McMillan CV, Bradley C, Gibney J, Russell-Jones DL, Sönksen PH: **Preliminary development of the new individualised HDQoL questionnaire measuring quality of life in adults hypopituitarism**. *J Eval Clin Pract* **12** (5) 501-514.

Preliminary development of the new individualised HDQoL questionnaire measuring quality of life in adult hypopituitarism

Carolyn V. McMillan PhD,[1] Clare Bradley PhD,[1] James Gibney MD MRCPI,[2] David L. Russell-Jones MD FRCP,[2] and Peter H. Sönksen MD FRCP.[2]

Corresponding author

Dr Carolyn McMillan PhD, Research Health Psychologist,
Department of Psychology, Royal Holloway, University of London, Egham, Surrey, UK, TW20 0EX.
Tel: +44-1784-443718; Fax: +44-1784-471168.
E-mail: c.mcmillan@rhul.ac.uk.

Institutions at which the work was carried out

[1]Royal Holloway, University of London, Egham, Surrey, TW20 0EX, UK.
[2]St Thomas' Hospital, Lambeth Palace Road, London, SE1 7EH, UK.

Co-authors and current addresses if different from above

Prof Clare Bradley PhD, Professor of Health Psychology and Director of Health Psychology Research, Department of Psychology, Royal Holloway, University of London.

Dr James Gibney MD, MRCPI, Department of Endocrinology, Adelaide & Meath Hospitals, incorporating the National Children's Hospital, Tallaght, Dublin 24, Eire.

Prof David L Russell-Jones MD, FRCP, Professor of Diabetes and Endocrinology, Royal Surrey County Hospital, Egerton Road, Guildford, Surrey, UK, GU2 7XX.

Prof Peter H Sönksen MD, FRCP, Emeritus Professor of Endocrinology, St Thomas' Hospital, London.

Key words

Quality of life, adult growth hormone deficiency, hypopituitarism, questionnaires, psychometrics, validation studies.

Running Head: Measure of QoL in adult hypopituitarism

Abstract

Objectives The objectives were: (1) to report the preliminary development of the Hormone deficiency-Dependent Quality of Life (HDQoL) questionnaire, a new individualised questionnaire in which respondents rate personally applicable domains for importance and impact of hormonal deficiency and its treatment; (2) to evaluate the HDQoL's psychometric properties for adults with hypopituitarism including growth hormone deficiency (GHD).
Methods Internal consistency reliability, aspects of validity, and sensitivity to change of the HDQoL were investigated in: (1) a cross-sectional survey of 157 adults with treated or untreated GHD; (2) a randomised, placebo-controlled study of three months' growth hormone (GH) withdrawal from 12 of 21 GH-treated adults.
Results Thirteen of the original 18 HDQoL domains were relevant and important for GH-deficient adults. The shorter 13-item HDQoL had excellent internal reliability (Cronbach's alpha coefficient = 0.914, N = 109), and was sensitive to sex differences (cross-sectional study): women perceived worse present QoL than men [$t(149.8) = 2.33$, $P = 0.021$]. The HDQoL was sensitive to change (GH-Withdrawal study) with a significant between-group difference in change in domain scores for *things I can do physically* [$t(16) = 2.47$, $P = 0.025$, 2-tailed], patients withdrawn from GH reporting greater negative impact of hormone deficiency on this domain at end-point. Qualitative work resulted in the addition of seven new HDQoL domains, including energy and bodily pain.
Conclusion The HDQoL, although at an early stage of development, proved useful in identifying expected changes following GH withdrawal. The extended 20-item version is recommended for further evaluation in assessing the impact of hypopituitarism on QoL.

Introduction

Hypopituitarism is a condition involving deficiencies in one or more of the eight pituitary hormones (for example growth hormone (GH), thyroid stimulating hormone, adrenocorticotrophic hormone, and antidiuretic hormone). The condition is most commonly caused by the presence of a pituitary adenoma and/ or its treatment (Smith 2004). Replacement of some hormones, e.g. corticosteroids and antidiuretic hormone, is mandatory to avoid life-threatening conditions, but GH replacement remains controversial as there is uncertainty whether the benefits outweigh the high financial costs and a treatment regimen requiring daily injections. The physical symptoms of adult growth hormone deficiency (GHD) include abnormal body composition with reduced lean body mass and increased central adiposity; reduced muscle strength and exercise performance (Carroll *et al.* 1998). However, psychological symptoms may be as important as physiological (Powrie *et al.* 1995) and psychological variables need to be considered when assessing patients for GH replacement (Bengtsson *et al.* 2000). Psychological symptoms reported by adults with untreated GHD include low energy, tiredness, sleepiness, poor concentration, poor memory, irritability (Hunt *et al.* 1993), anxiety, depression and mood swings (Wallymahmed *et al.* 1996).

Sensitive measures of patient-reported outcomes are required in addition to clinical outcomes to assess the effects of GH treatment. The Nottingham Health Profile (NHP) (Hunt & McKenna 1989) and the Psychological General Well-being Index (PGWB) (Dupuy 1984) were the most frequently used questionnaires to measure psychological symptoms in early studies of GH replacement in adult GHD. Some studies found improvements after six months' GH treatment (McGauley *et al.* 1990; Mardh *et al.* 1994; Carroll *et al.* 1997), but others did not find significant effects (Whitehead *et al.* 1992; Baum *et al.* 1998) perhaps because such generic measures are insufficiently sensitive (Wiren *et al.* 2001). Condition-specific measures are usually more sensitive than generic, and the condition-specific Quality of Life-Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) (McKenna *et al.* 1999) has been increasingly widely used (Ahmad *et al.* 2001; Malik *et al.* 2003; Svensson *et al.* 2004). However, the QoL-AGHDA has been criticised on several grounds including the fact that respondents are not asked whether they attribute their reduced quality of life (QoL) to growth hormone deficiency, there is no time reference, and the response options are dichotomous, thus it is not possible to determine the degree of perceived impairment (Barkan 2001; Barkan & Wren 2001). Another questionnaire, Questions on Life Satisfaction, hypopituitarism module (QLS-H) (Henrich & Herschbach 2000), appears to be more specifically about satisfaction with aspects of health than QoL *per se*.

This paper concerns the evaluation of the psychometric properties of a new condition-specific measure of QoL in hypopituitarism: the Hormone deficiency-Dependent Quality of Life Questionnaire (HDQoL) (Bradley 1999). The HDQoL offers a very different approach to the measurement of QoL from that of the QoL-AGHDA. QoL-AGHDA design assumes that all symptoms or experiences universally detract from QoL and that they are equally important to all respondents. The HDQoL uses an individualised approach, measuring the perceived *impact* of hormone deficiency on those aspects of life relevant to the individual, and allowing the individual's view of the importance of each aspect of life for their QoL to influence the scores. The psychometric properties of the HDQoL were evaluated in two studies at St Thomas' Hospital, London. (1) A cross-sectional survey of 157 adults with hypopituitarism including severe GHD, GH-treated or non-GH-treated, investigated internal consistency reliability, factor structure, and aspects of validity of the questionnaire. (2) A

randomised placebo-controlled study of three months' withdrawal of GH treatment from 12 of 21 GH-treated adults with hypopituitarism, where nine continued with GH, investigated sensitivity to change. The Guy's and St Thomas' Hospital Trust Ethics Committee gave approval for both studies.

Methods

Materials

The HDQoL questionnaire

Design of the HDQoL was based on the Audit of Diabetes-Dependent Quality of Life (ADDQoL) (Bradley *et al.* 1999; Bradley & Speight 2002) and a subsequent adaptation of the ADDQoL for renal patients, the RDQoL (Bradley 1997). The ADDQoL was influenced by the generic individualised interview method known as SEIQoL (Schedule for the Evaluation of Individual Quality of Life) (McGee *et al.* 1991). Although, patients were involved in generating versions for diabetes and renal disease, time constraints prevented qualitative research in adult hypopituitarism and adjustments were made to the condition referred to in the RDQoL to make it suitable for patients with hypopituitarism, and one item deleted as it appeared to be irrelevant to hypopituitarism. The HDQoL was designed with 18 domains covering work, family, social life, sex life, physical appearance, self-confidence, physical capabilities, holidays/ leisure, travel, motivation, spiritual life, society's reaction, worries about the future, finances, dependence, others fussing, living conditions, and freedom to eat as wished. Being individualised, the HDQoL gives respondents the opportunity to indicate whether a particular domain is not applicable (N/A), specifically in questions concerning work, family, sex and religious life.

The first section has two overview items. Question A (QA:*present QoL*) asks people to rate their present QoL on a 7-point scale from 'as good as it could possibly be' to 'as bad as it could possibly be'. Question B (QB:*hormone deficiency-dependent QoL*) asks people to rate what their QoL would be if they did not have hormone deficiency, on a 7-point scale from 'very much better' to 'very much worse'. Each domain is introduced by the hypothetical statement: *If I did not have hormone deficiency, my [domain] would be……* and is followed by a 7-point Likert scale from 'very much better' to 'very much worse' (the impact rating). Respondents then rate how important that domain is to their QoL on a 4-point Likert scale from 'very important' to 'not at all important'. (Fig. 1 provides an example of a domain item and scores). There is also a 'free comments' section where patients may describe any other ways in which they perceive hormone deficiency and its treatment to affect their QoL. This section allows for the addition of further HDQoL domains in the future, as part of its continuing development.

Scoring: A weighted domain score is obtained by multiplying the domain's impact rating by the corresponding importance rating. An overall HDQoL score, the Average Weighted Impact score (HDQoL AWI), is obtained by summing all applicable weighted domain scores, before dividing by the number of domains applicable to the individual. Weighted domain scores and HDQoL AWI range from -9 to +9 (maximum negative to maximum positive impact of hormone deficiency on that domain or on overall QoL). The overview items are not weighted by importance ratings. QB:*hormone deficiency-dependent QoL* is scored the same way as the impact ratings on the domains, from -3 to +3, but QA:*present QoL* is scored from +3 to -3, a lower score indicating poorer QoL.

Other questionnaires used in the studies

Other questionnaires were also completed in these studies including the NHP, Short-form 36 (SF-36) (Ware & Sherbourne 1992), General Well-being Index, (British version of the PGWB) (Hunt & McKenna 1992) and the Well-being Questionnaire (Bradley 1994), the full results for which have been reported previously (McMillan 2001; McMillan *et al.* 2001; McMillan *et al.* 2003a; McMillan *et al.* 2003b)

Study 1. Cross-sectional survey of GH-treated and non-GH-treated adults with GHD

Recruitment procedures

Recruitment procedures have been fully described elsewhere (McMillan *et al.* 2003b), but in brief they were as follows. All participating patients had been diagnosed severely GH deficient as determined by an Insulin Tolerance or Pituitary Function Test in which insulin reduced blood glucose to ≤2.5 mmol/L with peak GH concentration ≤10 mU/L. All patients had either received GH-replacement therapy for at least six months immediately prior to the study or had not received GH treatment in the previous six months; were aged between 18-70 years; had received appropriate adrenal, thyroid and gonadal hormone replacement therapy as required by their hormonal condition, for at least 12 months prior to the study. Patients might have had adult or childhood onset of GHD. Exclusion criteria were diabetes mellitus, active malignancy or pregnancy.

Statistical analyses

Combining the patient recruitment/ treatment subgroups

There were four recruitment/ treatment subgroups: (1) GH-treated/ archive (names identified from the hospital database and approached by mailshot); (2) GH-treated/ clinic (patients identified at clinic and approached personally or via mailshot); (3) Non-GH-treated/ archive; (4) Non-GH-treated/ clinic. It was necessary to determine whether these four samples could be treated as one for the purposes of factor and reliability analyses where larger sample size is desirable. The procedure adopted was that used in the development of the ADDQoL where data also came from several sources (Bradley *et al.* 1999). HDQoL item scores were first converted to z scores for each recruitment subgroup and then recombined. All questionnaire items were forced onto one factor in a Principal Components Analysis of (1) raw scores and (2) the recombined z scores, and loadings then compared by regression analysis.

Normality issues

Normality of distributions was investigated through histograms and standardised z(skew) values where z(skew) scores between ±2.58 are indicative of normality (Tabachnik & Fidell 1983). The HDQoL is not a questionnaire where a normal spread of scores and normal distributions would be expected as the bi-polar scale allows for some respondents having positive scores, indicating their perception that hormone deficiency had some positive effects on their lives, but positive scores were expected to be uncommon. Ideally data should be normal for reliability and factor analyses. However, finding transformations for skewed variables that did not adversely affect normal distributions of other items in the questionnaire proved difficult. Item data were not transformed to normality, thereby sacrificing some of the accuracy of reliability and factor analyses for the convenience of having interpretability of original units. The assumption was made that if reliability were

high, the factor analysis robust, and the number of respondents sufficiently high, then a degree of non-normality was acceptable.

Internal consistency reliability and factor structure
Cronbach's alpha coefficient (Cronbach 1951) was determined, with an acceptable minimum alpha being taken as 0.7 to 0.8, depending on the number of items in a scale (Todd & Bradley 1994), noting that some consider 0.9 as the minimum for measures of differences between individuals (Nunnally 1978). Acceptable item-total correlations are those >0.2 (Kline 1993). Factor structure was explored using Principal Components Analysis with Varimax rotation (to investigate the existence of any subscales), and a one-factor solution was forced to confirm the validity of calculating the overall HDQoL AWI score. Salient loadings were taken as $\geq$0.5, higher than the recommended minimum 0.3 (Kline 1994), erring on the side of caution in an effort to reduce the risk of spurious loadings that owed their origin to non-normality of item distributions and to avoid multiple loadings.

The 'Not Applicable' response option and loss of data
No data from any respondent selecting a N/A response option would normally be included in factor and reliability analyses, as SPSS treats N/A responses as missing data. Furthermore, if the SPSS default of listwise deletion of missings is used, all cases that have *any* missing values across all questionnaire items are lost to analysis, so considerable data could be lost. However, in preliminary psychometric analyses of the data set, when the N/A option was set to zero with pairwise deletion of missings [a method fully described for the original development of the ADDQoL (Bradley *et al.* 1999)] there was little difference from the results obtained using the default. Only results where SPSS default settings were used are reported.

Sub group differences and 'familywise' error in multiple tests
The questionnaire's sensitivity to some sub-group differences was investigated (GH-treatment groups, sex, age of onset of GHD). The Holm's sequential Bonferroni procedure for multiple tests (Holm 1979) was adopted. A minimum significance value of 0.017 was required if three similar statistical tests were performed on the HDQoL AWI, and overview items, QA and QB (regarded as one 'family'), and a minimum significance of 0.004 if similar tests were performed on the 13 domains of the final questionnaire (another 'family').

Study 2. GH-Withdrawal study

The HDQoL's sensitivity to change was assessed in a randomised, double-blind, placebo-controlled study where severely GH-deficient patients were allocated to placebo or continued treatment with GH for a period of three months. This study has been fully described elsewhere (McMillan *et al.* 2003a), and only a brief description follows.

The HDQoL (in a battery of several questionnaires) was completed at baseline and end-point, and a psychologist conducted semi-structured interviews with the patients at these points. There was a general clinical expectation of deterioration in physiological factors during the study period for those withdrawn from GH treatment and that this might be accompanied by reduced QoL. It was therefore hypothesised that after three months' GH withdrawal the Placebo group would exhibit more negative scores in HDQoL domains for which there had been significant findings in previous studies (using other questionnaires)

when patients had been given GH treatment (namely *social life* and *physically do* and in *present QoL*), but GH-treated patients would show little change.

Means are reported as mean (standard deviation).

Results (1: Cross-sectional study)

The patient sample

Of 219 questionnaires distributed, 163 were returned (74% response rate), but six patients did not meet all inclusion criteria, leaving 157 data sets, (91 GH-treated and 66 non-GH-treated patients). Most patients (96%) had multiple pituitary hormone deficiencies including GHD; the remainder had isolated GHD. (See Table 1 for sample characteristics).

(Table 1 here)

The initial 18-item HDQoL

Frequency analysis

Completion rates for HDQoL impact and importance ratings were 97% and 96% respectively. The data of four respondents with large amounts of missing data were excluded, leaving 153 HDQoL questionnaires for analysis. Numbers of participants selecting the N/A response option were as follows: *working life*: 21 (14%); *family life*: 6 (4%); *sex life*: 17 (11%); *religious life*: 29 (19%). Only 13% of patients had a negative score for their present QoL (QA:*present QoL*), whereas 68% took a positive view of their current QoL, the remainder choosing 'neither good nor bad'. Most patients considered that their QoL would be improved if they did not have hormone deficiency, (QB:*hormone deficiency-dependent QoL*) (79%), but 7% indicated that it would be worse.

Deletion of five items from the 18-item questionnaire

On the basis of early frequency, reliability and forced 1-factor analyses, five domain items (*religious life, society's reaction, others fuss, living conditions* and *freedom to eat*) were excluded from the questionnaire for the following reasons:

- all five domains had severely negatively skewed distributions;
- a relatively high proportion of respondents perceived hormone deficiency as having no impact on the domain [*society's reaction* (67%), *living conditions* (72%), *religious life* (81%), *freedom to eat (71%*), *others fuss* (40%)], or that the domain was not important [*religious life* (24%), *others fuss* (19%)];
- low loadings (<0.42) on the forced 1-factor analysis (*religious life* and *freedom to eat*).

All further analyses were conducted with the shortened 13-item HDQoL.

The 13-item HDQoL

Analyses showed that the four recruitment/ treatment subgroups could be combined for the purposes of psychometric analyses where large N is desirable. Regression analysis of the forced 1-factor loadings obtained for the raw scores against the recombined z scores showed no significant difference between the two sets of loadings. The correlation of 0.99 was close to a perfect 1, the constant (0.004) was close to zero [$t(12) = 1.36$, $P > 0.05$] and the slope (0.95) was also close to 1 [$t(12) = 21.8$, $P < 0.001$].

Reliability and factor analyses
Cronbach's alpha for the whole scale was 0.914 (N = 109). 'Alpha if item deleted' values (all ≤0.914) indicated that no item detracted from internal consistency reliability. Corrected item-total correlations were also all satisfactory and ≥0.44, (Table 2). To assess the effects of missing data on HDQoL reliability, reliability analyses were run sequentially, deleting the strongest item each time, i.e. deleting the item having the lowest 'alpha-if-item-deleted' value and therefore contributing most to the scale's internal reliability (Mitchell & Bradley 2001). Calculation of HDQoL AWI was reliable at alpha = 0.9 with maximum one item of missing data, and reliable at alpha = 0.8 with up to five items missing.

The single factor produced in a forced 1-factor analysis accounted for 51% of the variance. All 13 items loaded satisfactorily ≥0.5, (supporting the uni-dimensionality of the measure and calculation of HDQoL AWI score), (Table 3). Unforced analysis produced two factors, accounting for 39% and 20% of the variance respectively, with 10 items loading ≥0.5 on Factor 1, (Table 3). Three items (*travel, finances*, and *dependence*) loaded on Factor 2, however, Cronbach's alpha for the Factor 2 'subscale' was only 0.67, falling short of optimal reliability. Furthermore, *travel* (referring to problems with travelling) is negatively-worded unlike the other 12 items. In more recent versions of the ADDQoL this item has been changed to be positively-worded and it now loads with the other items. It is expected that, if the wording were reversed to be positive on the HDQoL, the item would load on Factor 1. It was decided to retain the 13-item scale as one without any subscales, particularly as previous experience with the ADDQoL has not found subscales.

It was concluded that:
- the 13-item HDQoL was a reliable scale;
- there were no useful subscales;
- weighted items could be summed into an overall HDQoL AWI score.

(Tables 2 and 3 here)

Whole sample frequencies
All 13 weighted domains had negative means, (indicating QoL was impaired by hormone deficiency), ranging from -1.2 (*travel*) to -3.08 (*physical appearance*), (Table 4). Hormone deficiency had most negative weighted impact on *physical appearance*, *physically do*, and *sex life*. It had the least impact on *travel, dependence* and *finances.* The HDQoL AWI score for the whole patient group was mean (SD) -2.32 (2.22), N = 153, indicating overall negative impact of hormone deficiency on QoL. QA:*present QoL* score was 1.0 (1.23), N = 152, indicating good QoL.

(Table 4 here)

Sub-group and correlational analyses
Mann-Whitney tests found no significant differences between GH-treatment groups in HDQoL AWI or the two overview items. (Fig. 2 shows the domain weighted impact scores for the GH treated and untreated groups in the cross-sectional study). GH-treated patients tended to have less negative weighted impact scores on every domain compared with the non-GH-treated group, indicating less negative impact of hormone deficiency. Whilst none of these differences was significant in itself, the fact that the between-treatment-group differences in all 13 domains were in the same direction was highly significant on a sign test (P <0.001). A significant positive correlation was found for *QA:present QoL* and

duration of GH treatment in the GH-treated group: [rho = 0.28, *P* = 0.009, N = 86] indicating improved QoL with longer duration of treatment.

Women, median -2.38, had significantly lower scores than men, median -1.69, for HDQoL AWI [U = 2227.5, *P* = 0.012], for QB: *hormone deficiency-dependent QoL (*women, median -2.0 compared to men, median -1.0), [U = 2048.5, *P* = 0.002] and also for QA:*present QoL* (women, mean 0.79 (1.25) compared to men, 1.24 (1.16)); [t(149.8) = 2.33, *P* = 0.021] suggesting significantly greater negative impact of hormone deficiency on QoL and lower present QoL than men. There were no significant differences in AWI or the overview items between those with adult or childhood onset of GHD.

There was a moderately high correlation between HDQoL AWI and *QA:present QoL* (rho = 0.53, *P* <0.001, N = 152). The correlation between HDQoL AWI and QB:*hormone deficiency-dependent QoL* was higher, (rho = 0.71, *P* <0.001, N = 152), not surprisingly because both concern impact of hormone deficiency.

(Fig 2 here)

Results (2: GH-Withdrawal study)

The data of 21 patients [age range 25-68 years], all but two with multiple pituitary hormone deficiencies, were available for analysis: 12 placebo-treated (6 men and 6 women) and nine GH-treated (4 men and 5 women). Three months after baseline the serum total IGF-I of placebo-treated patients fell from normal, age-related levels, mean 26.6 (13.2) nmol/L, to levels indicative of severe GHD, 11.6 (6.7) nmol/L, (*P* <0.001). Only a small, non-significant decrease was noted in GH-treated patients.

HDQoL completion rates dropped as the study progressed: impact ratings from 96.2% at baseline to 94.2% at end-point, and importance ratings from 93.1% to 91.9%. It was not possible to calculate HDQoL AWI for two placebo-group patients with more than five missing weighted domain scores as internal reliability was <0.8 with this amount of missing data. As the sample size was small, Bonferroni corrections were not applied in the case of variables for which direction of change was predicted to reduce the chance of Type II errors and as it was unlikely that a significant result would be obtained by chance. The required significance level was set at <0.05.

Whilst GH-treatment group means exhibited some variation in direction of change over the study, placebo-group means showed a non-significant tendency to drop (indicating greater perceived negative impact of hormone deficiency by end-point) for HDQoL AWI, the overview items and for all domains except *sex life* and *future* (results not shown). As expected a significant between-group difference in change was found for domain *physically do* [t(16) = 2.47, *P* = 0.025, 2-tailed], with scores of placebo-treated patients dropping from -0.25 (3.02) at baseline to -1.80 (1.81) at end-point, (indicating greater negative impact of hormone deficiency on physical capabilities by end-point) while scores of GH-treated patients increased from -3.5 (2.51) at baseline to -2.38 (1.19) at end-point. Patients withdrawn from GH reported reduced physical capabilities at end-point.

Adding new domains to the HDQoL

Owing to time constraints the HDQoL was initially developed without involving patients in item generation, but the questionnaire's free comments section was designed to allow respondents to mention areas of life affected by their hormone deficiencies, and not already covered in the questionnaire. The free comments section (cross-sectional study) and data from patient interviews (GH-Withdrawal study) were analysed with a view to improving the content validity of the HDQoL. Ten domains were mentioned that are already covered in the HDQoL, (*physical functioning, physical appearance*, *work*, *self-confidence*, *sexual functioning*, *sociability*, *motivation/ mental drive, dependence, worries about the future* and *travel*), which lend support to the content validity of the questionnaire; however, several additional domains were mentioned as follows.

- Interviews: patients described key areas of improvement that they had noticed in the past on initiation of GH therapy, and those on placebo (GH-Withdrawal study) described areas of deterioration in QoL and functioning over the course of the study, particularly in *energy*, *memory, sleep pattern*, *stress-tolerance*, *feeling depressed/ anxious* and *bodily pain*.
- Free comments analysis: *energy*, *weight, bodily pain* and *feeling depressed/ anxious* were most frequently mentioned. Table 5 provides details of the seven most frequently mentioned new domains that will be added to the 13-item questionnaire in the future to improve its content validity.

(Table 5 here).

Discussion

The HDQoL is a new measure of the impact of hormone deficiency on QoL, and which is under continuing development. It is individualised in that patients rate only relevant domains, and both the impact of the condition on life domains and the importance of each domain to their quality of life are taken into account in scoring. Being bi-polar it assesses both positive and negative ends of the QoL continuum, although this resulted, as expected, in skewed data distributions because few patients perceived any positive benefits of hormone deficiency on QoL. There were relatively high completion rates in the cross-sectional study although these fell over the course of the GH-Withdrawal study, thus the questionnaire had good acceptability to the majority of respondents – an indication of face validity.

Psychometric analyses indicated that the original 18-item HDQoL, which had been adapted from the renal version, the RDQoL, would be improved by dropping five items. Internal consistency reliability, item-total correlations and factor analyses were supportive of the shorter 13-item HDQoL. There was insufficient evidence for subscales, but support for summing the 13 items into a single HDQoL Average Weighted Impact score. The two overview items are useful. QB, concerning impact of hormone deficiency on QoL, could replace the full HDQoL for some purposes, such as clinical audit, as the correlation between QB and overall HDQoL AWI was sufficiently high (0.71). Furthermore, rich information can be obtained by analysing individual domains separately, and this could prove valuable in routine clinical monitoring and clinical trials, to ascertain the impact of hormone deficiency on specific aspects of life. For example, in the cross-sectional study, hormone deficiency had most negative impact on patients' physical appearance, physical capabilities, sex life, family and working life. Averaging across domains, patients felt that

they would have better QoL if they did not have hormone deficiency, but that their current QoL was good.

As might be expected, there were consistent trends (albeit non-significant) indicating that GH-treated patients perceived less impact of hormone deficiency than non-treated patients on each of the 13 domains, but the consistent direction of those trends on all domains was significant. It seems, therefore, that there were no large differences in QoL of GH-treated and non-GH-treated patients in the cross-sectional survey, indeed none of the other questionnaires used in the study found GH-treated patients to have significantly better patient-reported outcomes (including health status and well-being) than non-treated patients (McMillan 2001). It may well be that people prescribed GH treatment presented with more serious symptoms of mental and physical ill-health, compared with those who were not prescribed GH treatment, and might have had much worse QoL if they had *not* been treated. In one study, British patients who *refused* GH treatment had significantly better QoL-AGHDA median scores than those awaiting treatment, furthermore their scores were the same as for those *receiving* GH-treatment in Sweden and Germany (McKenna *et al.* 1999). In the present study, only 11 of the 66 non-GH-treated patients eventually received GH replacement, once the survey was completed: the great majority were not awaiting treatment at the time of the survey.

There was some preliminary evidence of construct validity in that there were significant correlations indicating improving current QoL with increasing duration of GH treatment. In one study of longer-term GH treatment, well-being and health status were still improving even after periods of 20-50 months of treatment (Wiren *et al.* 1998). The HDQoL also found significant sex differences, with women showing greater negative impact of hormone deficiency on QoL than men, and reduced present QoL. This finding may also support the questionnaire's construct validity. The literature shows that women in the general population have worse health status than men (Hunt & McKenna 1989; Brazier *et al.* 1992), that there are substantial sex differences in physiological variables in untreated GHD (Burman *et al.* 1997) and that there are sex differences in responsivity to GH therapy, with a risk of under-treatment in women and over-treatment in men (Span *et al.* 2000). All these factors may help explain the greater impact of hormone deficiency on QoL for women in comparison with men that were found by the HDQoL. The HDQoL did not find a difference in QoL between those with childhood and adult-onset of GHD, and this is in line with some other research (Abs *et al.* 1999).

Despite the small sample size of the GH-Withdrawal study and resulting low power of analysis, the HDQoL exhibited some sensitivity to change in GH-deficient patients. There was a significant finding for *physically do* - a greater change in the Placebo group (withdrawn from GH treatment) than the GH-treatment group as predicted by hypotheses and indicating increased negative impact of hormone deficiency on physical capabilities for placebo-treated patients by end-point. There were similar, albeit non-significant, trends for the great majority of domains. The overall HDQoL AWI score showed no significant change, but the advantage of the questionnaire is that individual domains can be analysed separately, providing additional information. The lack of significant differences between GH-treated and non-GH-treated patients in the cross-sectional study and the lack of significant findings in the GH-withdrawal trial should not be considered evidence that GH treatment has no effect on QoL. Trends in the data were in the expected direction (less impact of hormone deficiency in GH-treated compared with non-GH-treated patients in all domains in the cross-sectional study; greater impact of hormone deficiency on placebo-treated patients in most domains after three months' GH withdrawal). However, any future clinical trial of GH treatment to use the HDQoL needs a larger sample size to supply greater power of analysis.

Although the relevance of the 13 items of the HDQoL was confirmed (most domains mentioned by patients in the free comments section or during interviews are already covered in the questionnaire), qualitative work should ideally have been performed in the initial development of the questionnaire prior to first use (but was not, owing to time constraints). Qualitative work conducted during the study itself, however, has led to the consideration of seven new domains being added to the questionnaire: *energy, weight, memory, sleep pattern, stress-tolerance*, *depression/ anxiety* and *bodily pain*. Further work will now be needed to assess the properties of the extended 20-item scale and its sensitivity to change with bigger samples of patients with hypopituitarism.

Conclusion

The HDQoL is a new individualised measure of the impact of hormone deficiency and its treatment on QoL, where individuals complete only those items of relevance to their lives, and the importance of life domains to an individual's QoL is taken into account in the scoring. Although it is still at an early stage of development, the 13-item questionnaire is performing well and has good acceptability to the great majority of respondents, and good internal consistency reliability. There is some preliminary evidence for construct validity and sensitivity to change. An overall score, the Average Weighted Impact score may be calculated and domains can be analysed separately if wished. Content validity may be improved by the inclusion of seven additional domains and further work is now needed to assess the properties of the extended scale and its sensitivity to change with bigger samples. Even at this present stage, the 13-item HDQoL appears to be a useful tool and is recommended for assessing impact of hormone deficiency on QoL in adult hypopituitarism including GHD.

Acknowledgements
C V McMillan was funded by a research studentship from Lilly Industries Ltd, which also provided partial funding for J Gibney. We acknowledge valuable assistance from Louise Breen, Research Nurse at the Endocrine Clinic of St Thomas' Hospital, and from John Valentine, statistician at Royal Holloway, University of London, and the essential contributions of participants in the studies.

References

Abs, R., Bengtsson, B.A., Hernberg-Stahl, E., Monson, J.P., Tauber, J.P., Wilton, P. & Wuster, C. (1999) GH replacement in 1034 growth hormone deficient hypopituitary adults: demographic and clinical characteristics, dosing and safety. *Clinical Endocrinology*, **50**, (6), 703-713.

Ahmad, A.M., Hopkins, M.T., Thomas, J., Ibrahim, H., Fraser, W.D. & Vora, J.P. (2001) Body composition and quality of life in adults with growth hormone deficiency; effects of low-dose growth hormone replacement. *Clinical Endocrinology*, **54**, (6), 709-717.

Barkan, A.L. (2001) The "quality of life-assessment of growth hormone deficiency in adults" questionnaire: Can it be used to assess quality of life in hypopituitarism?" *Journal of Clinical Endocrinology and Metabolism*, **86**, (5), 1905-1907.

Barkan, A. & Wren, P. (2001) Author's response: The QoL-AGHDA Questionnaire - Can it be used to assess quality of life in hypopituitarism? *Journal of Clinical Endocrinology and Metabolism*, **86**, (12), 5997.

Baum, H.B.A., Katznelson, L., Sherman, J.C., Biller, B.M.K., Hayden, D.L., Schoenfeld, D.A., Cannistraro, K.E. & Klibanski, A. (1998) Effects of physiological growth hormone (GH) therapy on cognition and quality of life in patients with adult-onset GH deficiency. *Journal of Clinical Endocrinology and Metabolism*, **83**, (9), 3184-3189.

Bengtsson, B.A., Johannsson, G., Shalet, S.M., Simpson, H. & Sönksen, P.H. (2000) Treatment of growth hormone deficiency in adults. *Journal of Clinical Endocrinology and Metabolism*, **85**, (3), 933-937.

Bradley, C. (1994) The Well-being Questionnaire. In: *Handbook of Psychology and Diabetes: A Guide to Psychological Measurement in Diabetes Research and Practice*. (ed C. Bradley) pp. 89-109. Harwood Academic Publishers, Chur, Switzerland.

Bradley, C. (1997) Design of a renal-dependent individualised quality of life questionnaire: RDQoL. *Advances in Peritoneal Dialysis*, **13**, 116-120.

Bradley, C. (1999) Achieving accessibility with quality: questionnaire measurement of condition-specific individualised quality of life. *Proceedings of the British Psychological Society*, **7**, (2), 143.

Bradley, C., Todd, C., Gorton, T., Symonds, E., Martin, A. & Plowright, R. (1999) The development of an individualized questionnaire measure of perceived impact of diabetes on quality of life: the ADDQoL. *Quality of Life Research*, **8**, (1-2), 79-91.

Bradley, C. & Speight, J. (2002) Patient perceptions of diabetes and diabetes therapy: assessing quality of life. *Diabetes Metabolism Research and Reviews*, **18**, (Suppl 3), S64-S69.

Brazier, J.E., Harper, R., Jones, N.M.B., Ocathain, A., Thomas, K.J., Usherwood, T. & Westlake, L. (1992) Validating the SF-36 Health Survey Questionnaire - new outcome measure for primary care. *British Medical Journal*, **305**, (6846), 160-164.

Burman, P., Johansson, A.G., EdenEngstrom, B. & Karlsson, F.A. (1997) GH-deficient men are more responsive to GH replacement therapy than women - Response. *Journal of Clinical Endocrinology and Metabolism*, **82**, (10), 3515-3515.

Carroll, P.V., Christ, E.R. & Growth Hormone Research Society Scientific Committee (1998) Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. *Journal of Clinical Endocrinology and Metabolism*, **83**, (2), 382-395.

Carroll, P.V., Littlewood, R., Weissberger, A.J., Bogalho, P., McGauley, G., Sönksen, P.H. & Russell-Jones, D.L. (1997) The effects of two doses of replacement growth

hormone on the biochemical, body composition and psychological profiles of growth hormone-deficient adults. *European Journal of Endocrinology*, **137**, (2), 146-153.

Cronbach, L.J. (1951) Coefficient alpha and the internal structure of tests. *Psychometrika*, **16**, 297-334.

Dupuy, H.J. (1984) The Psychological General Well-being Index (PGWB). In: *Assessment of Quality of Life in Clinical Trials of Cardiovascular Therapies*. (ed N.K. Wenger, M.E. Mattson, C.D. Furburg & J. Elinson) pp. Le Jacq Publishing Inc, New York.

Henrich, G. & Herschbach, P. (2000) Questions on Life Satisfaction (FLZ^M) - A short questionnaire for assessing subjective quality of life. *European Journal of Psychological Assessment*, **16**, (3), 150-159.

Holm, S. (1979) A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics*, **6**, 65-70.

Hunt, S.M. & McKenna, S.P. (1989) The Nottingham Health Profile. In: *European Guide to the Nottingham Health Profile*. The European Group for Quality of Life and Health Measurement.

Hunt, S.M. & McKenna, S.P. (1992) A British adaptation of the General Well-being Index: a new tool for clinical research. *British Journal of Medical Economics*, **2**, 49-60.

Hunt, S.M., McKenna, S.P. & Doward, L.C. (1993) Preliminary report on the development of a disease-specific instrument for assessing quality-of-life of adults with growth hormone deficiency. *Acta Endocrinologica*, **128**, 37-40.

Kline, P. (1993) *A Handbook of Test Construction*. Routledge, London.

Kline, P. (1994) *An Easy Guide to Factor Analysis*. Routledge, London.

Malik, I.A., Foy, P., Wallymahmed, M., Wilding, J.P. & MacFarlane, I.A. (2003) Assessment of quality of life in adults receiving long-term growth hormone replacement compared to control subjects. *Clinical Endocrinology*, **59**, (1), 75-81.

Mardh, G., Lundin, K., Borg, G., Jonsson, B. & Lindeberg, A. (1994) Growth hormone replacement therapy in adult hypopituitary patients with growth hormone deficiency: combined data from 12 European placebo-controlled clinical trials. *Endocrinology and Metabolism*, **1**, (Suppl.A), 43-49.

McGauley, G., Cuneo, R.C., Salomon, F. & Sönksen, P. (1990) Psychosocial well being before and after growth hormone treatment in adults with growth hormone deficiency. *Hormone Research*, **33**, (Suppl. 4), 52-54.

McGee, H.M., O'Boyle, C.A., Hickey, A., O'Malley, K.M. & Joyce, C.R.B. (1991) Assessing the quality of life of the individual: The SEIQoL with a healthy and a gastroenterology unit population. *Psychological Medicine*, **21**, 749-759.

McKenna, S.P., Doward, L.C., Alonso, J., Kohlmann, T., Niero, M., Prieto, L. & Wiren, L. (1999) The QoL-AGHDA: An instrument for the assessment of quality of life in adults with growth hormone deficiency. *Quality of Life Research*, **8**, (4), 373-383.

McMillan, C.V. (2001). A psychometric evaluation of measures of quality of life and related health outcomes in adults with growth hormone deficiency. (PhD Thesis). Psychology Department, Royal Holloway, University of London.

McMillan, C.V., Bradley, C., Gibney, J., Russell-Jones, D.L. & Sönksen, P.H. (2001) Measuring psychological well-being in adult growth hormone deficiency (GHD). *Proceedings of the British Psychological Society*, **9**, (1), 71.

McMillan, C.V., Bradley, C., Gibney, J., Healy, M.L., Russell-Jones, D.L. & Sönksen, P.H. (2003a) Psychological effects of withdrawal of growth hormone therapy from adults with growth hormone deficiency. *Clinical Endocrinology*, **59**, (4), 467-475.

McMillan, C.V., Bradley, C., Gibney, J., Russell-Jones, D.L. & Sönksen, P.H. (2003b) Evaluation of two health status measures in adults with growth hormone deficiency. *Clinical Endocrinology*, **58**, 436-445.

Mitchell, J. & Bradley, C. (2001) Psychometric evaluation of the 12-item Well-being Questionnaire for use with people with macular disease. *Quality of Life Research*, **10**, (5), 465-473.

Nunnally, J.C. (1978) *Psychometric Theory*. McGraw Hill, New York.

Powrie, J., Weissberger, A. & Sönksen, P. (1995) Growth hormone replacement therapy for growth hormone-deficient adults. *Drugs*, **49**, (5), 656-663.

Smith, J.C. (2004) Hormone replacement therapy in hypopituitarism. *Expert Opinion in Pharmacotherapy*, **5**, (5), 1023-1031.

Span, J.P.T., Pieters, G., Sweep, C.G.J., Hermus, A. & Smals, A.G.H. (2000) Gender difference in insulin-like growth factor I response to growth hormone (GH) treatment in GH-deficient adults: Role of sex hormone replacement. *Journal of Clinical Endocrinology and Metabolism*, **85**, (3), 1121-1125.

Svensson, J., Mattsson, A., Rosen, T., Wiren, L., Johannsson, G., Bengtsson, B.A. & Koltowska Haggstrom, M. (2004) Three-years of growth hormone (GH) replacement therapy in GH-deficient adults: effects on quality of life, patient-reported outcomes and healthcare consumption. *Growth Hormone and IGF Research*, **14**, (3), 207-215.

Tabachnik, B.G. & Fidell, L.S. (1983) *Using Multivariate Statistics*. Harper and Row, New York.

Todd, C. & Bradley, C. (1994) Evaluating the design and development of psychological scales. In: *Handbook of Psychology and Diabetes: A Guide to Psychological Measurement in Diabetes Research and Practice*. (ed C. Bradley) pp. 15-42. Harwood Academic Publishers, Chur, Switzerland.

Wallymahmed, M.E., Baker, G.A., Humphris, G., Dewey, M. & MacFarlane, I.A. (1996) The development, reliability and validity of a disease specific quality of life model for adults with growth hormone deficiency. *Clinical Endocrinology*, **44**, (4), 403-411.

Ware, J.E. & Sherbourne, C.D. (1992) The MOS 36-Item Short-Form Health Survey (SF-36). 1. Conceptual framework and item selection. *Medical Care*, **30**, (6), 473-483.

Whitehead, H.M., Boreham, C., McIlrath, E.M., Sheridan, B., Kennedy, L., Atkinson, A.B. & Hadden, D.R. (1992) Growth-hormone treatment of adults with growth-hormone deficiency - Results of a 13-month placebo controlled cross-over study. *Clinical Endocrinology*, **36**, (1), 45-52.

Wiren, L., Bengtsson, B.A. & Johannsson, G. (1998) Beneficial effects of long-term GH replacement therapy on quality of life in adults with GH deficiency. *Clinical Endocrinology*, **48**, (5), 613-620.

Wiren, L., Johannsson, G. & Bengtsson, B.A. (2001) A prospective investigation of quality of life and psychological well-being after the discontinuation of GH treatment in adolescent patients who had GH deficiency during childhood. *Journal of Clinical Endocrinology and Metabolism*, **86**, (8), 3494-3498.

Legends

Fig. 1: HDQoL domain item with scoring

Fig. 2: Mean HDQoL weighted impact scores comparing GH-treated and non-GH-treated groups in the cross-sectional study

Table 1 Characteristics of the 157 patients in the cross-sectional survey

		GH treatment	**No GH treatment**
	Women	51	33
	Men	40	33
	Childhood onset of GHD	21	9
	Adult onset of GHD	70	57
	Isolated GHD	5	1
Multiple pituitary hormone deficiencies		86	65
Mean age (SD) in years		47.1	51.32
	[range]	(12	(1

		.59)	2.41)
		[23.75 – 70.92]	[23.83 – 70.92]
Mean duration GHD (SD) in years (adult onset patients)		13.02 (6.78)	13.18 (7.84)
	BMI (kg/m^2) (SD)	27.16 (5.54)	27.99 (5.25)
	Height (cms) (SD)	167.5	168.7

	(10.53)	(10.6)
Maximum N	91	66

GH: growth hormone
GHD: growth hormone deficiency
BMI: body mass index
SD: standard deviation
N: sample size

Table 2 Reliability analysis of the 13-item HDQoL

	Corrected item-total correlations	**Alpha if item deleted**
Working life	0.736	0.903
Family	0.62	0.90

y	5	8
Life		
Social Life	0.618	0.908
Sex Life	0.613	0.908
Physical appearance	0.566	0.910
Physica	0.762	0.902

Ily do		
Holiday s/ Leisure	0.718	0.904
Travel	0.500	0.912
Confidence	0.792	0.901
Motivation	0.787	0.901
Fu	0.	0.

ture	54911	
Finances	0.6370	0.9077
Dependence	0.4433	0.9144

Overall alpha = 0.914 (N = 109).
HDQoL: Hormone deficiency-Dependent Quality of Life questionnaire.

Table 3 Unforced and forced 1-factor analyses[a] of the 13-item HDQoL

	Unforced	Forced 1-factor
Working Life		0.800
Family Life		0.684
Social Life		0.693

Sex	0.674
Life	
Physical appearance	0.624
Physically do	0.817
Holidays/ Le	0.782

Leisure	
Travel	0.568
Confidence	0.842
Motivation	0.842
Future	0.612
Finances	0.691
Depen	0.504

dence	
%variance	50.5%

[a]Principal Component Analysis (with Varimax Rotation in unforced analysis). Loadings ≥0.5 are shown.

Table 4 HDQoL. Wording and descriptive statistics (cross-sectional study)

No.	Item wording… (response option)	Abbreviation	Valid N	Mean (SD)	Range	Median
QA	In general, my present quality of life is …(as good as it could possibly be …. as bad as it could possibly be)	*present QoL*	152	1.00 (1.23)	-2 to 3	1
QB	If I did not have hormone deficiency, my quality of life would be …(very much better …. very much worse)	*hormone deficiency-dependent QoL*	152	-1.36 (1.40)	-3 to 3	-1.5
	If I did not have hormone deficiency, …					
1[a]	…my working life and work-related opportunities would be …(very much better ….very much worse)	*work*	129[a]	-2.64 (3.34)	-9 to 9	-2
2[a]	…my family life would be …(very much better ….very much worse)	*family life*	144[a]	-2.89 (3.73)	-9 to 9	-3
3	…my friendships and social life would be …(very much better ….very much worse)	*social life*	152	-2.11 (3.06)	-9 to 6	-1
4[a]	…my sex life would be …(very much better ….very much worse)	*sex life*	136[a]	-2.96 (3.56)	-9 to 9	-2
5	…my physical appearance would be …(very much better ….very much worse)	*physical appearance*	153	-3.08 (3.44)	-9 to 9	-2
6	…the things I could do physically would be …(very much increased ….very much decreased)	*physically do*	153	-3.01 (3.03)	-9 to 9	-3

No.	Item wording… (response option)	Abbreviation	Valid N	Mean (SD)	Range	Median
7	…my holidays or leisure activities would be …(very much better ….very much worse)	*holidays/ leisure*	153	-2.44 (3.03)	-9 to 6	-2
8	…problems with travelling (either local or long distance) would be …(very much decreased ….very much increased)	*travel*	153	-1.2 (3.15)	-9 to 9	0
9	…my confidence in my ability to do things would be …(very much increased ….very much decreased)	*confidence*	153	-2.31 (3.11)	-9 to 9	-2
10	…my motivation to achieve things would be …(very much increased ….very much decreased)	*motivation*	152	-2.23 (3.27)	-9 to 9	-2
11	…my worries about my future and the future of others close to me would be …(very much decreased ….very much increased)	*future*	150	-2.48 (3.71)	-9 to 9	-2
12	…my finances would be …(very much better ….very much worse)	*finances*	151	-1.61 (2.9)	-9 to 9	0
13	…my need to depend on others for things I would like to do for myself would be …(very much decreased ….very much increased)	*dependence*	150	-1.45 (2.84)	-9 to 9	0

[a]Item has a not applicable response option, with valid N reflecting the numbers who chose the N/A option.

Maximum possible score ranges: QA:*present QoL* (+3 to -3), (from good to poor QoL), QB:*hormone deficiency-dependent QoL* (-3 to +3) (from maximum negative to maximum positive impact of hormone deficiency on QoL), 13 domain items (-9 to +9), (from maximum negative to maximum positive importance-weighted impact of hormone deficiency on QoL).

SD: standard deviation.

Table 5 Domains to be added to the 13-item HDQoL[a]

Domain	Cross-sectional study: free comments	GH-Withdrawal study: interviews	
		Improvements noti	Deterioration on

			ced when first prescribed GH	**GH withdrawal**
	Energy	6	20	9
	Weight	5		
	Memory	1	4	3

Sleep pattern	2	8	5
Tolerance of stress	1	3	4
Depressed/ anxious	4	6	4

Bodily pain	5	4	4
Maximum	56	21	12
N			

[a]Numbers of patients mentioning each domain either in the HDQoL free comments section (cross-sectional study) or during interviews (GH-Withdrawal study).

Figures

Fig. 1: HDQoL domain item with scoring

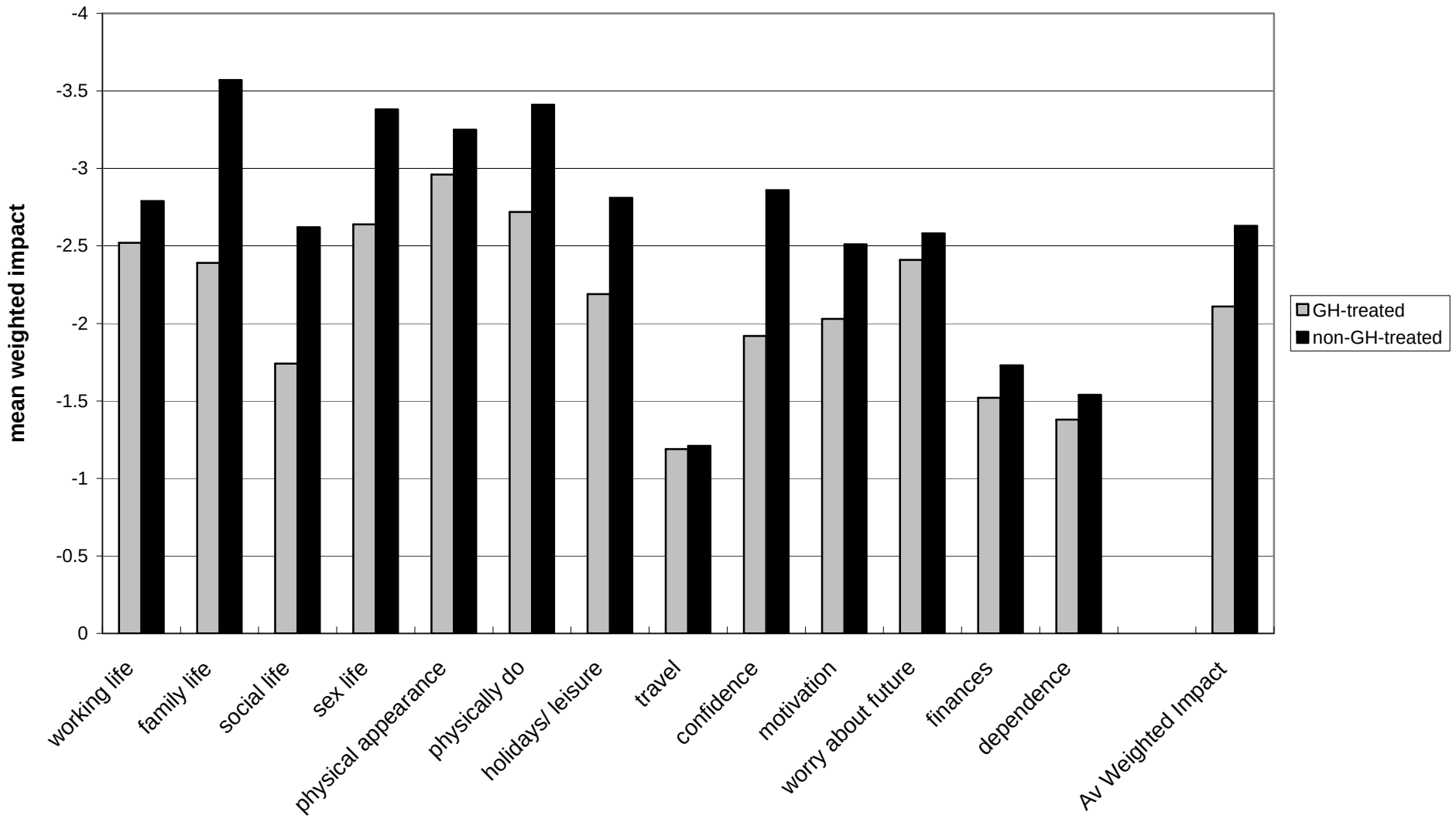
If I did not have hormone deficiency, my family life would be:

-3	-2	-1	0	1	2	3	
very much better	much better	a little better	the same	a little worse	much worse	very much worse	N/A

This aspect of my life is *(please circle the answer that applies for you)*

3	2	1	0
very important	important	somewhat important	not at all important

Fig. 2: Mean HDQoL weighted impact scores comparing GH-treated and non-GH-treated groups in the cross-sectional study


mean weighted impact
-4
-3.5
-3
-2.5
-2
-1.5
-1
-0.5
0
working life
family life
social life
sex life
physical appearance
physically do
holidays/ leisure
travel
confidence
motivation
worry about future
finances
dependence
Av Weighted Impact
GH-treated
non-GH-treated