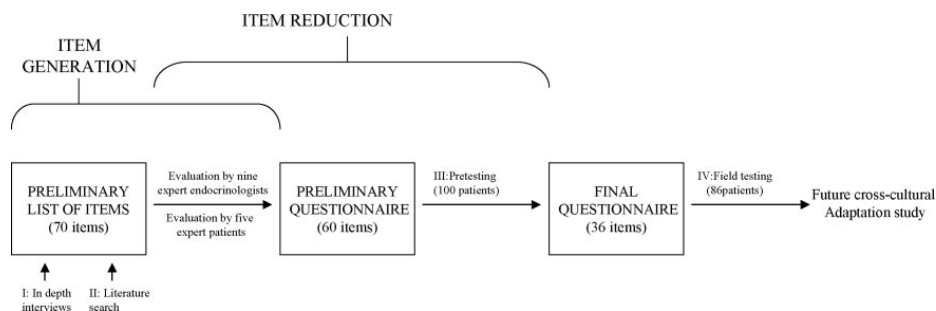


FIG. 1. Flow chart of study design.

TABLE 1. Age and sex distribution of the patients

	Age range (yr)						Unknown	Total
	<30	30–40	40–50	50–60	60–70	70+		
Males	1	4	9	8	8	2	1	33
Females	3	9	16	23	9	4	3	67
Total	4	13	25	31	17	6	4	100

Data represent number of patients.

Stage 3: pretesting of the questionnaire in a patient cohort (item reduction)

The preliminary questionnaire was pretested in a group of 100 anonymized patients with Addison's disease, recruited from the UK Addison's disease self-help group; only patients with primary adrenal insufficiency treated with fludrocortisone and hydrocortisone were invited to participate. Patients with well-controlled concomitant hypothyroidism were included; insulin-treated diabetes mellitus or severe diseases such as cancer or inflammatory diseases treated with glucocorticoids precluded participation. The patients returned questionnaires without personal identification, indicating only age group and gender, as shown in Table 1. Their responses to each item were scored on a five-point Likert scale with scores ranging from 1 (strongly disagree) to 5 (strongly agree), or 1 (almost never) to 5 (almost all the time). For statistical analysis, the scores for the negatively phrased items were reversed, rendering higher scores favorable.

The process whereby items were further reduced was based on both statistical analysis and clinical considerations. First, the distribution of the responses to each item was analyzed. Items were discarded if the distribution of responses was either narrow or highly skewed toward higher scores, indicating little relevance or inappropriate wording of that item. Second, when two items correlated significantly with Spearman's R above 0.7, one of them was discarded. Third, Cronbach's α was calculated to assess internal consistency of the selected items. The final selection of items was made to ensure breadth of coverage and to include items that were most likely to respond to treatment changes.

Stage 4: field testing of the final questionnaire

We selected the six-point scale 1 (none of the time)—6 (all of the time) to indicate frequency, and 1 (strongly disagree)—6

(strongly agree) to indicate severity. The final 36-item questionnaire was sent to the 100 patients above for determination of reliability and for initial analysis of dimensional structure, applying Rasch analysis (RUMM2020 software, Rasch Unidimensional measurement models; RUMM Laboratories, Perth, WA, Australia), as described in *Statistics*.

Statistics

For the pretest, the distributions of the responses to each item were analyzed by descriptive statistics. When two items correlated significantly ($P < 0.01$) and with Spearman's R above 0.7 (pair-wise correlation of all items), one of them was omitted. Internal consistency was evaluated by Cronbach's α and by the Person Separation Index given by the Rasch analysis.

The Rasch model is an item response theory that can be used to assess whether a group of items measure the same HRQoL dimension (unidimensional construct). The Rasch model allows quantitative assessment from data that are originally ordinal but not necessarily linear (additive), based on logistic transformation of the item responses (23). Within the mathematic model of Rasch analysis, the items and the persons are organized in an ordered hierarchy in which the item location represents item difficulty, or the level of HRQoL impairment targeted by the item. Item difficulty is calculated from the proportion of the patient sample that endorsed each item. The person location represents person ability or the patient's level of HRQoL impairment. Person ability is estimated from the proportion of items that each person endorsed. By placing both measures on the same scale, the Rasch analysis makes it possible to explore how well the items are targeted for the sample population. The RUMM software calculates residual fit statistics for each person and each item, applying χ^2 statistics for item-trait test-of-fit to the

TABLE 2. Published mean scores in HRQoL studies applying the generic questionnaires SF-36 or GHQ in Addison's disease cohorts in Norway (15), United Kingdom (3, 5), and Germany (16, 25)

HRQoL domain	Scale	Score	Normative
General health	Vitality (SF-36)	47–52 ^a	58–60
	General health (SF-36)	56–59 ^a	71–77
	Self-esteem (GHQ)	8.1 ^b	7.6
	Coping (GHQ)	10.3	9.8
Physical health	Role-physical (SF-36)	46–66 ^a	78–87
	Physical functioning (SF-36)	PF 80–84	87–88
	Bodily pain (SF-36)	BP 76–79	75–79
Mental health	Role-emotional (SF-36)	57–75 ^a	82–86
	Social functioning (SF-36)	75–80	83–86
	Mental health (SF-36)	67–78	72–79
	Depression (GHQ)	7.2	7.3
	Anxiety (GHQ)	16 ^a	14

SF-36, Short Form-36; high scores are favorable. GHQ, General Health Questionnaire; low scores are favorable.

^a $P < 0.001$; ^b $P < 0.01$; differences from the normative data tested with Student *t* test (3, 5, 15) or Mann-Whitney *U* test (3, 5, 16, 25).

Rasch model. A statistically nonsignificant probability value ($P \geq 0.05$) indicates no substantial deviation from the model. Individual items or persons fit residual values of at least ± 2.5 , or probability values below the Bonferroni adjusted α -value are also used to indicate misfit to the model.

Results

Literature review

Studies that addressed HRQoL explicitly in primary adrenal insufficiency with validated questionnaires are presented in Table 2; they reproducibly indicate reduced vitality and general health perception and limitations in physical and emotional functioning. Four large-scale surveys undertaken by patient associations [The Netherlands, 1994 (P. Zelissen), $n = 91$; UK1, 1997 (S. Baker, personal communication), $n = 150$; North America, 1999 (P. Marquies and J. Miller), $n = 580$; and UK2, 2006 (K. White *et al.*, personal communication), $n = 386$] were found and reviewed. Most of these were uncontrolled surveys reporting various symptoms occurring frequently in the patients, but essentially complied well with the picture from the controlled studies. A few symptoms like heat intolerance, sweating, thirst, waking in the night to pass water, and gastrointestinal symptoms were frequently reported in these surveys.

In-depth interviews

The interviews corroborated the reports of fatigue as the most important HRQoL issue in Addison's disease but showed great interindividual variation in symptoms. Many felt a reduction in their physical endurance, but few thought that Addison's disease limited their physical strength. Emotional stress was considered more problematic than physical challenges. Some described altered somatic response to stress; they would stay calm in stressful situations with a paradoxical decrease in heart rate. Depression and anxiety were not common in the interviewed patients. Forgetfulness was a common concern among the patients and their partners. Subjectively, Addison's disease did not impose significant limitations for most of the patients. Worries about adrenal crises were not particularly common, but it would keep many from traveling to remote areas without proper emergency care. Some claimed to be healthier with Addison's disease than they would otherwise have been because they would not let the disease take control of their lives.

Item generation and item reduction

The consultation process with experts reduced the number of items from 70 to 55 and added five more items, yielding a preliminary questionnaire of 60 for the

TABLE 3. Thirty-six items included in the AddiQoL questionnaire and the results of Rasch analysis of the responses from 86 patients with Addison's disease

	Location	Fit residual	P value
I feel lightheaded	-1.55	-0.08	0.316
I get nauseous	-1.29	-0.05	0.518
I worry about my health	-1.03	-0.63	0.667
I find it difficult to think clearly	-1.01	0.20	0.020
I am happy	-0.93	-0.86	0.133
I feel low or depressed	-0.63	-0.08	0.419
I have to struggle to finish jobs	-0.59	-1.95	0.049
I sweat for no particular reason	-0.57	3.45	0.011
I am irritable	-0.54	0.27	0.053
My legs feel weak	-0.53	0.01	0.587
I get headaches	-0.51	2.48	0.194
I lose track of what I want to say	-0.49	0.34	0.802
I feel unwell first thing in the morning	-0.38	-0.39	0.294
I can concentrate well	-0.29	-0.51	0.314
I have salt cravings	-0.28	2.63	0.009
Normal daily activities make me tired	-0.13	-1.12	0.102
My ability to work is limited	-0.11	-0.72	0.542
My joints and/or muscles ache	-0.10	-0.29	0.355
I have back pain	-0.08	0.80	0.425
I have to push myself to do things	-0.03	-1.51	0.057
I feel good about my health	0.11	-2.18	0.008
I sleep well	0.18	0.93	0.609
I am relaxed	0.44	0.21	0.880
I get ill more easily than others	0.45	1.70	0.121
I feel physically fit	0.55	-1.63	0.085
I have lost interest in sex	0.55	4.04	0.001
I need to get up during the night to pass water	0.61	4.14	0.008
I can keep going during the day without feeling tired	0.61	-1.17	0.202
I feel rested when I wake up in the morning	0.73	-0.95	0.129
I am satisfied with my sex life	0.78	3.29	0.126
I take a long time to recover from illnesses	0.80	0.26	0.759
I put on weight easily	0.83	2.12	0.011
I cope well in emotional situations	0.84	1.15	0.094
I have dry skin	0.92	2.59	0.043
Emotional stress makes me exhausted	1.04	1.76	0.376
I feel full of energy	1.63	-2.26	0.031

Location indicates hierarchical order of items; higher number reflects that an item addresses higher level of HRQoL impairment. Fit residuals reflect departure of the observed responses from the Rasch model; absolute fit residuals > 2.5 indicate lack of fit with a Rasch structure. P values represent testing of fit to the Rasch model (χ^2 statistics).

pretesting in patients (Table 1S, published as supplemental data on The Endocrine Society’s Journals Online web site at <http://jcem.endojournals.org>). The scoring by 100 patients of this preliminary 60-item questionnaire showed high internal consistency (Cronbach’s α 0.94). Aided by further statistical analyses as outlined above and in Table 1S, the number of items was reduced to 36.

Internal consistency and dimensional structure

The final 36-item questionnaire was completed by 86 of 100 patients. Their responses showed high internal consistency as evaluated by Cronbach’s α 0.95 and Person separation index 0.94. Further Rasch analysis revealed misfit to the Rasch model of the total 36 items, with item-trait interaction $\chi^2 = 260$ ($P < 0.0001$). The item fit residuals (Table 3) indicated departure of the observed scores from the Rasch model, such that items with fit residuals of at least ± 2.5 might not measure the same dimension as the total questionnaire. Exclusion of six items with extreme fit residuals yielded satisfactory fit to the Rasch model (item-trait interaction $\chi^2 = 141$; $P > 0.09$). Figure 2 shows the distribution of patient locations (spread in HRQoL) and item locations (spread in item difficulty), indicating that the selection of items produces a satisfactory coverage of spread in HRQoL for this particular patient group. The items located on the extreme left of the graph are those easiest to endorse, whereas the items on the extreme right are the most difficult to endorse. The average mean person location of 0.355 suggests that the scale was well-targeted for use in this group, with patients on average a slightly higher level of HRQoL than the average of the scale items.

Discussion

Here, we present a newly developed, disease-specific questionnaire for assessment of HRQoL in Addison’s disease. In endocrine disorders, disease-specific HRQoL questionnaires have become useful for both clinical management and research in various contexts, such as GH replacement therapy and tumor suppressive treatment in acromegaly (18, 19). No questionnaire specific for adrenal insufficiency has as yet been formulated.

Previous studies of HRQoL in Addison’s disease and the current in-depth interview study showed that fatigue, *i.e.* reduced energy and vitality, is a major problem during steroid replacement therapy. Previous studies also found reduced role-emotional scores, or limitations due to emotional problems (5, 15, 16); likewise, our clear impression from the in-depth interviews was that impaired coping with emotional stress is a salient feature of this disease. Notably, among all the items we tested, the patients scored worst on the item “Emotional stress makes me exhausted.” Mental health issues were frequently reported in the patient association surveys, and a recent registry-based study found increased prevalence of affective disorders in patients with adrenal insufficiency (24). Some of the formal studies in Addison’s disease (16, 25), but not all (5, 15), have found slightly impaired mental health scores. Specifically, the patients scored worse than matched controls on anxiety but not on depression (16). One clinical trial showed beneficial effects of DHEA replacement on sexuality in females with adrenal insufficiency (primary and secondary) (2), but this was not replicated in studies that only included Addison’s disease patients (3, 5). In fact, very little is known about sexuality and dysfunction in patients with Addison’s disease on conventional treat-

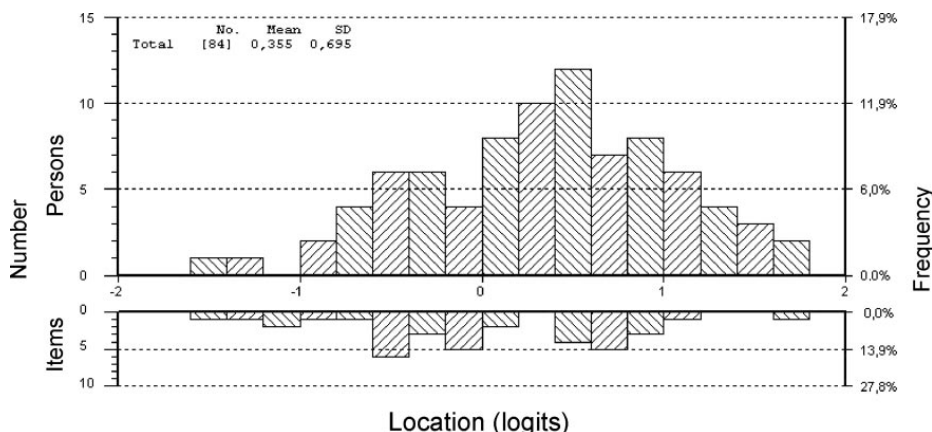


FIG. 2. The person-item location distribution showing item locations (spread in difficulty) and person locations (spread in HRQoL), suggesting that the scale was well-targeted for use in this group, with patients on average at a slightly higher level of HRQoL than the average of the scale items.

ment. Forgetfulness was quite frequently reported in the patient surveys and was also a concern expressed in the in-depth interviews, although it was not found by formal cognitive testing (3, 5). Formal questionnaire studies found bodily pain scores normal (5, 15) or better than normal (16), whereas the patient organization surveys revealed frequent muscle and joint pain. In the current study, items addressing pain generally yielded positive scores (little pain).

A comprehensive list of items was generated to cover the issues above; some items were adapted from existing questionnaires and others were newly formulated. A few items addressed issues such as heat tolerance, sweating, thirst, and nighttime urge to pass water, which had not previously been tested in formal studies but which patient surveys suggested were relevant. We added both positively and negatively worded phrasings to approach the issues from different angles. We sought to select items that indicate *state* as opposed to *trait*, because state is more likely to change within individuals in response to treatment (26). The item reduction process was an iterative process using clinical and statistical analyses. After the process and analyses described here, we have developed a questionnaire that maintains a high degree of internal consistency as well as a satisfactory breadth of coverage of HRQoL issues and also targets the patient population very well.

Further validation studies in larger populations are needed to verify and explore the dimensional structure of AddiQoL and to determine test-retest reliability and its validity as a tool for measurement of treatment effects. The questionnaire will be translated into other languages for cross-cultural validation. The patients in our study did volunteer via a patient organization, such that some selection bias in their responses cannot be excluded. Further Rasch analysis of the responses in several unselected patient and control populations is required to determine its psychometric properties and to develop scoring algorithms.

In conclusion, we envisage this novel Addison's disease-specific questionnaire (AddiQoL) having utility in trials of hormone replacement and management of patients with Addison's disease, analogous to questionnaires in GH deficiency (AGHDA) and acromegaly (AcroQoL).

Acknowledgments

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The study was supported by grants from the European Union Framework Program 7 (Grant 201167, Euradrenal) and the

National Institute for Health Research, Cambridge Biomedical Research Centre.

Disclosure Summary: The authors have nothing to disclose.

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Supplementary Table S1 Preliminary 60-item questionnaire presented to 100 Addison’s patients. The scores of negatively phrased items are reversed.

Median and 25-centile scores on a 1-5 Likert scale; higher values indicate less important. Selected items in bold

Included	Median	25-percentile	Comments, reasons for inclusion
I feel good about my health	4	2	Wide distribution, general issue
Normal daily activities make me tired	3	2	Proper distribution, central issue
I feel physically fit	3	2	Proper distribution, central issue
I have to struggle to finish jobs	3	2	Proper distribution, central issue
I can keep going during the day without feeling tired	2	2	Low median, central issue
I have to push myself to do things	3	2	Proper distribution, central issue
I often feel unwell first thing in the morning	4	2	Wide distribution, central issue
I find it difficult to stay awake in the evening	3	2	Proper distribution, central issue
I sleep well	3	2	Proper distribution, central issue
I seem to get ill more often than others	4	2	Wide distribution, central issue
I am satisfied with my sex life	3	2	Proper distribution, central issue
I have lost interest in sex	3	2	Proper distribution, central issue
I often lose track of what I want to say	3	2	Proper distribution, central issue

I cope well in emotional situations	3	2	Proper distribution, central issue
Emotional stress makes me exhausted	2	1	Low scores, central issue
I sweat for no particular reason	2	2	Low scores, breadth of coverage
I put on weight easily	2	1	Low scores, breadth of coverage
I have dry skin	2	2	Low scores, breadth of coverage
I worry about my health	3	2	Proper distribution, central issue
My ability to work is limited	3	2	Proper distribution, central issue
I feel full of energy	3	2	Proper distribution, central issue
I feel rested when I wake up in the morning	3	2	Proper distribution, central issue
I need to get up during the night to pass water	2	1	Low scores, breadth of coverage
I can concentrate well	4	3	Proper distribution, central issue
I forget things	3	3	Narrow distribution, central issue, rephrased
I have back pain	4	3	Proper distribution, breadth of coverage
My joints ache	4	2	Proper distribution, breadth of coverage (these two items collapsed in final questionnaire)
My legs feel weak	4	3	collapsed in final questionnaire
I get headaches	4	3	Proper distribution, central issue
I feel lightheaded	4	3	Proper distribution, central issue

I have salt cravings	3	2	Proper distribution, central issue
I feel nauseous	4	3.25	Narrow distribution, central issue
I am happy	4	3	Proper distribution, general issue
I am irritable	3	3	Narrow distribution, breadth of coverage
I feel low or depressed	4	3	Proper distribution, breadth of coverage
I am relaxed	3	2	Proper distribution, breadth of coverage
Excluded			
I worry about going into adrenal crisis	4	2	Duplication
I take a long time to recover from illnesses	2	2	Narrow distribution
I bruise easily	3	2	Clinical sign; not subjective symptom
I tolerate heat well	2	2	Narrow distribution, depends on external factors
I am often thirsty	2	2	Narrow distribution, depends on external factors
My skin pigmentation bothers me	4	3	Proper distribution, high median, trait rather than state
I often have dry eyes	3	2	Proper distribution, depends on external factors
I lose weight easily	4	3	High median, covered by other items
When things go wrong in my life, it generally takes me a long	3	2	Duplication

time to get back to normal

I feel I make a valuable contribution to the lives of my family

and friends 4 4 Narrow distribution

I am able to enjoy my normal daily activities 4 3 Duplication

I feel a strong need to sleep during the day 3 3 Narrow distribution

I have difficulty falling asleep 4 3 Duplication

My muscles ache 4 3 High median, covered by other items

I get muscle spasms or cramps 4 3 High median, covered by other items

My hands or feet are uncomfortably cold 4 3 High median, depends on external factors

I have a good appetite 4 3 High median

I have hunger pangs 3 3 Narrow distribution

I feel bloated 4 3 High median

I have diarrhoea 5 4 High median

I feel anxious 4 3 High median

I look forward to each new day 4 3 High median

I am calm and peaceful 3 2 Duplication

I am optimistic about my future 4 3 High median