Health-related quality of life and IGF-1 in GH-deficient adult patients on GH replacement therapy: analysis of the German KIMS data and the Study of Health in Pomerania

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*(T Kohlmann and H Wallaschofski contributed equally)

Abstract

Objective: To analyse 12-month response to GH treatment in a single-country cohort of hypopituitary adult patients with GH deficiency (GHD) in regards to health-related quality of life (HRQoL) and insulin-like growth factor-1 (IGF-1) compared with values from general population sample. Moreover, association between the response in HRQoL and the IGF-1 values in patients and in the background population was investigated.

Design: HRQoL was assessed by quality of life assessment of GH deficiency in adults (QoL-AGHDA) in 651 patients retrieved from the German KIMS (Pfizer International Metabolic Database) before and after 12 months of GH replacement and in a sample drawn from a cross-sectional study in Germany (n=2734). IGF-1 was measured in KIMS patients and in the population-based study with the same assay technique.

Results: In KIMS patients, mean QoL-AGHDA scores before GH replacement were 9.2 ± 6.8 (8.7 ± 6.8) in women (men) and in the general population sample 4.5 ± 5.3 (4.3 ± 5.0) in women (men). Mean differences in QoL-AGHDA scores were statistically significant for all age categories (P<0.05). The mean IGF-1 SDS of KIMS patients before GH replacement was −1.1 ± 1.4 (−0.8 ± 1.4) in women (men). After GH replacement, a significant increase of IGF-1 concentration and a significant decrease of QoL-AGHDA scores near to age- and gender-specific population-based values were observed.

Conclusions: This study confirms an improvement in HRQoL and an increase of IGF-1 SDS in GH-replaced adults, which approximated the values of general population. However, there was no association between IGF-1 values and HRQoL assessment as one of the important treatment outcomes.

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Introduction

GH deficiency (GHD) in adults is a well-recognized distinct clinical condition (1). One of the most important impairments from a patient’s point of view is the decline in health-related quality of life (HRQoL). The HRQoL decay is perceived in the areas of energy, emotional reaction, social behaviour, general health, self-control, anxiety, vitality, mood and sense of well-being measured by Nottingham Health Profile and the Psychological General Well-Being Schedule (2). Most studies showed a benefit of GH replacement on HRQoL (1). Although extensive data are now available documenting the impaired QoL associated with adult GHD, the mechanisms underlying this observation remain poorly understood. There are specific receptors expressed in the brain and after GH treatment, GH and insulin-like growth factor-1 (IGF-1) concentrations increase in cerebrospinal fluid (3). The highest concentration of GH and IGF-1 receptors has been found in the choroid plexus, followed by the pituitary, hippocampus, putamen, hypothalamus and thalamus (4, 5). These areas offer potential access into the CN, and key limbic system structures known to be pivotal for the physiology of vegetative functions and in the control of behaviour, emotion and motivation, suggesting a possible central role for GH effects on QoL. However, the underlying mechanism and the effects of GH treatment on cognitive function as well as QoL are unclear. Moreover, there is little known about the association between changes in QoL and biochemical markers of GHD, especially IGF-1. However, these mechanisms appear to have a rapid onset
of action, as most of the QOL improvement is observed to occur rapidly in affected GHD adults within the first 3 months of GH replacement (6, 7).

Apart from comparing the effect of GH replacement with placebo, another approach to assess HRQoL in GHD adults is to compare the effect of GH therapy with the values from the general population. Furthermore, population-based data are the background for the evaluation of HRQoL as a standard endpoint in clinical studies and for economic evaluation or health care decision making. Furthermore, there are only few studies on HRQoL in GHD patients in relation to their country-specific population-based data (8–11).

Therefore, the objectives of our present study were first to evaluate 12-month response to GH treatment in the German KIMS (Pfizer International Metabolic Database (12)) cohort of hypopituitary adult patients with GHD in regards to HRQoL and IGF-1 and in comparison with the values generated from a general population sample and secondly to investigate the association between quality of life assessment of growth hormone deficiency in adults (QoL-AGHDA) scores and IGF-1 concentrations in the German KIMS cohort as well as in the general population.

Material and methods

Instrument

HRQoL was measured by the QoL-AGDHA, a diseasespecific, one-dimensional, patient needs-based HRQoL instrument, developed specifically for the detection of deficits, needs achievement in areas that are affected in GHD adults (13–16). The measure consists of 25 questions with ‘yes’ or ‘no’ answers; a ‘yes’ answer indicates that the patient perceives a problem. The sum of ‘yes’ answers constitutes a score, with a high score denoting a poor HRQoL. The QoL-AGHDA showed satisfactory psychometric properties across a wide range of languages (15).

Patient sample

GH-deficient patients’ information was retrieved from the German KIMS, a pharmaco-epidemiological survey of adult GH-deficient patients, and included socio-demographic characteristics, background clinical characteristics, QoL-AGHDA scores and IGF-1 values, at baseline and 12-month follow-up. In KIMS patients, until November 2002, serum IGF-1 was determined by RIA after acid–ethanol precipitation of IGF-binding proteins (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Thereafter, a chemiluminescence immunoassay (Nichols Advantage System, Bad Vilbel, Germany) was introduced. Long-term reproducibility, measured during >1 year, showed a coefficient of variation <9% of 130–850 µg/l. The assay detection limit was 30 µg/l (12).

General population sample (SHIP)

About 3925 eligible participants of the ‘Study of Health in Pomerania’ (SHIP) consented to participate in this study. SHIP is a population-based study in the north-eastern region of Germany, situated on the Baltic coast. The study was designed to provide comprehensive information of the state of health as well as the health-related behaviour and living conditions of the population in western Pomerania (17).

Information on HRQoL assessed by the QoL-AGHDA and socio-demographics were collected using a postal questionnaire. The questionnaire was administered in the first half of 2006 to the SHIP participants. IGF-1 concentrations were measured in all participants of the SHIP study. The blood samples were drawn from the cubital vein. Serum IGF-1 concentrations were determined by automated two-site chemiluminescence immunoassays (Nichols Advantage; Nichols Institute Diagnostica GmbH, Bad Vilbel, Germany) in the SHIP population (18). The analytical sensitivity of the assay was 6 ng/ml. The IGF-1 assay has been calibrated against the World Health Organization International Reference Reagent 1988. IGF-I 87/518. Reference ranges of IGF-1 for the SHIP population have been computed and described elsewhere (19).

The medical ethics committee of the University of Greifswald approved the study protocol. All participants gave written informed consent.

Statistical analysis

Descriptive statistics included means, S.D.s, medians and proportions for demographic properties. Distributional comparisons between responders and non-responders were done by χ2-test. ANOVA and t-tests were used to examine subgroup differences. Dunnett’s t-test, multiple comparison method, was performed to compare QoL-AGHDA scores from age groups 20–59 years against the age group 60 years or older as post hoc assessment. Bivariate correlation analyses were performed using Pearson’s correlation coefficient. A P value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA).

IGF-1 concentrations are described as SDS. SDS were calculated as (observed serum IGF-1 level – SHIP population mean serum IGF-1 level (standardized for age and gender))/SHIP population standardized S.D.).

Results

Characteristics of KIMS patients

The analysis was performed using data of 651 consecutively documented adult patients (n = 288 women, n = 363 men) with GHD enrolled in the German KIMS database. These patients had either never received
GH replacement or had not received GH for at least 6 months before entry into KIMS. All patients included in the study had GHD proven by insulin-induced hypoglycaemia, arginine or glucagon as primary stimulus. Childhood onset-GHD was reported in 173 of 651 patients. At entry to KIMS (baseline visit), the mean age was 44.8 ± 13.3 years (45.7 ± 12.8 for women and 44.2 ± 13.8 for men). Details of the aetiology, clinical characteristics and other hormone treatments of the KIMS patients are detailed in Tables 1 and 2. The most common causes of GHD in the KIMS cohort were non-functioning pituitary adenoma n = 227 (34.9%), craniopharyngioma n = 106 (16.3%), idiopathic/empty sella n = 76 (11.7%) and prolactinoma n = 64 (9.8%). All patients received a low starting dose of GH (0.1–0.3 mg/day), which was administered as a daily s.c. injection and was adjusted individually for each patient according to the clinical response and serum IGF-1 concentrations. The mean daily doses were 0.31 ± 0.13 mg/day after 6 months of treatment, and 0.29 ± 0.15 mg/day after 12 months. In addition, most of the patients received pituitary hormone replacement therapy (Table 2). QoL-AGHDA scores and IGF-1 concentrations were obtained at baseline and after 12 months of GH replacement therapy.

Characteristics of the general population sample (SHIP)

In total, 3925 participants of SHIP received a postal questionnaire. Of these, 78 (2.0%) were returned because target subjects had moved, or were deceased. Of the remaining 3847 subjects, 25 (0.7%) refused participation, by calling the study centre. Around 2814 subjects returned completed questionnaires. Of these, 78 (2.0%) were returned because target subjects had moved, or were deceased. In total, 2768 questionnaires (n = 1486 women, n = 1282 men) were available for analysis. The overall response was 71.6%. The mean age of SHIP participants was 49.3 ± 15.3 (48.1 ± 15.2 for women and 50.8 ± 15.2 for men).

Age, gender and IGF-1 concentrations were known variables for non-responders. IGF-1 means did not differ between responders and non-responders with respect to age and gender (data not presented).

QoL-AGHDA scores of KIMS patients and SHIP participants

Age- and gender-specific mean QoL-AGHDA scores of KIMS patients and SHIP individuals are presented in Table 3. The overall mean QoL-AGHDA score of KIMS patients was 8.9 ± 6.8 and 4.5 ± 5.1 of SHIP respondents. ANOVA indicated that variability in QoL-AGHDA scores was not statistically significantly explained by gender (P = 0.075), whereas age was a significant predictor (P < 0.001). Dunnett’s post hoc analysis revealed that, QoL-AGHDA scores from the younger groups (20–59 years) were significantly lower, indicating better HRQoL compared with respondents aged 60 years or older (all P values < 0.001).

QoL-AGHDA scores: comparisons between KIMS patients and SHIP participants

Compared with SHIP participants, KIMS patients at baseline had reduced HRQoL, according to QoL-AGHDA scores (overall mean difference: 4.3 ± s.e.m. 0.2, P < 0.001). Mean QoL-AGHDA scores at baseline were significantly higher in the KIMS cohort compared with SHIP participants when analysed by gender (women: 9.2 ± 6.8 (KIMS) vs 4.5 ± 5.3 (SHIP), P < 0.001; men: 8.7 ± 6.8 (KIMS) vs 4.3 ± 5.0 (SHIP), P < 0.001). In both KIMS patient groups (men and women), baseline QoL-AGHDA scores increased with age until the age of 50–59 years, dropping subsequently in patients aged 60 years or older (Table 3 and Fig. 1a and c). Moreover, mean QoL-AGHDA scores by gender and age for KIMS

Table 1 Aetiology of GH deficiency (GHD) patients in KIMS Germany.

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Total</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>651</td>
<td>100</td>
<td>108</td>
<td>16.6</td>
<td>144</td>
<td>22.1</td>
</tr>
<tr>
<td>Idiopathic/empty sella</td>
<td>76</td>
<td>11.7</td>
<td>29</td>
<td>38.2</td>
<td>19</td>
<td>25.0</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>106</td>
<td>16.3</td>
<td>29</td>
<td>27.4</td>
<td>28</td>
<td>26.4</td>
</tr>
<tr>
<td>Pituitary adenoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-functioning</td>
<td>227</td>
<td>34.9</td>
<td>4</td>
<td>1.8</td>
<td>28</td>
<td>12.3</td>
</tr>
<tr>
<td>Prolactinoma</td>
<td>64</td>
<td>9.8</td>
<td>7</td>
<td>10.9</td>
<td>22</td>
<td>34.4</td>
</tr>
<tr>
<td>ACTH</td>
<td>33</td>
<td>5.1</td>
<td>7</td>
<td>21.2</td>
<td>6</td>
<td>18.2</td>
</tr>
<tr>
<td>GH</td>
<td>11</td>
<td>1.7</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
<td>27.3</td>
</tr>
<tr>
<td>Trauma</td>
<td>27</td>
<td>4.2</td>
<td>4</td>
<td>14.8</td>
<td>17</td>
<td>63.0</td>
</tr>
<tr>
<td>Sheehan/post partum necrosis</td>
<td>20</td>
<td>3.1</td>
<td>5</td>
<td>5.0</td>
<td>25.0</td>
<td>7</td>
</tr>
<tr>
<td>CNS tumours</td>
<td>19</td>
<td>2.9</td>
<td>8</td>
<td>42.1</td>
<td>6</td>
<td>31.6</td>
</tr>
<tr>
<td>Others</td>
<td>68</td>
<td>10.4</td>
<td>16</td>
<td>23.5</td>
<td>11</td>
<td>16.2</td>
</tr>
</tbody>
</table>
patients’ were significantly higher, indicating lower HRQoL, compared with the SHIP individuals ($P<0.001$ in most age categories. Table 3).

Mean QoL-AGHDA scores in KIMS patients at baseline and 12-month-follow-up are shown by age groups in Fig. 1a (women) and 1c (men) and in comparison with mean QoL-AGHDA scores of SHIP participants. The HRQoL of patients with GHD improved after GH replacement therapy. This was revealed by a decrease in mean QoL-AGHDA of 3.1 ± 5.5 points ($P<0.001$) in women and 2.1 ± 5.1 points ($P<0.001$) in men at 12-month follow-up respectively. Despite the decrease in the mean QoL-AGHDA scores in KIMS patients after 12 months of GH treatment, the QoL-AGHDA scores in patients remained higher compared with those in the SHIP cohort. Overall, mean difference of QoL-AGHDA scores between KIMS patients’ and the SHIP subjects after 12 months of GH therapy was 1.6 points ($±$ S.E.M. 0.34, $P<0.001$).

**IGF-1 concentrations: comparisons between KIMS patients and SHIP participants and relation with QoL-AGHDA**

Mean baseline and 12 month IGF-1 concentrations in KIMS patients and SHIP participants (relative to values in the SHIP subjects) are presented in Fig. 1b (women) and 1d (men). Mean IGF-1 levels at baseline were 84.4 ± 55.9 and 107.1 ± 62.5 ng/ml in female and male patients respectively. After 12 months of GH replacement therapy, serum IGF-1 concentrations had increased by 175.4 ± 82.9 and 224.6 ± 105.4 ng/ml in women and men. This corresponded to 12-month increases in IGF-1 SDS from −0.8 to 1.6, in men and from −1.2 to 0.7 in women. With respect to age, mean IGF-1 levels of the KIMS cohort were between the −2 and −1 S.D. of the general population in SHIP at baseline and have increased after 12-months GH replacement therapy to the upper reference range for all age groups. Increasing IGF-1 levels and decreasing QoL-AGHDA scores were observed in both gender and all age groups.

From a visual impression, KIMS patients with IGF-1 SDS below −2 and above +2 SDS, showed higher QoL-AGHDA scores than patients who had IGF-1 SDS between −2 and +2 SDS (Fig. 2a and b). However, there was no statistically significant association between IGF-1 values and QoL-AGHDA scores in both the general population sample ($r=−0.048$, $P=0.093$) and the KIMS cohort (baseline: $r=0.019$, $P=0.709$; 12-month follow-up: $r=−0.021$, $P=0.770$). Furthermore, correlation of mean differences of IGF-1 values

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**Table 2** Baseline clinical characteristics of pituitary insufficiency, replacement regime and additional therapy of KIMS patients.

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Total</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60+</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (% )</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Pituitary replacement therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>496</td>
<td>100</td>
<td>80</td>
<td>16.1</td>
<td>100</td>
<td>20.2</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>521</td>
<td>100</td>
<td>85</td>
<td>16.3</td>
<td>114</td>
<td>21.9</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>420</td>
<td>100</td>
<td>65</td>
<td>15.5</td>
<td>62</td>
<td>14.8</td>
</tr>
<tr>
<td>Female</td>
<td>266</td>
<td>100</td>
<td>25</td>
<td>9.4</td>
<td>60</td>
<td>22.6</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>189</td>
<td>100</td>
<td>38</td>
<td>20.1</td>
<td>46</td>
<td>24.3</td>
</tr>
</tbody>
</table>

**Table 3** Quality of life assessment of GH deficiency in adults (QoL-AGHDA) scores in GH-deficient patients in KIMS before GH replacement (baseline) and the Study of Health in Pomerania (SHIP) individuals.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age group</th>
<th>KIMS patients (baseline)</th>
<th>General population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>s.d.</td>
</tr>
<tr>
<td>Women</td>
<td>20</td>
<td>6.6</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>8.5</td>
<td>7.0</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>9.9</td>
<td>6.9</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>10.6</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>60+</td>
<td>8.9</td>
<td>7.3</td>
</tr>
<tr>
<td>Total</td>
<td>9.2</td>
<td>6.8</td>
<td>9.0</td>
</tr>
<tr>
<td>Men</td>
<td>20</td>
<td>8.2</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>8.0</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>9.8</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>9.1</td>
<td>6.5</td>
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<tr>
<td></td>
<td>60+</td>
<td>8.5</td>
<td>6.6</td>
</tr>
<tr>
<td>Total</td>
<td>8.9</td>
<td>6.8</td>
<td>8.0</td>
</tr>
</tbody>
</table>

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Discussion

This study reports the results of QoL-AGHDA scores and IGF-1 levels in a cohort of patients with GHD of the German KIMS cohort at baseline and after 12 months of GH replacement, and compares them with the results obtained in a general population sample from the German SHIP study. Mean QoL-AGHDA scores of the German KIMS cohort are consistent with those from the previously published studies in Sweden and the Netherlands respectively, which indicate a substantial HRQoL deficit in untreated hypopituitary patients with GHD independent of gender and age (10). However, there were no differences in mean QoL-AGHDA scores between males and females in either the KIMS cohort or as in the general population sample, which runs counter to previous studies (20–22).

Our results demonstrated a significant improvement in HRQoL and an increase of IGF-1 concentration in GHD patients, approaching QoL-AGHDA scores and IGF-1 levels of the SHIP population after 12 months of GH replacement therapy. We demonstrated that the positive effect of GH replacement on HRQoL was independent of gender or age, even in patients > 60 years. On the other hand, our data indicate differences in age groups with a smaller decrease of QoL-AGHDA scores especially in patients > 40 years compared with patients in the 20 years group. This might depend on differences in GH replacement regimens in study subjects. All patients received a low starting dose of GH (0.1–0.3 mg/day), which was administered as a daily s.c. injection and was adjusted individually for each patient according to the clinical response and serum IGF-1 concentrations in the different study centres. The mean daily doses were 0.31 ± 0.13 mg/day after 6 months of treatment, and 0.29 ± 0.15 mg/day after 12 months.

Koltowska-Häggstrom and colleagues demonstrated that long-term GH replacement maintained the initial positive improvement of HRQoL after 3.5–7 years (10). As reported in this study, the most improvement of HRQoL occurred within the first 12 months of GH replacement therapy. Mean differences in QoL-AGHDA scores between the general population and GHD patients at 12-month follow-up ranged between 1.5 (Sweden) and 3.3 (Spain) points (10). Based on our

Figure 1 (a–d) Decrease of QoL-AGHDA score and increase of IGF-1 concentration in GHD patients compared with the general population (SHIP). (a) Mean QoL-AGHDA scores at baseline and 12-month follow-up (women). (b) Mean IGF-1 values at baseline and 12-month follow-up (women). (c) Mean QoL-AGHDA scores at baseline and 12-month follow-up (men). (d) Mean IGF-1 values at baseline and 12-month follow-up (men).
results, the German KIMS patients are located at immediate vicinity to Sweden, with an overall mean difference of 1.6 points after 12 months of GH replacement between KIMS patients and the SHIP respondents.

However, there are few limitations to our study, which should be considered in the interpretation of the present results. First, the sample was drawn in one region of Germany only. It is unclear whether this population is representative for the whole country due to its low population density and different socio-economic structure. On that condition, QoL-AGHDA scores of the SHIP sample should not be treated as population-based norm scores.

Secondly, our results suggest that GH replacement in adults with GHD is related to an increase in IGF-1 concentrations and an improvement in overall HRQoL. During the first 12 months of treatment, the IGF-1 levels increased and the QoL-AGHDA scores decreased to approximate population reference levels. But the results failed to show an association between QoL-AGHDA scores and IGF-1 levels in the general population sample as well as in our KIMS cohort at baseline and at 12-month follow-up respectively. Thus, our study results indicate that total serum IGF-1, measured by commercially available assays do not correlate with HRQoL assessment in patients with GHD as well as in the general population. This important finding is in line with the previous studies, which failed to demonstrate a statistical significant relationship between HRQoL assessed by QoL-AGHDA and IGF-1 concentrations in patients with GHD (22–24), with the exception of Svensson et al. and Giusti et al. (25, 26). Svensson and colleagues reported a weak correlation ($r < 0.20$) between baseline QoL-AGHDA scores and IGF-1 SDS, suggesting that patients with the most impaired HRQoL had the highest IGF-1 SDS. Giusti et al. reported a weak correlation between IGF-1 values and QoL assessment by Hamilton Depression scale ($n = 13$; $r = -0.56$; $P = 0.05$) (26). Both latter studies are limited by low numbers of investigated patients and these results cannot be reproduced in our large cohort of patients and control subjects. Moreover, studies investigating HRQoL and IGF-1 in patients with acromegaly confirmed our lack of association between IGF-1 levels and HRQoL assessment (27, 28). We conclude that the improvement of HRQoL in GHD patients seems to be a complex mechanism that cannot be simply reflected by IGF-1 values or favourable changes in body composition for example (29). We do not know the specific reasons of these findings. Non-specific effects of treatment, natural history, response shift or even physiological actions of GH may have influenced this finding and patients' subjective perception addressing HRQoL is likely to be multifactorial in origin.

In conclusion, the results described in this report reconfirm the presence of impaired HRQoL in patients with GHD, relative to general population values. In addition, our findings suggest that GH replacement therapy increases IGF-1 concentrations and improves HRQoL to near general population values, but that there is no clear association between the two.

Declaration of interest
J Moock, C Albrecht, N Friedrich, H Völkle, M Nauck, T Kohlmann, H Wallaschofski have nothing to declare. M Koltowska-Haggström is a current employee of Pfizer.

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