Influence of baseline parameters on one-year physical, mental, and health-related quality of life in patients with heart failure and preserved ejection fraction

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Abstract

**Aims** To identify baseline parameters longitudinally influencing overall health-related quality of life (HRQoL), physical function and mental health 1 year later in patients with chronic heart failure and preserved ejection fraction (HFpEF).

**Methods and results** We performed post hoc analyses of the randomized aldosterone in diastolic heart failure (Aldo-DHF) trial, including 422 patients with HFpEF and NYHA class II or III. Overall HRQoL, measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ), physical functioning and mental health, both measured by the Short Form 36 Health Survey (SF-36), after 12 months were predicted in correlation analyses and multivariate regression analyses with continuous values and worst versus three better HRQoL quartiles as dependent variables. The mean age of the study population was 66.8 ± 7.6 years, 52.4% were female, and 86.0% had NYHA class II. All HRQoL variables at 1 year were predicted by their respective baseline values (all \( P < 0.001 \)), which were also the best variables to predict lowest versus higher HRQoL quartiles (all \( P < 0.001 \)). For overall HRQoL, six-minute-walking-distance (\( P = 0.009 \)), Borg-score (\( P = 0.001 \)), coronary heart disease (\( P = 0.036 \)) and SF-36 role-emotional (\( P = 0.005 \)) independently predicted one-year-outcome, while depression diagnosis (\( P = 0.044 \)), self-reported health status (\( P = 0.023 \)) and PHQ depression (\( P = 0.001 \)) were only significant predictors when excluding MLHFQ total score at baseline. In logistic regression analyses, only SF-36 role-emotional (\( P = 0.016 \)) independently predicted overall HRQoL group status at follow up. For physical functioning, Borg-score (\( P \leq 0.001 \)), 6 min walking distance (\( P = 0.005 \)), coronary heart disease (\( P = 0.009 \)), and SF-36 vitality (\( P = 0.001 \)) were significant independent predictors, also when excluding baseline physical functioning. Low SF-36 vitality (\( P = 0.021 \)) and presence of coronary heart disease (\( P = 0.027 \)) independently predicted a patient’s membership in the lowest quartile 1 year later. For mental health, SF-36 physical functioning (\( P = 0.025 \)) and HADS anxiety (\( P = 0.046 \)) were independent predictors, while self-rated fatigue and poor performance (\( P = 0.033 \)) and SF-36 vitality (\( P = 0.008 \)) only served as significant predictors when excluding mental health at baseline. HADS anxiety (\( P = 0.009 \)) also served as independent predictor of a patient’s group status after 1 year.

**Conclusion** Overall HRQoL, physical functioning, and mental health of HFpEF patients 1 year later are mainly influenced by their respective baseline values. Other self-rated baseline parameters also showed independent effects while objective severity measures had limited predictive value.

**Keywords** Heart failure with preserved ejection fraction; Quality of life; Physical functioning; Mental health

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Introduction

Heart failure (HF) is a major health problem, as approximately 1–2% of people over 18 and even ≥10% of people >70 years in the developed countries suffer from heart failure. The increasing number of cases in the last years may be explained by the aging of the population, the rising rates of survival after myocardial infarction, and the increasing number of patients with obesity and diabetes. Approximately 50% of all HF patients have a preserved ejection fraction, meaning that their left ventricular ejection fraction (LVEF) measured by echocardiography is ≥50% with evidence of diastolic dysfunction. To diagnose HFrEF, there have to be clinical symptoms or signs of heart failure in addition, such as dyspnoea, fatigue, fluid retention, and reduced exercise capacity.

Despite its frequent occurrence, there are still few therapy options for treating HFrEF sufficiently. Even under optimal therapy, patients suffer from progressive symptoms and die prematurely. Moreover, QoL of HFrEF patients may be massively restricted and associated with psychological distress, anxiety, and depression. By identifying predictors of future QoL, one might be able to treat those and improve patient’s overall QoL early in the disease process. Several studies including patients with heart failure and reduced ejection fraction (HFrEF) or mixed collectives of HF patients found, that QoL is, amongst others, influenced by physical and psychological symptoms, age, sex, and New York Heart Association (NYHA) class. However, to date, little is known about influencing factors on overall quality of life (QoL) in patients with HFrEF.

In our analyses of the HFrEF patient sample of the aldosterone in diastolic heart failure (Aldo-DHF) trial, we studied the impact of 48 sociodemographic, medical, physical, and psychosocial baseline variables on patient’s QoL after 12 months, as we hypothesized those to be influencing parameters of QoL. To our knowledge, this is the first longitudinal study of its kind.

Methods

Trial design and patients

The study design was published in detail elsewhere. Briefly, Aldo-DHF was designed as a prospective, randomized, placebo-controlled, and double-blind trial with 422 participants. At 10 trial sites in Germany and Austria, HFrEF patients were randomly distributed into two parallel, same-sized groups, the medication group and the placebo group, to find out whether the treatment with 25 mg of spironolactone daily is beneficial. The trial complied with the Declaration of Helsinki, the Good Clinical Practice Guidelines, and national regulations. The protocol and amendments were approved by the institutional review board at each participating centre.

To participate in the trial, men and women aged 50 years or older needed to have HF with NYHA class II or III, an echocardiographic LVEF of ≥50% with evidence of diastolic dysfunction or atrial fibrillation and an exercise capacity of 25 mL/kg/min at maximum. Each patient gave written informed consent before the trial began.

Study procedure

As no impact of medication on QoL was found in the primary analyses, we did not differentiate between the medication and the placebo group for our analyses. We used the data collected using a standardized protocol at baseline and after 12 month follow-up. Predictors of interest for our analyses were patient’s medical history, results of echocardiography, and physical capacity as measured by cardiopulmonary exercise testing and 6 min walking distance (6MWD).

As additional predictors, we used sociodemographic factors (age, sex, partnership, marital status, level of education, and employment) and validated German versions of the Hospital Anxiety and Depression Scale (HADS), the ENRICHD Social Support Instrument (ESSI), and the Patient Health Questionnaire (PHQ). QoL as dependent variable was assessed by the following instruments:

- The Minnesota Living with Heart Failure Questionnaire, which was especially developed for patients with HF to measure their overall HRQoL. It contains 21 questions about the impact of HF on patient’s daily life. A total score between 0 and 105 can be achieved, with a higher score indicating poorer QoL. For our analyses, we used the MLHFQ total score as dependent variable to assess patient’s overall HRQoL.
- The Short Form 36 Health Survey, the most widely used generic questionnaire to assess patient’s HRQoL. It contains 36 items of which 34 create eight subscales together with a physical component summary score and a mental component summary score. For each subscale, a score between 0 and 100 can be reached, with a higher score indicating better HRQoL. As in previous research the subscale ‘physical functioning’ was the best to judge physical QoL and the subscale ‘mental health’ was the best to judge psychological QoL, we used those subscales as dependent variables to assess the corresponding dimension of QoL.

Statistical analysis

For statistical analysis SPSS Statistics, Version 26.0 by IBM was used. The influence of 48 baseline variables defined as
priori on the follow-up variables ‘SF-36 physical functioning’, ‘SF-36 mental health’, and ‘MLHFQ total score’ was tested. The confidence interval was set at 95% to confirm a result as statistically significant, which means \( P \leq 0.05 \). Because of the sufficiently large sample size, normal distribution of data was assumed. It must be mentioned that we had missing values for some variables as not all patients answered all questions or completed all tests at baseline and follow up. Descriptive analysis was executed at the beginning to characterize the patient sample. Afterwards, bivariate correlation analyses were performed for 28 continuous predictors, and two-sided \( t \)-tests were computed for 20 dichotomous predictors. Significant variables from those analyses were then used for multiple linear regression analysis (MRA). In parallel analyses of collinearity variables showing tolerance \( \leq 0.2 \) or variance inflation factor \( \geq 10 \) were identified as variables with high multicollinearity and excluded from the model. For each of the three follow-up variables, one model without the baseline score on the respective follow-up variable was created, while a second model included that information. Finally, logistic regression analysis (logRA) was executed to find out, whether the significant predictors found in MRA may also forecast a patient’s group membership after 12 months. Because of the wide range of the data in the lowest and the highest quartiles, we decided to create a dichotomous variable representing the lowest versus the upper three quartiles for each follow-up parameter to especially identify patients likely to core in the lowest QoL quartile at 1 year.

**Results**

**Descriptive statistics**

A total of 422 patients participated in the Aldo-DHF trial. Baseline characteristics of all 48 variables as well as characteristics of the three follow-up variables are shown in Tables 1 and 2.

**Correlation analyses**

Supporting Information, Tables S1 and S2 show the results of bivariate correlation analyses and \( t \)-tests. MLHFQ total score at follow up was predicted by 30 variables. We found 33
variables to influence physical functioning after 1 year and 25 baseline variables predicted mental health after 12 months.

**Multiple linear regression analyses**

Supporting Information, Figure S1 gives an overview of the results of MRA.

**Overall health-related quality of life**

The results of the MRA are shown in Figure 1. The total model significance for both models was *p* < 0.001. Corrected $R^2$ was 0.640 for Model 1 and 0.689 for Model 2.

In Model 1, when MLHFQ total score at baseline was not included, 6MWD, Borg-score, coronary heart disease, depression diagnosis, self-reported health status, vitality, role-emotional, and PHQ depression were significantly influencing overall HRQoL after 12 months. When including MLHFQ total score at baseline in Model 2, it became the strongest predictor of MLHFQ at follow-up. 6MWD, Borg-score, coronary heart disease, and role-emotional stayed independent significant predictors of overall HRQoL after 1 year.

In the first model of logRA, we found that 6MWD, coronary heart disease, vitality, and role-emotional significantly predicted a patient’s group belonging after 1 year. The total percentage of patients that were correctly classified was 85.6%. In the second model, when including MLHFQ total score at baseline, we found that besides the MLHFQ total score, role-emotional was a significant predictor of a patient’s group membership after 12 months. The total percentage of patients that were correctly classified was 87.5%. Both models were significant at *p* < 0.001. Nagelkerke’s $R^2$ was 0.540 for Model 1 and 0.603 for Model 2.

**Physical functioning**

The results of MRA with SF-36 physical functioning as dependent variable are shown in Table 3. Total model significance of both models was *p* < 0.001. Corrected $R^2$ was 0.544 for Model 1 and 0.622 for Model 2.

In the first model that did not consider baseline physical functioning higher Borg-score, shorter 6MWD, presence of coronary heart disease, and lower vitality were significantly related to lower physical functioning after 1 year. When including physical functioning at baseline in Model 2, baseline physical functioning emerged as strongest predictor. In addition, all significant variables of Model 1 stayed independent significant predictors of physical functioning after 12 months.

**Figure 1** Multiple linear regression analysis with MLHFQ score as dependent variable. *N* = 267 for Model 1 and 264 for Model 2. Beta-values are shown in columns; **$p$ < 0.001, *$p$ ≤ 0.05. NYHA class, self-rated fatigue, and poor performance, dyspnoea at rest, peak VO$_2$, anaerobic threshold, exercise duration at cardiopulmonary exercise testing, body mass index, physical functioning, role-physical, bodily pain, general health, social functioning, mental health, HADS depression, HADS anxiety, social support, age, and sex had no independent predictive effect. SF-36 component summary scores, MLHFQ subscale scores, and the maximum work level at cardiopulmonary exercise testing were dropped due to multicollinearity. Angina pectoris was not an independent predictor in initial analyses and was therefore excluded due to a large number of missing values.
In the first model of logRA, shorter 6MWD and lower vitality were significant forecast parameters for belonging to 25% with poorest physical functioning in the first model. The total percentage of patients that were correctly classified was 81.2%. Model 2 showed significant prediction of poor physical functioning after 12 months by lower physical functioning, lower vitality, and presence of coronary heart disease at baseline. The total percentage of patients that were correctly classified was 84.9%. Both models were significant at \( p < 0.001 \) and Nagelkerke's \( R^2 \) was 0.330 for Model 1 and 0.476 for Model 2.

In the second model, besides low baseline mental health, higher levels of anxiety predicted poor mental health 1 year later; 79.9% of patients were correctly classified. The total model significance was \( p < 0.001 \) for both models. Nagelkerke's \( R^2 \) was 0.446 for Model 1 and 0.454 for Model 2.

**Discussion**

The aim of our analyses was to identify baseline parameters which predict HRQoL in patients with HFpEF 1 year later. To our knowledge, it is the first study to examine the influence of a large number of both, psychological and somatic variables on physical, psychological and overall HRQoL in patients with HFpEF. Most of the comparable studies included only HFrEF patients or mixed samples of HFrEF and HFpEF patients. In our bivariate analyses, we found numerous factors longitudinally predicting all three dimensions of patient HRQoL. To identify the variables with the strongest independent influence and for predicting low HRQoL after 1 year, we conducted multivariate linear and logistic regression analyses.

In bivariate analyses, the overall HRQoL at 1 year was predicted by all three dimensions of HRQoL with lowest influence of social factors, which is underlined by the result, that baseline MLHFQ total score as representative of physical

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**Table 3** Multiple linear regression analysis with SF-36 physical functioning as dependent variable

| t0-variable                | Model 1                      | Model 2                      |
|---------------------------|------------------------------|------------------------------|
|                           | Regression coefficient B     | Beta                         | Regression coefficient B | Beta                         | p-value          | Regression coefficient B | Beta                         | p-value          |
| Borg-score                | -2.699                       | -0.186                       | **<0.001**                  | -2.522                       | -0.174                       | **<0.001**                  |
| 6MWD                      | 0.065                        | -0.232                       | **<0.001**                  | 0.043                        | 0.154                        | 0.005                      |
| Coronary heart disease    | -6.691                       | -0.144                       | 0.004                       | -5.641                       | -0.122                       | 0.009                      |
| SF-36: Physical functioning| -                            | -                            | -                           | 0.482                        | 0.464                        | **<0.001**                  |
| SF-36: Vitality           | 0.390                        | 0.327                        | **<0.001**                  | 0.316                        | 0.264                        | 0.001                      |

\( N = 250 \) for Model 1 and 249 for Model 2. NYHA-class, self-rated fatigue and poor performance, dyspnoea at rest, exercise duration at cardiopulmonary exercise testing, peak VO2, anaerobic threshold, body mass index, depression diagnosis, LVEF, higher education level, self-reported health status, role-physical, bodily pain, general health, social functioning, role-emotional, mental health, MLHFQ total score, HADS depression, HADS anxiety, PHQ depression, sex, and age did not show influence on physical functioning after 1 year. SF-36 component summary scores, MLHFQ subscale scores and max. work level at cardiopulmonary exercise testing were dropped due to multicollinearity.

**Table 4** Multiple linear regression analysis with SF-36 mental health as dependent variable

| t0-variable                | Model 1                      | Model 2                      |
|---------------------------|------------------------------|------------------------------|
|                           | Regression coefficient B     | Beta                         | Regression coefficient B | Beta                         | p-value          | Regression coefficient B | Beta                         | p-value          |
| Fatigue and poor performance| 3.996                       | 0.109                        | 0.033                       | 3.361                        | 0.092                        | 0.067                      |
| SF-36: Physical functioning| -0.123                       | -0.149                       | 0.039                       | -0.131                       | -0.159                       | 0.025                      |
| SF-36: Vitality           | 0.208                        | 0.221                        | 0.008                       | 0.150                        | 0.158                        | 0.054                      |
| SF-36: Mental health      | -1.343                       | -0.281                       | **<0.001**                  | -0.747                       | -0.156                       | 0.046                      |
| HADS anxiety              | -1.732                       | -0.281                       | **<0.001**                  | -0.747                       | -0.156                       | 0.046                      |

\( N = 258 \) for Model 1 and 257 for Model 2. NYHA class, dyspnoea at rest, Borg-score, 6MWD, depression diagnosis, self-reported health status, role-physical, bodily pain, general health, social functioning, role-emotional, mental health, MLHFQ total score, sex, and age had no independent predictive effect. SF-36 component summary scores and MLHFQ subscale scores were dropped due to multicollinearity. Angina pectoris was not an independent predictor in initial analyses and was therefore excluded due to a large number of missing values.
and psychological QoL was the strongest predictor of overall HRQoL after 12 months. Hwang et al. also found that both, physical and psychological experiences, influence HF patient’s QoL, and Heo et al. described that in HFrEF patients, physical and emotional symptoms equally influence global HRQoL.

In contrast to former studies on HF patients, we found no impact of gender on overall HRQoL. While other authors described gender predicting overall HRQoL in HF patients, we found no impact of gender on MLHFQ total score, which is consistent with the finding of another study with HfPEF patients. Another sociodemographic predictor of overall HRQoL was social support. Similar results were found by others in HFrEF or mixed samples of HF patients. While other authors described literacy or socio-economic status to predict HF patient’s overall HRQoL, we found no predictive effect of education level or employment in patients with HfPEF, just like Nesbitt et al. in HF patients.

All baseline parameters representing psychological QoL were significant predictors of overall HRQoL. Higher anxiety and depression scores and depression diagnoses predicted a higher MLHFQ total score at follow-up. This result is consistent with former HF patient studies. Furthermore, the mental component summary score of SF-36 and all its defining subscales as well as the emotional dimension of MLHFQ showed significant predictive effects on MLHFQ total score at 1 year.

Some of the somatic baseline parameters were also strong predictors of the overall HRQoL after 12 months. A higher body mass index led to higher MLHFQ total scores, indicating lower overall HRQoL. The influence of a HF patient’s body mass index on overall HRQoL has been described before, even for HfPEF patients. Like many other authors, we confirmed that a patient’s NYHA class is a predictor of overall HRQoL. Also in agreement with the literature, we found no correlation between LVEF and overall HRQoL in patients with HfPEF. In contrast, symptoms of HF, self-rated fatigue and poor performance and dyspnoea at rest were significant predictors of overall HRQoL. Consistently, dyspnoea at rest was observed to cause lower HRQoL in patients with HfPEF, and Volz et al. found vital exhaustion to influence both MLHFQ subscales in a mixed sample of HF patients. Furthermore, lower self-reported health status at baseline resulted in lower overall HRQoL at follow-up. While in HfREF or mixed samples of HF patients no predictive effect of co-morbidities was found, our analyses identified Angina pectoris and coronary heart disease as predictors of overall HRQoL. Angina pectoris was also identified as HRQoL predicting factor for HF patients by Lewis et al.

As the influence of physical performance on HF patient’s overall HRQoL has been described before by others, we expected also an impact for HfPEF patients. Exercise duration, maximum work level, and anaerobic threshold at cardiopulmonary exercise testing as well as the Borg-score served as significant predictors of overall HRQoL. Lower peak VO₂ and shorter 6MWD were significantly related to lower overall HRQoL after 1 year, which is consistent with the result of Reddy et al. who also studied a HfPEF population. Furthermore, the physical component summary score of SF-36 and all its defining subscales as well as the physical dimension of MLHFQ showed significant predictive effect on MLHFQ total score.

In multivariate analyses, physical and psychological baseline parameters contributed to predict overall HRQoL. In the fully adjusted model, the MLHFQ total score at baseline remained the strongest predictor of overall HRQoL at 1 year. Besides, 6MWD, Borg-score, coronary heart disease, and role-emotional were significant independent predictors.

For predicting the overall HRQoL in the lowest quartile, 6MWD, coronary heart disease, vitality, and role-emotional were significant predictors, while only role-emotional was an independent contributor besides the MLHFQ total score at baseline.

Also, physical functioning and mental health as two core elements of HRQoL were predicted by numerous physical and psychological baseline variables in our bivariate analyses, while sociodemographic and interpersonal variables were of subordinate relevance.

In multivariate analyses, the only independent somatic predictors of physical function were Borg-score, 6MWD, and a diagnosis of coronary heart disease. For patients with HfREF, the influence of 6MWD on physical functioning was described before. Regarding the impact of co-morbidities, Gott et al. found that HF patients having ≥2 co-morbidities have worse physical functioning, and Müller-Tasch et al. reported that multi-morbidity has impact on HfREF patient’s physical functioning. Besides, the Borg-score the vitality subscale of the SF-36 as another self-rating item was an independent predictor of physical functioning in both adjusted models, which shows that patients’ subjective perception is a reliable predictor of future limitations and should be taken seriously. None of the social variables contributed independently to the multivariate models.

For predicting physical functioning in the lowest quartile at 1 year, baseline physical function, vitality, and presence of coronary heart disease were independent predictors in the fully adjusted model.

In the multivariate analyses with mental health at 1 year as dependent variable, this aspect of HRQoL was predicted by several self-rated physical and psychological scales. In the first model excluding baseline mental health, self-rated fatigue and poor performance, physical functioning, vitality, and anxiety were significant predictors. Physical functioning and anxiety remained significant predictors in the fully adjusted model besides baseline mental health as the strongest predictor.

Vitality and anxiety also served as parameters to predict mental health in the lowest quartile in the first model of
logRA, while only anxiety and mental health at baseline were independent predictors of patient’s mental health group belonging 1 year later.

**Strengths and limitations**

One strength of our study is the relatively large sample size and the comprehensive characterization of this clearly defined sample of patients with HFpEF who were prospectively followed over 1 year. Generalization of our findings is limited by the fact that only German and Austrian patients with NYHA class II and III were included and that co-morbid atrial fibrillation was underrepresented. As another limitation it must be considered that most of our variables did not show normal Gaussian distributions, but given the size of the study population, it can be assumed that the results are not substantially affected by non-normal distribution. Due to loss of patients until follow up, we had dropout rates around 20%, which is in a normal range. As only patients with data for each independent and respective dependent variable were included in the regression analyses, we lost additional valid data. When including Angina pectoris, the dropout rate rose to more than 40%. We recalculated the multiple linear regression analyses models without Angina pectoris, which was by the way no significant independent predictor anyway, to keep the dropout rates within 20%. We found slightly different variables to be significant predictors, but the overall pattern of results was similar. Additionally, many of our results are based on patients’ self-ratings, which are subjective and may underlie some information bias. However, QoL is an inherently subjective construct as it reflects the individual patient’s perception and cannot better be measured by objective parameters. Because QoL is an accepted and patient-relevant endpoint of treatment, the subjective nature of the assessment is rather a necessary consequence. Interestingly, patients’ initial self-ratings, weak as they may be, appeared to be better predictors of QoL 1 year later than any of the ‘hard’ medical predictors.

**Conclusion**

In our sample of patients with HFpEF, we found a number of psychological and somatic baseline parameters that significantly predicted the dimensions of physical, psychological, and overall HRQoL after 1 year. In general, each dimension was best predicted by its baseline value, which already allows a reasonable estimate for future QoL on its particular dimension. In addition, mainly other self-rated baseline variables predicted HRQoL at 1 year, while objective medical findings had little independent effect. These findings demonstrate that patients’ self-reports are reliable prospective predictors of QoL. They can also be used to identify patients at risk of particularly poor HRQoL 1 year later who might benefit most from optimal medical treatment and psychological support. Early identification of low QoL levels and treatment of its causes may then result in ameliorated QoL of HFpEF patients in the course of the disease. Our results should encourage clinicians to take patients’ self-reports seriously when discussing treatment options and researchers to develop patient-centred interventions to improve the QoL of patients with HFpEF.

To our knowledge, this is the first study reporting an impact of physical, psychological, and socio-economic baseline parameters on physical, mental, and overall health-related QoL in the course of time. This finding should result in expanding specific treatment options known to improve QoL domains where it is compromised. Such treatments may include, besides optimal medication and device therapy, exercise training as well as psychological and socio-economic interventions. However, the effect of such interventions on the three core dimensions of QoL is not well investigated to date. This topic should be studied in future trials with HFpEF patients.

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**Conflict of interest**

All authors have completed the ICMJE Form for disclosure of potential conflicts of interest. Mrs. Fitz, Dr. Edelmann, Dr. Sandek, Dr. Nolte, Mr. Hashemi, and Dr. Trippel have nothing to disclose. Dr. Hasenfuß reports personal fees from AstraZeneca, personal fees from Bayer, personal fees from Berlin Chemie, personal fees from Boehringer, personal fees from Corvia, personal fees from Impulse Dynamics, personal fees from Novartis, personal fees from Servier, personal fees from Springer and personal fees from Vifor Pharma, outside the submitted work. Dr. Wachter reports personal fees from...
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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline-variables with significant impact on follow-up HRQoL dimensions in bivariate correlation analyses.

Table S2. Baseline-variables with significant impact on follow-up HRQoL dimensions in t-tests.

Figure S1. Supporting Information.

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