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Metric properties of the MacDQoL, individualized macular-disease-specific quality of life instrument, and newly identified subscales in French, German, Italian, and American populations

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ABSTRACT

Objectives: The aims of this analysis were to confirm the UK results in other countries and to explore the possibility of subscales of the 25-Item Macular disease Dependent Quality of Life (MacDQoL) questionnaire.

Methods: Two clinical studies were pooled. Principal components analyses (Varimax) were conducted on baseline data from each country and from all combined. Factorial structures were compared between countries, and Cronbach alpha values were used to identify item clusters. Four groups of patients were created according to visual acuity (VA) in the best eye (BE<10/20; BE ≥10/20) and worst eye (WE<10/100; WE≥10/100). These groups were used to investigate (analysis of variance) the sensitivity of MacDQoL to VA impairment and to compare it with the NEI-VFQ-25 generic visual function questionnaire.

Results: A total of 797 patients (mean age 76.8 years; 55.8% women) had wet age-related macular degeneration (AMD). Strong correlations between the MacDQoL items (r>0.48) and factor loadings >0.49 on a forced one-factor analysis supported the use of an average weighted impact score. Four constructs (Cronbach alpha >0.8) were derived, represented by the labels: Essential tasks, Family/social life, Activities/capabilities, and Embarrassment. The structure did not differ among the four countries involved, excepted one item (Finance), which has been excluded. Patients with BE VA<10/20 and WE VA<10/100 produced significantly worse overall scores than those with BE VA>10/20 and WE VA>10/100 (MacDQoL p<0.0001; NEI-VFQ-25 p<0.0001).

Conclusions: The analysis confirmed the metric properties of the MacDQoL. The MacDQoL offers a broad individualised measure of the impact of MD on quality of life.

Introduction

Age-related macular degeneration (AMD) affects the central portion of the retina (macula) responsible for central vision. As opposed to peripheral vision, central vision is essential for driving, reading, face recognition, and fine visual tasks [1]. The disease occurs in two forms, atrophic (or dry) AMD characterized by localized atrophy and exudative (or wet) AMD characterized by choroidal neovascularization (CNV) [2]. Atrophic AMD is more frequently encountered than the exudative form. Atrophic AMD progresses slowly over a variable period, usually 5 to 10 years, and eventually results in legal blindness (visual acuity <20/200). In contrast, exudative AMD affects no more than 10% to 20% of patients with AMD, in general, but presents a far greater threat to vision, accounting for 80% to 90% of all blindness in these patients [3].

AMD is the most common cause of all adult blindness in Western developed countries [4,5] and is the major reason for severe vision loss in people above 65 years of age [6,7]. End stage (blinding) AMD is found in about 1.7% of all people aged over 50, and incidence rises with age (0.7% to 1.4% in people aged 65 to 75, 11.0% to 18.5% in people older than age 85) [8]. The 5-year incidence rate of late-stage AMD was estimated as between 0.49% and 1.1% [9,-10]. AMD incidence rate is increasing exponentially with age [11]. The burden of ocular morbidity and visual disability due to AMD will increase further with an expanding older population [11]. A steady increase in the number of people now registering as blind/severely sight impaired in the UK [12] suggests that the incidence of AMD is already growing in most Western populations [11]. As a result, AMD is an increasing public health concern for decision makers.

Awareness of the impact of AMD on quality of life (QoL) remains low amongst clinicians and the general public and, as pointed out elsewhere [13], considerable confusion is caused by the misuse of health status tools and utilities to measure QoL in people with AMD. In a direct comparison of a time trade-off (TTO) utilities measure with scores from the Macular disease Dependent QoL (MacDQoL) questionnaire, Mitchell and Bradley [14] found that TTO was not a valid indicator of QoL in this elderly population whose willingness, or, more often, unwillingness to trade years of life was influenced by many factors other than the severity of their MD. TTO also has been shown to be unrelated to visual acuity by Hill et al. [15], who showed that 50% of participants with varying severity of MD were unwilling to trade any time for perfect vision. For those who would trade some time, there was no relationship between TTO and visual acuity. We suggest that health status instruments are inappropriate also, because they can measure only perceived health, not QoL, and respondents will not necessarily even consider their vision when rating their health [13]. It is not unusual for individuals who are registered blind to report that they have excellent health on measures such as the EQ-5D and SF-36 while nevertheless reporting severe impairment to their quality of life as a result of their vision loss.

AMD has been shown to be associated with significantly impaired scores using the NEI-VFQ-25 measure of visual function [16] and the Quality of Well-being Scale [17]. Functional independence also has been shown to be negatively impacted as measured by the Instrumental Activities of Daily Living index, self-rated general health status, the Profile of Mood States [8,18,19], and other patient-reported outcome measures [13]. People with AMD are particularly susceptible to depression [13,20,21]. Also, visual impairment is strongly associated with incapacity, dependency [22,23], and institutionalization [24]. Visual function (measured with the NEI-VFQ-25) deteriorates as soon as the first eye is affected in AMD patients [16] or in patients with other types of eye diseases [25], though the association between visual function and best eye (BE) vision remains strongest [16]. Although visual function measures (e.g., NEI-VFQ-25 [16]) and well-being (e.g., the Well-being Questionnaire W-BQ12 [17]) are likely to correlate to some degree with QoL, they are not in themselves measures of QoL. Finger et al. in 2008 [26] and van Nispen et al. [29] in 2009 provide useful reviews of vision-specific questionnaires available for people who have AMD. Although Finger et al. entitled their article "Quality of life in Age-Related Macular Degeneration," in fact most of the measures included in the review are measures of visual function. Few measures used in studies of AMD actually measure QoL, although the MacDQoL is an exception [27].

Treatments are now available for wet AMD [28-29]. Public health authorities are increasingly insisting that patient reported outcome assessment [30] be included in trials evaluating new treatments; many have demanded health status measures such as the EQ-5D [31], but these have been shown to be unsuitable for evaluating the impact of AMD on QoL [13]. The need for a valid instrument to measure the impact of AMD on QoL led to the development of an individualized questionnaire specific to macular disease including AMD. The resulting MacDQoL questionnaire [32,33] asks about the impact of MD on aspects of life that have personal relevance for the individual and the importance of those aspects of life for their QoL. The strategy of weighting QoL domains on the basis of their importance to an individual was previously adopted in an interview method developed by McGee et al. [34] and was adapted for questionnaire use by Bradley et al. with the diabetes-specific Audit of Diabetes Dependent QoL [35,36], which provided a model for the MacDQoL. Bradley et al. [39] followed McGee et al. in defining QoL as "how good or bad you feel your life to be," and it is this definition that is included in the instructions for completion of the Specific Audit of Diabetes Dependent QoL, MacDQoL, and related measures. The design [32] and psychometrics [33,37] of the MacDQoL questionnaire are published elsewhere. In a sample of UK patients, the MacDQoL showed excellent internal consistency reliability, test-retest reliability [33, 38], and a single-factor structure. The MacDQoL showed that macular degeneration has a considerable negative impact on many aspects of life important for QoL [32,37]. To be used in multinational clinical trials, the instrument requires validation in other languages. The aim of this article is to report the factorial structure of the MacDQoL in French, German, Italian and American AMD patients and to explore the possibility that there may be useful subscales.

Material and Methods

Institutional review board or ethics committee approvals were obtained by all centers participating in a clinical trial that contributed data to the present analysis. Written informed consent was obtained from all patients, and investigations performed in the United States were Health Insurance Portability and Accountability Act-compliant (HIPAA).

Concerning the cross-sectional survey, institutional review board approval was obtained in Germany and Italy. In France, the protocol was reviewed by the Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé. Informed consent was obtained from all patients.

Data sources

The reported analyses were performed on baseline data obtained from a randomized clinical trial and a separate cross-sectional survey.

The experimental design of the clinical trial is published elsewhere [**Error! Bookmark not defined.**]. The trial was conducted according to a prospective, randomized, double-masked, multicenter, parallel-group, active-controlled, and noninferiority design. It compared photodynamic therapy (with anecortave acetate, 15 mg) at centers in the United States, Canada, Italy, The Netherlands, Belgium, Spain, Israel and Australia. Enrolled patients were of any race, either sex, and age more than 50 years, provided they also met criteria that included clinical diagnosis of AMD manifesting as a predominantly classic subfoveal CNV lesion in the study eye (either primary or recurrent after laser photocoagulation) and, at the screening visit, a best-corrected visual acuity between 0.30 LogMAR (20/40 Snellen) and 1.30 LogMAR (20/400 Snellen) in the study eye, which conforms to the Early Treatment Diabetic Retinopathy Study. Responses to the MacDQoL questionnaire were elicited by telephone during the 2 days after the baseline visit. In total, 530 patients were enrolled. The

NEI-VFQ-25 was not included in this trial. The full files of the trial were accessed, but we used only baseline data (before randomization) for the current analysis. Their average age was 76.6 years (range 51 to 96 years). Most patients were Caucasian (98%), and 52% were women. Mean baseline visual acuity was 0.72 logMAR units (20/100 Snellen).

In addition, patient data were obtained from the Microeconomic Impact of Macular Disease survey, conducted in three countries (France, Germany, and Italy) [21, 39, 40]. The design was multicenter, cross-sectional, and stratified by level of AMD severity. The survey assessed QoL and the consumption of medical and non-medical resources by a sample of patients with AMD (exudative, wet form). Clinical data were collected retrospectively and during a consultation visit. Patients completed questionnaires at the end of the visit. They were required to meet the following criteria: 1) age >50 years; 2) consultation for exudative AMD (i.e., predominantly classic, sub-foveal CNV, documented by clinical notes, fundus photography, and fluorescence angiography); 3) consent to medical dossier access for relevant information; 4) able to answer the questionnaire, either personally or with the aid of a care-giver; and 5) consent to participate in the survey. Data collection included: 1) patient socio-demographics; 2) AMD history; 3) visual acuity (each eye) and binocular vision, at diagnosis and at the visit; 4) MacDQoL replies; and 5) NEI-VFQ-25 replies. Three hundred and sixty patients, mostly women (60%), were enrolled. Their mean age was 77 years, and the mean time elapsing since AMD diagnosis was 2.3 years. On the day of the visit, mean VA was 0.49 LogMAR for the BE and 1.0 LogMAR for the worst eye (WE).

Validation of the MacDQoL was based on data from countries with population samples sufficiently large to allow precise country estimates. Countries included were France, Germany, Italy, and the United States.

MacDQoL

The MacDQoL individualized measure of the impact of macular disease on QoL begins with two single-question overview items that investigate present QoL and the impact of MD on QoL. Twenty-three items follow which each investigate specific aspects of life. Each item has two parts; the first part asks about the impact of MD on that aspect of life and the second part asks about the importance of that aspect of life to the individual's QoL. The two scores are multiplied together to give a weighted impact score. Some items have a preliminary question that acts as an inapplicable option (e.g., working life). An average-weighted impact score is obtained by summing the weighted impact scores and dividing by the number of applicable items. The language versions other than English used in the present study were linguistically validated, including cultural adaptation, by Mapi Research Institute from the original English with two forward translations, reconciliation, back translation, review, and discussion with the developer and further translation and back translation as needed, review of terminology by ophthalmologist, and international harmonization with other language versions. Cognitive debriefing interviews were conducted during design work of the original UK English version, and during the linguistic validation process for the Italian version before use, but few substantive changes were made to the Italian as a result of these interviews. No cognitive debriefing interviews were conducted in France, Germany, or the US before the use of the questionnaires in the work reported here. The US English was adapted from the UK English by a native US English consultant living in the United States before review by ophthalmologist and international harmonization.

Statistical analysis

Statistical analyses were performed with SAS software release 9.1.3. (SAS institute; Cary, NC, USA). The current work is a confirmatory factorial analysis (CFA) of the exploratory factorial analyses (EFA) performed by Mitchell et al. [37]. Therefore, the strategy was to focus the confirmatory analysis on a four-factor solution. This follows the principles stated by Brown [41]: although both EFA and CFA are based on the common factor model and often use the same estimation method, the specification of CFA is strongly driven by theory or prior research evidence. Thus, unlike the approach in EFA, in which the researcher can only pre specify the number of factors, the CFA researcher usually tests a much more parsimonious solution by indicating the number of factors and the pattern of factor loadings.

Principal components analysis (PCA with Varimax rotation) was used to compare the four-factor structure initially reported to have been found in exploratory analyses by Mitchell et al. [37]. Accordingly, four factors were forced. Analyses were performed on the whole sample and on each country separately. Comparisons were performed using linear structural equation modeling (SAS Proc Calis). The response category *Not applicable* was analyzed twice: first, by recoding the not applicable response as zero; and second, by listwise deletions of participants with missing data. Lastly, PCAs were performed on raw data and the correlation matrix, with coefficients estimated pairwise in order to minimize missing data effects.

Three items (Table 1) were not included in the analysis following the findings reported by Mitchell et al. [37] and confirmed with our data. Originally, Work (item #4) was applicable to very few people and was not included in the weighted overall score because the factor structure and reliability could not be assessed with Work included; it was examined separately. Long journeys (#11) were strongly correlated with Holidays (item #12), and this item was excluded. Society's reaction (item #18) was dropped because of poor comprehension. Lastly, Hobbies (item #14) and Leisure activities (item #13) were merged into one item as they were tapping into very similar experiences.

Assessment of unidimensionnality:

The Backward Cronbach Alpha Curve (CAC) is an essential confirmatory tool to assess the unidimensionnality of the set of items. It is performed after the exploratory step, and it allows us to confirm definitively the best item clustering.

The Spearman-Brown formula indicates a simple relationship between CAC and the number of variables. It is easy to show that the CAC is an increasing function of the number of variables. This formula is obtained under the parallel model.

A step-by-step curve of CAC can be built to assess the one-dimensionality of a set of variables [42 , 43]. The first step uses all variables to compute CAC. Then, at every successive step, one variable is removed from the scale. The removed variable is the one that leaves the scale with its maximum CAC value. This procedure is repeated until only two variables remain. If the parallel model is true, increasing the number of variables increases the reliability of the total score, which is estimated by Cronbach alpha. Thus, a decrease of such a curve after adding a variable would cause us to suspect strongly that the added variable did not constitute a one-dimensional set with the other variables.

After an initial rough clustering of items based on previous forced PCA with Varimax rotation, Cronbach alpha coefficient curves [44, 45] were used to identify a precisely one-dimensional cluster of items. One single dimension (all items of the cluster measuring the same underlying construct) means that the above curves are increasing monotonically. Otherwise, items should be allocated to another subscale. However, because these results are influenced by sample fluctuations, they should be interpreted cautiously, especially when subscales contain few items. Detailed information can be found at : 10.1016/j.jval.2010.10.27.

Coefficient curves were plotted with all countries combined. Lastly, a correlation matrix was computed relating questionnaire items to constructs (an item was expected to be more highly correlated with its own construct than with others). The goodness of fit of the final multidimensional measurement model (parallel model within each subscale) was tested using SAS Proc Calis, and, successively, for each country. No significant departure from the model was obtained. All subscales were calculated using impact ratings weighted by importance ratings to estimate the overall average-weighted impact score to reflect each individual patient's view of the effects of MD on their QoL.

Construct validity was established by matching the predicted relationships between derived constructs with clinical or psychological attributes. The NEI-VFQ-25 has been shown to be sensitive to VA in the BE and the WE, independently, with 10/20 and 10/100 as VA thresholds for BE and WE, respectively [16]. Construct validity was checked by comparing a subset of patients with good VA (BE ≥10/20 and WE ≥10/100) versus patients with poor VA (BE<10/20 and WE<10/100). Comparisons were performed using analysis of variance.

Sensitivities of MacDQoL and NEI-VFQ-25 to VA differences were estimated in those patients with measurements on both instruments. Differences between good and poor VA populations were obtained by dividing the corresponding VA ranges (dispersion indicator) of the total population. To allow comparison, both MacDQoL and NEI-VFQ-25 questionnaires were normalized, 0 being the worst and 100 the best patient-reported outcome, after having weighted the scores as recommended by the instrument authors.

All statistical tests were interpreted two-sided with alpha fixed at 5%. Alpha adjustment for test multiplicity was not performed.

Results

A total of 797 patients were included in the PCA (France: 120; Italy: 126; Germany: 139; and the United States: 412). Their mean age was 76.8 years, and 55% were women. Mean BE VA was 0.38 LogMAR (51.9% >10/20) and WE VA 0.94 LogMAR (65.1% >10/100). The proportion of patients with BE VA ≥10/20 and WE VA ≥10/100 was 40.3%, and that with BE VA <10/20 and WE VA <10/100 was 23.3%. No major differences were found between countries.

Strong correlations between the 22 items (r > 0.50) and factor loadings > 0.48 on a forced one-factor analysis supported the use of an average weighted impact score. The overall Cronbach alpha curve increases steadily (Fig. 1) to 0.94.

Table 1 describes the principal component analysis results according to the original analysis [37] and three scenarios (patients with missing data were deleted; pseudocorrelation matrix computed after pairwise deletion; suppression of item #12, holidays), with all countries pooled together. One of the analyses was conducted without item #12 to document the impact of its high percentage of missing data (32.1%) on the factorial structure. The factorial structure was very close to that reported by Mitchell et al. [37] (last column of Table 1), and the three analyses produced similar results, except for items 10, 15, 19 and 22. The first axis explained 48.8% to 48.88% of the variance and comprised questionnaire items 1 (Household tasks), 2 (Personal affairs), 3 (Shopping), and item 21 (Independence shared with axis 3). The second axis explained 5.99% to 6.39% of the variance and included questionnaire items

5 (Personal relationship), 6 (Family life), 7 (Social life), and item 8 (Physical appearance shared with axis 4). The third axis explained 4.20% to 4.48% of the variance and included questionnaire items 9 through 16 (9, Do physically; 10, Get out and about; 11, Long journeys; 12, Holidays; 13 through 14, Leisure activities and hobbies; 15, Self-confidence; 16, Motivation); item 19 (Future) and 26 (Enjoy nature); and items 22 (Do for others) and 23 (Mishaps). The two last items were shared with axis 4. The fourth axis explained 4.00% to 4.10% of the variance and included questionnaire items 17 (People's reaction), 20 (Finances), 24 (Enjoy meals), 25 (Time taken), and three items shared with the other axes, above. Analyses per country showed minor variations of the models described.

Questionnaire items belonging to more than one construct were allocated to whichever construct they best contributed to, demonstrated by a monotonic increment of Cronbach alpha curve. Questionnaire item 8 (Physical appearance) was allocated to construct C4 (Embarrassment); questionnaire items 21 (Independence), 22 (Do for others), and 23 (Mishaps) to construct C3 (Activities / capabilities). Step-by-step Cronbach curve analyses showed that item 20 (Finances) produced a deterioration in Cronbach alpha of axis 4 and could not be incorporated into any other construct without some damage to internal reliability. Results of the final Cronbach alpha curves are presented in Figure 2, where all alpha values were >0.77 (Table 2). Cronbach alpha curves were computed in each country and showed good reliability in each country. Cronbach alpha varied between countries from 0.94 to 0.95 for the Overall score, from 0.79 to 0.84 for the Essential Task score, from 0.75 to 0.84 for the Family /social life score, from 0.92 to 0.93 for the Activities /capabilities score, and from 0.71 to 0.81 for the Embarrassment score.

PCA and Cronbach alpha identified factors described by the following four constructs: Essential tasks (C1: questionnaire items 1, 2, and 3); Family /social life (C2: questionnaire items 5, 6, and 7); Activities /capabilities (C3: questionnaire items, 9, 10, 12, 13/14, 15, 16, 19, 21, 22, 23, and 26); and Embarrassment' (C4: questionnaire items 8, 17, 24 and 25). Questionnaire item 20, relating to finance, was not associated with any construct because a differential item functioning by country was identified: it works well within the Embarrassment set of items (C4) only with the US sample.

Table 2 presents the correlation coefficients between questionnaire items and constructs. All coefficients lay between 0.36 and 0.87, and all were statistically significant (p<0.0001). When the correlations between the construct without the item and the item were analyzed and compared with other correlations, two items (7 and 25) had a higher correlation with another construct. The discrepancy was very minor for item 7 (Social life) and a bit stronger for item 25 (Time taken). Figure 3 shows empirical distributions of the four constructs. Activities /

capabilities approximated a normal distribution, but the Essential tasks distribution was bimodal. Family /social life,and Embarrassment were right-skewed.

Table 3 shows scores of the NEI-VFQ-25 and MacDQoL for the set of patients assessed by both instruments. Patients with good vision (BE$\geq$10/20 and WE$\geq$10/100) were compared with those exhibiting poor vision (BE<10/20 and WE<10/100). Patients with good vision produced significantly better overall scores than those with poor vision (MacDQoL p<0.0001; NEI-VFQ-25 p<0.0001). In the overall population, 6 of the 13 NEI-VF-Q25 scores were lower than 50, the middle of the extreme ranges (0: worst visual function to 100: best visual function): General health, General vision, Near vision, Mental health, Role limitations and Driving. Three of the 5 MacDQoL scale/subscale scores were lower than 50 (0: greatest negative impact on QoL, 100: most positive impact on QoL): Overall weighted score, Essential tasks and Activities /capabilities. When comparing the two groups of vision severity, the differences (the mean of the good vision group minus the mean of the poor vision group) observed with the NEI-VFQ-25 varied between -0.21 (General health) and 22.87 (Driving) and for the MacDQoL between 4.96 (Family /social life) and 13.62 (Essential tasks). Lastly, variation coefficients of MacDQoL were always lower than 50.5, the Embarrassment scores being the lowest (30.63), suggesting a good ability to detect changes, if they have occurred.

Table 4 reports correlation coefficients between MacDQoL and NEI-VFQ-25 scores. As expected, the four MacDQoL subscale scores were highly correlated (all r^2>0.58) with each other but correlated only modestly with NEIVFQ scores. Low r^2 (<0.3) was reported between all MacDQoL subscale scores and two NEI-VFQ-25 scores, General health and Ocular pain. Moderate correlations (0.3<r^2<0.4) were found between three MacDQoL subscale scores (Essential task, Family/social life, Activities /capabilities) and two NEI-VFQ-25 scores (Color vision, Peripheral vision). The Family / social life score was the least often correlated to the NEI-VFQ-25 scores of all the four MacDQoL subscale scores.

Discussion

Principal components analyses supported by one-dimensional clustering of items using Cronbach Alpha curves of AMD patient samples drawn from American, French, Italian and German populations were performed to build one-dimensional and well separated MacDQoL simple subscales. Our results confirm with an international set of data the factorial structure of the MacDQoL, as established initially in a sample of United Kingdom patients, and provide newly identified subscales coherent with that factorial structure. A total of 797 patients contributed to the validation, about one-half of whom participated in a clinical trial conducted in the United States, with the remainder from a cross-sectional survey performed in three

European countries. Our global results were very similar to those reported by Mitchell *et al*. [37]. High inter-item correlations (estimated on 797 patients) supported the calculation of a weighted overall score with high internal reliability and good sensitivity to visual acuity differences.

Patients included in this survey all had wet age-related macular degeneration and all had CNV. Their AMD was the severe wet form, which leads rapidly to visual impairment, and was, therefore, more serious than the AMD of patients in the first MacDQoL validation. In one-quarter of our patients, AMD was bilateral, as compared with 181 of 187 patients in the original validation study. Nevertheless, the reliability was very similar, showing that the questionnaire is suitable for all levels of severity of AMD.

US patients responded to the MacDQoL questions by telephone, whereas the European patients completed the questionnaire themselves. However, the factorial structure of both patient populations was similar, showing that MacDQoL questionnaires completed directly by patients or by telephone interview produced a similar pattern of results.

Curves of Cronbach alpha values for all four constructs per country showed very high internal reliability for American patients, but minor inconsistencies with Family/ social life and Embarrassment constructs with French and German patients. Such small variations should be interpreted cautiously and in relation to empirical data, i.e. declining slopes in the graphic presentations were associated with variability and did not necessarily mean that Cronbach alpha values were truly decreasing. Also, the US sample was about two to three times larger than samples from other countries and so dominated the analysis.

Cronbach alpha values of our four MacDQoL weighted constructs (0.77 to 0.93) were less than the overall average weighted impact score (0.95) of UK patients, probably because of the reduced number of items.

A possible limitation of this study is that cognitive debriefing interviews with patients to establish their understanding of the items of the MacDQoL were only carried out in the design work in UK English and in the course of linguistic validation into Italian. No cognitive debriefing interviews were conducted in France, Germany or the United States before these data collections. No substantive changes were needed to the Italian questionnaire following cognitive debriefing, however, and it is unlikely, but remains possible, that substantive changes would have been indicated in the French, German, or US English versions.

We identified four constructs with a very similar structure to those reported by Mitchell et al. [37] and they were named Essential tasks, Family/ social life, Activities/ capabilities, and Embarrassment. Both Family/ social life and Embarrassment were right-skewed.

Therefore, future studies in similar patients might transform the data or use non-parametric analysis to get more precise estimations. Strictly speaking, both scores had some floor effect. However, we wouldn't want to drop items that were detecting negative impact in 70% and 55% of patients, respectively. In addition, Table 3, which gives differences between those with good vision and those with poor vision, shows that Embarrassment has the second largest difference shown by the four MacDQoL subscales. Therefore the size of the floor effect is not necessarily related to the ability of the subscales to discriminate between groups.

We are proposing the continued use of weighted scores, even for sub-scale scores. Trauer and Mackinnon [46] showed that weightings made no difference to life satisfaction measures, and it has been demonstrated that importance weightings add nothing to a diabetes treatment satisfaction measure because all items were seen as important [47]. However, importance ratings have been shown to be needed for the MacDQoL and related measures [32,35]. In the Mitchell and Bradley [37] 2004 article, it was found that the full range of importance scores was used for 14 of the 22 domains, showing that domains considered very important to some individuals were not at all important to others. See Brose et al. [48] for further discussion of this issue.

The MacDQoL questionnaire appeared to be more specific to VA impairment in MD patients than the NEI-VFQ-25 because the differences between good and poor vision groups were similar for the two scales despite the MacDQoL range being smaller. Four subscales may be relevant when evaluating the impact of VA impairment on the MacDQoL, the overall average weighted impact score, and subscale scores for Essential tasks, Activities/ capabilities, and Embarrassment. It would appear that Family/ social life was less sensitive to VA impairment than the other three MacDQoL subscales.

Among the 4 scores, Embarrassment had weaker properties than the others. The structure was more sensitive to the type of PCA; Cronbach alpha was lower although still satisfactory (>0.70). However, its variation coefficient was the smallest, but sensitivity to changes needs to be checked.

The weak correlations between General Health and"Ocular pain and the four MacDQoL scores might be related to the fact that these two NEI-VFQ-25 dimensions have little relevance for ARMD. The Family/ social life score of the MacDQoL was the least correlated of the MacDQoL scores, with the NEI-VFQ-25 scores suggesting that the impact of ARMD on family and social life has the least to do with visual functioning, whereas responses to the Essential tasks, Activities/capabilities and Embarrassment subscales are more closely related to visual function.

The Finance item (20) was the only item to show clear differences in item functioning between the European countries and the United States. It clustered well with the Embarrassment construct, but only with the US sample, so we decided to exclude it from the newly constructed subscales. Nonetheless, it remains very relevant and is included in the global score, and can be analyzed alone. It is understandable that Finances were perceived to be more impacted by macular disease in the United States than in France, Germany, or Italy, where national social security systems provide more financial support than in the United States.

When the present multinational trial and European survey were performed, only one, very expensive, drug (verteporfin) was available to all participating countries, and this was 100% reimbursed to all AMD patients showing choroidal neovascularisation. Accordingly, the impact of this medical cost would not have been noted by our patients. However, the costs of visual impairment are mostly borne by the individual/family and would have been noticed. These costs comprise mainly loss of family revenue and paid assistance for tasks formerly self-completed, and are equal to the national drug budget (in France, Italy, Germany, and the United Kingdom) [54,55].

Conclusion

The factorial structure of the MacDQoL, observed amongst US, French, Italian, and German patients with wet AMD, was similar to that published recently for UK patients. The MacDQoL is a reliable instrument that has a good ability to discriminate patients with good or poor vision. Preliminary results suggest that four MacDQoL constructs (Overall weighted score, Essential tasks, Activities/ capabilities, and Embarrassment) might be at least as sensitive as most NEI-VFQ-25 constructs. Whereas the NEI-VFQ captures the extent of general impairments to vision function, the MacDQoL goes beyond this to measure the particular impact of macular disease on QoL, taking account of individual differences in the relevance and importance of different aspects of life. The MacDQoL subscales identified here may prove useful measures for treatment evaluation in patients with AMD in addition to the overall average weighted impact score.

Access to MacDQoL

The MacDQoL questionnaires used in this work included the US English version adapted from the original UK English dated January 31, 2002 and linguistic validations of the same UK English version into German, Italian, and French by Mapi Research Institute in Lyon in close collaboration with the copyright holder, Clare Bradley, PHD.

The MacDQoL, associated guidelines and information, and a licence to use the questionnaire can be obtained from the copyright holder, Clare Bradley, PhD, Professor of Health Psychology at Royal Holloway, University of London, Egham, and Surrey, TW20 0EX, United Kingdom, via the website of Health Psychology Research Ltd.: www.healthpsychologyresearch.com.

Tables & Figures

Table 1: Principal component analysis (PCA) according to three scenarios (N=797).

Item No.	*Description**	PCA 1	PCA 2	PCA 3	Original*
MacD1	*Household tasks*	**C1**	**C1**	**C1**	**C1**
MacD2	*Personal affairs*	**C1**	**C1**	**C1**	**C1**
MacD3	*Shopping*	**C1**	**C1**	**C1**	**C1**
MacD4	*Work*		Excluded [42]		
MacD5	*Personal relationship*	C2	C2	C2	**C2**
MacD6	*Family life*	C2	C2	C2	**C2**
MacD7	*Social life*	C2	C2	C2	**C3 & C2**
MacD8	*Physical appearance*	C4	C2	C2	**C4**
MacD9	*Do physically*	***C3***	***C3***	***C3***	**C1 & C3**
MacD10	*Get out and about*	***C3***	***C3***	***C3***	**C1**
MacD11	*Long Journeys*		Excluded [42]		
MacD12	*Holidays*	***C3***	***C3***	**-**	**C3**
MacD13	*Leisure activities*		Replaced by MacD13&14 [42]		
MacD14	*Hobbies*				
MacD13 &14	*Leisure activities, Hobbies*	***C3***	***C3***	***C3***	**C1 & C3**
MacD15	*Self-confidence*	***C3***	***C3***	***C3***	**C1**
MacD16	*Motivation*	***C3***	***C3***	***C3***	**C3**
MacD17	*Peoples' reaction*	C4	C4	C4	**C4**
MacD18	*Society reaction*		Excluded [42]		
MacD19	*Future*	***C3***	***C3***	***C3***	**C4**
MacD20	*Finances*	C4	C4	C4	**C4**
MacD21	*Independence*	***C3***	**C1**	***C3***	**C1 & C3**
MacD22	*Do for others*	***C3***	C4	***C3***	**C1**
MacD23	*Mishaps*	***C3***	C4	***C3***	**C3 & C4**
MacD24	*Enjoy meals*	C4	C4	C4	**C4**
MacD25	*Time taken*	C4	C4	C4	**C4 & C3**
MacD26	*Enjoy Nature*	***C3***	***C3***	***C3***	**C3**

*** Item descriptions come from Mitchell *et al*. [42] as do the constructs on which the item loaded in the original UK data here shown in the final column**
C1: Essential tasks (F1 in Mitchell et al.)
C2: Family / social life (F4 in Mitchell et al. referred to as C2 here in the final column to facilitate comparisons)
C3: Activities / capabilities (F2 in Mitchell et al. referred to as C3 here in the final column)
C4: Embarrassment (F3 in Mitchell et al. referred to as C4 here in the final column)
PCA 1: patients with missing data were deleted
PCA 2: pseudo-correlation matrix computed after pair-wise deletion
PCA 3: suppression of item 12

Table 2: Correlation coefficients between MacDQoL questionnaire items and constructs. MTA Multi-trait analysis (N=797)

	Essential tasks	Family / social life	Activities / capabilities	Embarrass-ment	MTA £
Essential tasks (α = 0.82)					
MacD1 Household tasks	**0.84**	0.50	0.61	0.54	0.66
MacD2 Personal affairs	**0.87**	0.50	0.65	0.51	0.70
MacD3 Shopping	**0.87**	0.49	0.64	0.56	0.69
Family / social life (α = 0.82)					
MacD5 Personal relationship	0.42	**0.85**	0.56	0.56	0.67
MacD6 Family life	0.52	**0.87**	0.61	0.56	0.69
MacD7 Social life	0.53	**0.85**	0.67	0.62	0.67
Activities / capabilities (α = 0.93)					
MacD9 Do physically	0.62	0.60	**0.78**	0.59	0.73
MacD10 Get out and about	0.60	0.56	**0.77**	0.58	0.73
MacD12 Holidays	0.56	0.51	**0.73**	0.56	0.68
MacD1314 Leisure activities, Hobbies	0.61	0.49	**0.78**	0.52	0.75
MacD15 Self confidence	0.57	0.55	**0.79**	0.58	0.72
MacD16 Motivation	0.58	0.61	**0.80**	0.58	0.75
MacD19 Future	0.44	0.46	**0.68**	0.45	0.59
MacD21 Independence	0.55	0.51	**0.75**	0.54	0.69
MacD22 Do for others	0.53	0.56	**0.77**	0.59	0.69
MacD23 Mishaps	0.53	0.51	**0.73**	0.63	0.67
MacD26 Enjoy Nature	0.52	0.56	**0.74**	0.59	0.69
Embarrassment (α = 0.77)					
MacD8 Physical appearance	0.49	0.55	0.55	**0.76**	0.56
MacD17 People's reaction	0.36	0.54	0.53	**0.77**	0.60
MacD24 Enjoy meals	0.46	0.52	0.54	**0.79**	0.62
MacD25 Time taken	0.59	0.49	0.68	**0.78**	0.55

*** Coefficient correlation between the item and its subscale score with the item score subtracted.**
Nb: Those MTA (Multi-Trait Analysis) corrected-item subtotal coefficients that are not underlined are for those items for which the regular correlation coefficients show higher correlations with other constructs (underlined in previous columns).

Table 3: Comparison of MacDQoL and NEI-VFQ25 scores.

Instrument	*Construct*	Good vision BE≥10/20 WE≥10/100		Poor vision BE<10/20 WE<10/100		Difference Good vision – Poor vision	Variation coefficient*
		N	Mean	N	Mean	Mean	
NEI-VFQ-25	*Global score*	174	50.29	89	41.22	9.07	41.85
NEI-VFQ-25	*General health*	174	40.52	89	40.73	-0.21	46.86
NEI-VFQ-25	*General vision*	174	45.75	89	38.65	7.10	39.84
NEI-VFQ-25	*Ocular pain*	174	76.94	89	76.40	0.54	32.32
NEI-VFQ-25	*Near vision*	173	41.26	89	32.12	9.14	58.91
NEI-VFQ-25	*Distance vision*	173	49.25	89	36.19	13.06	54.70
NEI-VFQ-25	*Social function*	174	64.94	89	53.65	11.29	44.88
NEI-VFQ-25	*Mental health*	174	39.28	89	31.62	7.66	63.71
NEI-VFQ-25	*Role limitations*	174	39.44	89	30.62	8.82	66.66
NEI-VFQ-25	*Dependency*	174	51.96	89	38.21	13.75	63.39
NEI-VFQ-25	*Driving*	94	36.30	40	13.44	22.87	98.20
NEI-VFQ-25	*Color vision*	171	76.32	89	65.73	10.59	37.00
NEI-VFQ-25	*Peripheral vision*	173	60.55	88	51.14	9.41	47.93
MacDQoL	*Overall average weighted impact score*	174	48.14	89	38.39	9.75	35.89
MacDQoL	*Essential tasks*	174	39.35	89	25.73	13.62	51.01
MacDQoL	*Family / social life*	174	51.36	87	46.41	4.96	40.41
MacDQoL	*Activities / capabilities*	174	40.80	89	31.33	9.47	47.55
MacDQoL	*Embarrassment*	174	57.70	89	47.12	10.58	31.30

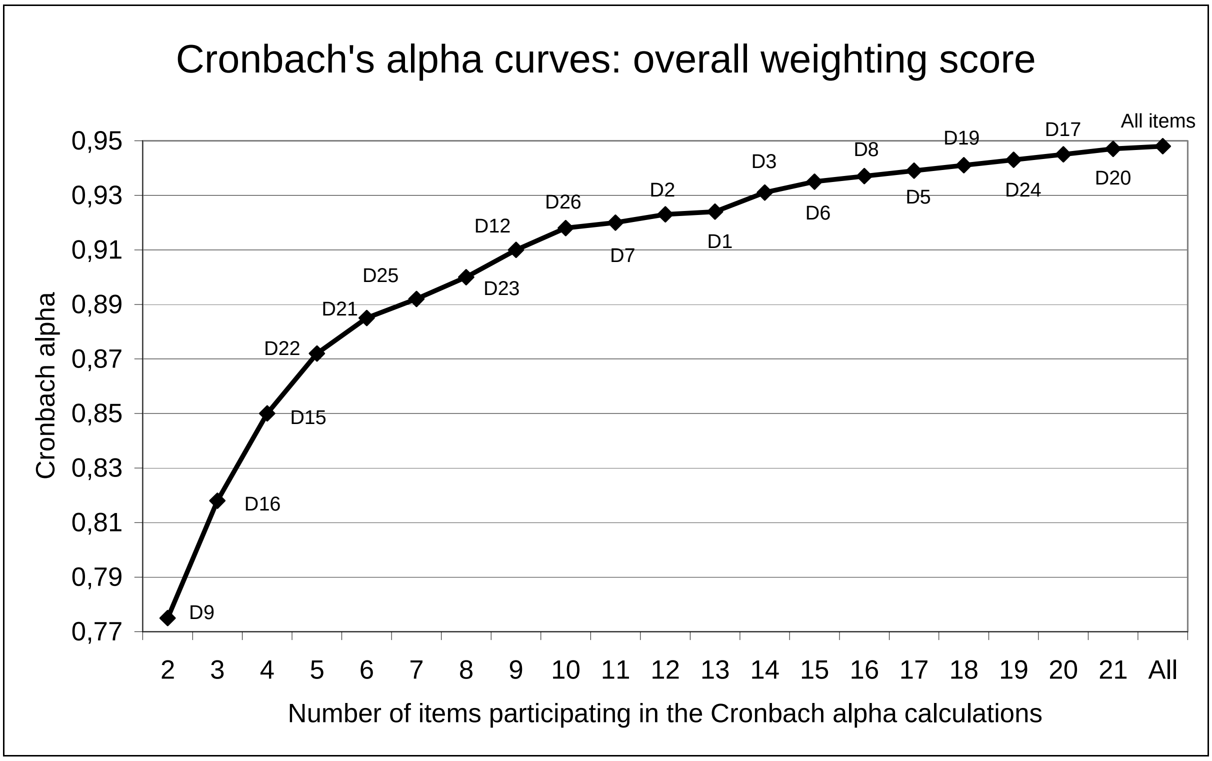
MacDQOL and NEI-VFQ-25 scores were standardized to allow comparisons. 0 is associated with a poor QoL and 100 a high QoL. BE : Best eye. WE: Worst eye. Variation coefficient = std/mean.

Table 4: Correlation matrix within MacDQoL Scores (N=797) and between MacDQoL and NEI-VFQ-25 (N=360)

Correlation coefficient	**MacDQoL**				
	Essential Tasks	**Family / social life**	**Activities / capabilities**	**Embarrassment**	**Overall**
MacDQol					
Essential tasks	1	-	-	-	n.a.
Family / social life	0.58	1	-	-	n.a.
Activities / capabilities	0.73	0.71	1	-	n.a.
Embarrassment	0.65	0.69	0.77	1	n.a.
NEI VFQ 25					
Global score	0.59	0.53	0.63	0.64	0.68
General health	0.16	0.16	0.15	0.14	0.17
General vision	0.47	0.40	0.50	0.48	0.53
Ocular pain	0.20	0.25	0.24	0.29	0.27
Near vision	0.50	0.38	0.49	0.46	0.52
Distance vision	0.52	0.39	0.50	0.54	0.55
Social function	0.45	0.39	0.46	0.50	0.51
Mental health	0.54	0.55	0.64	0.62	0.68
Role limitations	0.51	0.46	0.57	0.50	0.59
Dependency	0.54	0.54	0.58	0.61	0.64
Driving	0.47	0.33	0.51	0.42	0.51
Color vision	0.35	0.36	0.38	0.53	0.45
Peripheral vision	0.38	0.34	0.39	0.44	0.44

Correlation coefficients lower than 0.4 are underlined.

Figure 1 : Overall weighting score Cronbach's alpha curve (N=797)



The Dxx labels on the curve identify the item excluded to construct the Cronbach's alpha curve. Starting from the right to the left, the Dxx item contributing the most to the increase of the Cronbach's alpha curve is removed from it followed by the next greatest contributing item, until two items remain. When all items belong to the score, this curve is expected to increase.

Figure 2: Relationships between Cronbach's alpha values and questionnaire items underlying MacDQoL constructs (N=797)

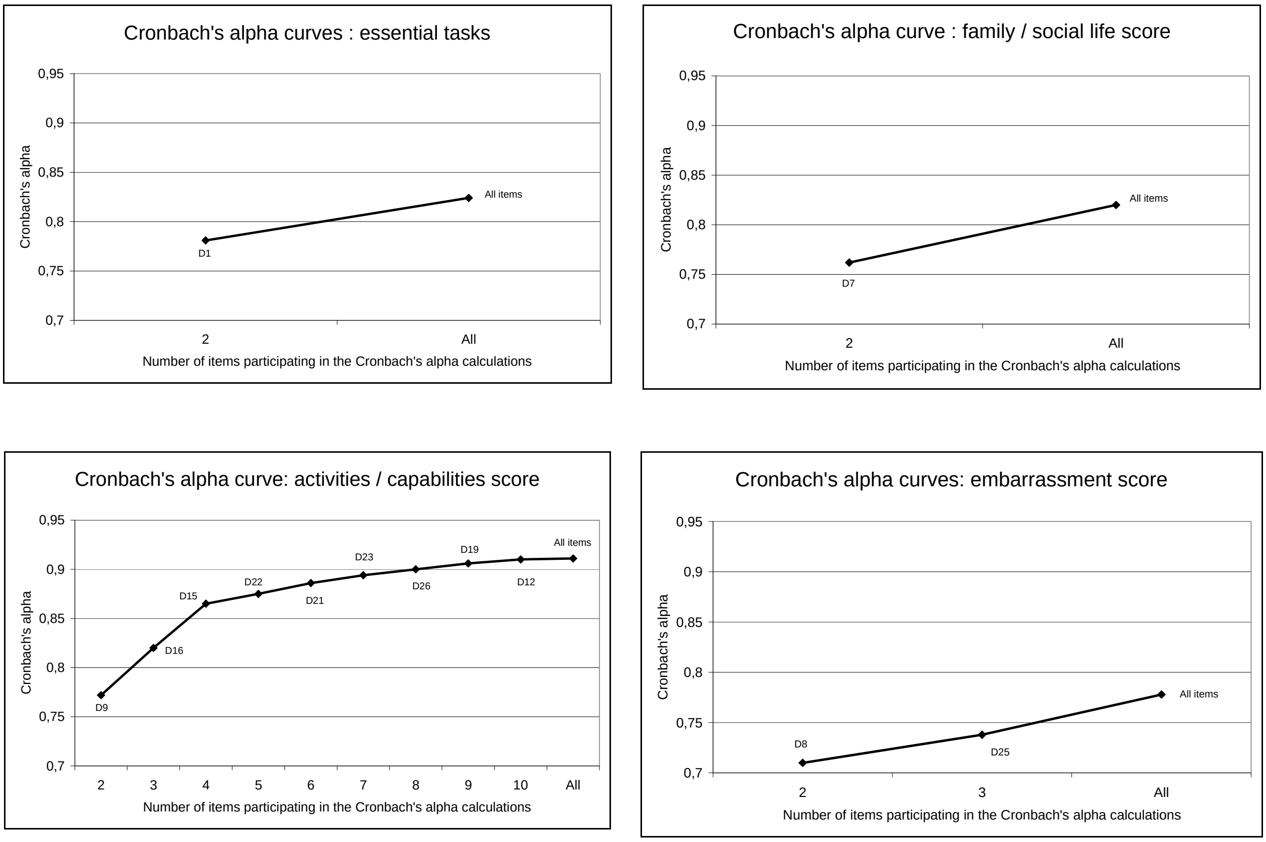
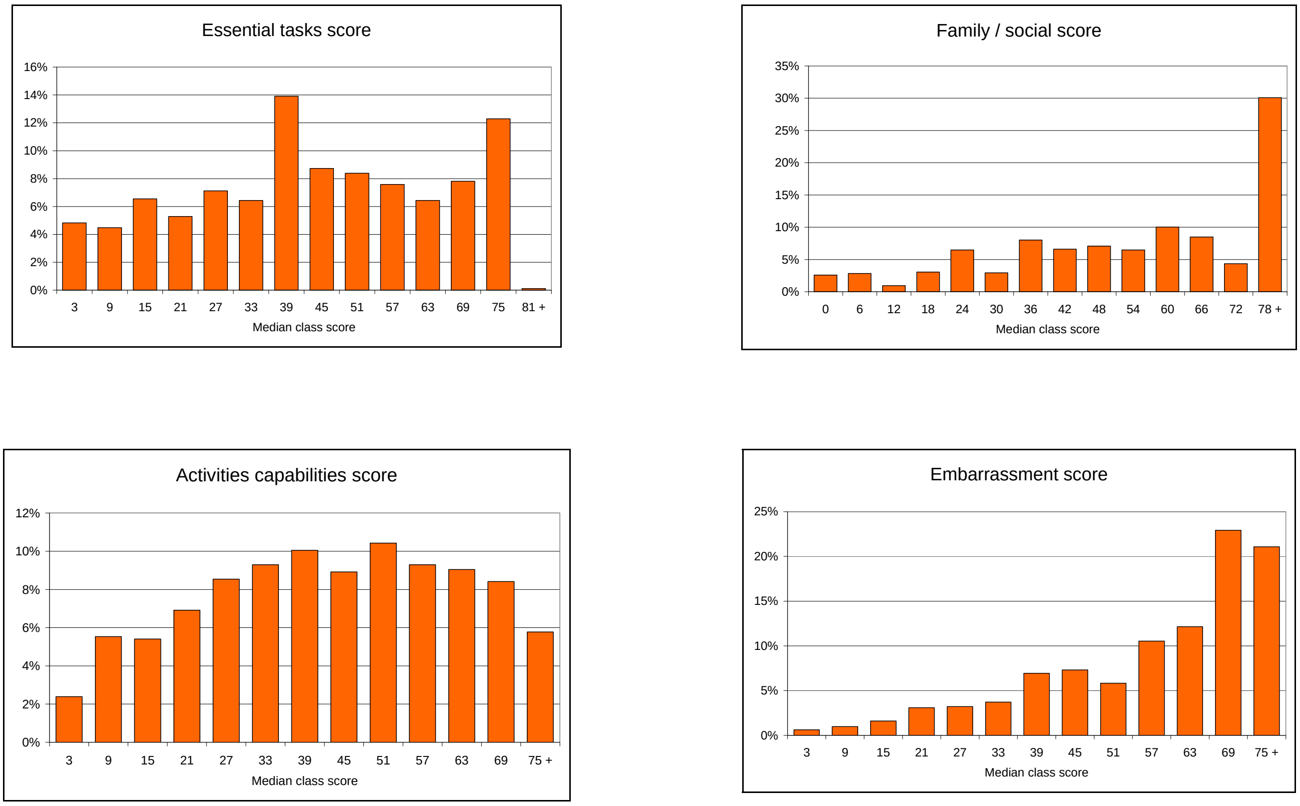


Figure 3: Distribution functions of the four MacDQoL constructs (N=797). Scores normalized from zero (greatest negative impact on quality of life) to 100 (greatest positive impact on quality of life)



Annex: Cronbach Alpha and the Backward Cronbach alpha curve.

The parallel model describing the unidimensionality of a set of variables:

Let X_1, X_2, ..., X_k, be a set of observed variables measuring the same underlying unidimensional latent (unobserved) variable. We define X_{ij} as the measurement of patient i, where i=1,..,n, given by a variable j, where j=1,..,k. The model underlying Cronbach's Alpha is a simple mixed one-way model: $X_{ij} = \mu_j + \alpha_i + \varepsilon_{ij}$,

where μ_j is a varying fixed (non-random) effect and α_i is a random effect with zero mean and standard error σ_α corresponding to patient variability. It produces the variance of the true latent measure ($\tau_{ij} = \mu_j + \alpha_i$). ε_{ij} is a random effect with zero mean and standard error σ corresponding to the additional measurement error. The true measure and the error are uncorrelated: $cov(\alpha_i, \varepsilon_{ij}) = 0$.

These assumptions are classical in experimental design. This model defines relationships between different kinds of variables: the observed score X_{ij}, the true score τ_{ij} and the error ε_{ij}.

Reliability of an instrument

A measurement instrument gives us values that we call observed values. The reliability ρ of an instrument is defined as the ratio of the true over the observed measure. Under the parallel model, one can show that the reliability of any variable X_j (as an instrument to measure the true value) is given by:

$$\rho = \sigma_\alpha \,/\, (\sigma_\alpha^2 + \sigma^2)$$

which is also the constant correlation between any two variables. This coefficient is also known as the intra-class coefficient. The reliability coefficient ρ can be easily interpreted as a correlation coefficient between the true and the observed measure.

When the parallel model is assumed, the reliability of the sum of k variables equals:

$$\tilde{\rho} = k\,\rho \,/\, (k\,\rho + (1-\rho))$$

This formula is known as the Spearman-Brown formula. Its maximum likelihood estimator, under the assumption of a normal distribution of the error and the parallel model, is known as Cronbach's Alpha Coefficient (CAC) [49]:

$$\alpha = (k / (k - 1)) (1 - (\sum_{j=1}^{n} S_j^2 / S_{tot}^2))$$

where $S_j^2 = 1/(n-1)\sum_{i=1}^{n} (X_{ij} - \overline{X}_j)^2$ and $S_{tot}^2 = 1/(nk-1)\sum_{i=1}^{n} \sum_{j=1}^{k} (X_{ij} - \overline{X})^2$

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