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Health-Related Quality of Life Trajectories during Predialysis Care and Associated Illness

Perceptions

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Abstract

Objective: To identify health-related quality of life (HRQOL) trajectories during 18 months of predialysis care and associated patient characteristics and illness perceptions. **Methods:** 396 incident predialysis patients participating in the prospective PREPARE-2 study completed every six months the SF-36 (i.e. mental and physical HRQOL) and Revised Illness Perception Questionnaire. HRQOL trajectories were examined using latent class growth models, and associated baseline factors were identified using logistic regression. Analyses for illness perceptions were adjusted for demographic and clinical characteristics. **Results:** Three physical HRQOL trajectories (low-stable [34.1% of the sample], medium-declining [32.5%], and high-increasing [33.4%]) and two mental HRQOL trajectories (low-stable [38.7%] and high-stable [61.3%]) were identified. Increased odds for a low-stable physical HRQOL trajectory were detected in older patients (OR=1.04), patients with cardiovascular disease (OR=2.1) and patients who believed to a lesser extent they can personally control their disease (OR_{adj}=0.88). Increased odds for both a low-stable physical and mental HRQOL trajectory were detected in patients who believed to a higher extent that their disease is cyclical, has negative consequences, causes negative feelings, and in patients who believed to a lesser extent they understand their disease (OR_{adj} ranged between 0.84 and 1.36). Additionally, patients who attributed more symptoms to their disease had increased odds for a medium-declining (OR_{adj}=1.21) and low-stable physical HRQOL trajectory (OR_{adj}=1.50). **Conclusions:** Older age and cardiovascular disease are markers for unfavorable physical HRQOL trajectories, and stronger negative illness perceptions are markers for unfavorable physical and mental HRQOL trajectories. Targeting negative illness perceptions could possibly optimize HRQOL during predialysis care.

Keywords: Chronic kidney disease (CKD); Health-related quality of life (HRQOL); Trajectories; Illness perceptions; Latent class growth model; Predialysis care.

Health-Related Quality of Life Trajectories during Predialysis Care and Associated Illness Perceptions

Individuals with chronic kidney disease (CKD) suffer from a gradual and irreversible loss of kidney function. For the majority of patients, this deterioration in kidney function is accompanied by an increase in symptoms, lifestyle restrictions, and dependency on complex treatment regimens. Consequently, this disease imposes a heavy burden on people's lives, and has a disruptive impact on their health, ability to work, emotional well-being, and social participation (Tong et al., 2009).

An important indication of how a disease affects the physical, psychological, and social aspects of patients' lives, is their rating of health-related quality of life (HRQOL). In patients with end-stage renal disease (ESRD), HRQOL is severely impaired (Lim, Yu, Kang, Foo, & Griva, 2016). However, a compromised HRQOL is also evidenced in patients with moderately reduced kidney function and in patients receiving predialysis care (i.e. CKD stages 3-5) (Chin et al., 2008; de Goeij et al., 2014; Kusek et al., 2002), and lower levels of HRQOL in these earlier stages of CKD have been associated with accelerated progression towards ESRD and mortality (de Goeij et al., 2014; Tsai et al., 2010). Therefore, predialysis care not only aims to maximize disease control, but optimizing HRQOL is considered an important treatment goal as well (Sijpkens, Berkhout-Byrne, & Rabelink, 2008).

Unfortunately, literature regarding HRQOL in patients receiving predialysis care is dominated by cross-sectional studies, and the longitudinal studies that have been conducted found contradictory results regarding the course of HRQOL; some studies found that mean levels of both physical and mental HRQOL decreased over time (de Goeij et al., 2014; Fukuhara et al., 2007; Mujais et al., 2009), other studies only found changes in one specific physical or mental HRQOL domain (e.g. increased mental health [Da Silva-Gane et al., 2012], increased social functioning [Hansen, Chin, Blalock, & Joy, 2009] and decreased physical function (Revicki et al., 1995)),

and there are also studies that found no change in physical or mental HRQOL over time [Di Micco et al., 2009; Gorodetskaya et al., 2005]. These contradictory results might be due to differences in study design or patient characteristics, but it is also possible that examining mean levels of HRQOL over time masks individual variation in the course of HRQOL. Individuals may differ to a large extent in how their HRQOL develops over time, and the identification of distinct HRQOL trajectories and associated factors could enable personalized treatment approaches in predialysis care. However, to the best of our knowledge, no studies have been conducted that identify HRQOL trajectories during predialysis care using optimal statistical methods such as latent class growth modelling (Nagin & Odgers, 2010) and identified factors associated with these trajectories.

Evidently, previous studies do not provide evidence about factors associated with distinct HRQOL trajectories during predialysis care, but they do point out potentially important factors, including age, gender, kidney function, comorbidities, body mass index (BMI), and levels of albumin and hemoglobin (Chin et al., 2008; Gorodetskaya et al., 2005; Hansen et al., 2009; Kusek et al., 2002; Mujais et al., 2009; Porter et al., 2012). Additionally, literature suggests that patients' cognitive appraisal of illness might play a key role in understanding HRQOL: according to the Common Sense Model of self-regulation (Leventhal, Meyer, & Nerenz, 1980; Leventhal, Nerenz, & Steele, 1984), illness perceptions affect how patients respond to and cope with a health threat, and subsequently contribute to health outcomes. Indeed, studies in patients with CKD show that stronger negative perceptions of illness are associated with various health outcomes, including depressive symptoms (Chilcot et al., 2013), faster disease progression (Meuleman et al., 2015), mortality (Chilcot, Wellsted, & Farrington, 2011; van Dijk et al., 2009) and impaired HRQOL (Covic, Seica, Gusbeth-Tatomir, Gavrilovici, & Goldsmith, 2004; Covic, Seica, Mardare, & Gusbeth-Tatomis, 2006; Fowler & Baas, 2006; Griva, Jayasena, Davenport, Harrison, & Newman, 2009; Timmers et al., 2008). However, until now, the relationship between illness perceptions and HRQOL has only been investi-

gated in patients with ESRD and information about the longitudinal association is scarce. Examining associations between illness perceptions and HRQOL trajectories during predialysis care could allow the identification of unhelpful illness perceptions and create opportunities to improve HRQOL in earlier stages of CKD.

Therefore, the aim of this study was to examine whether distinct physical and mental HRQOL trajectories during predialysis care could be detected, and to examine if these trajectories are associated with illness perceptions (eight domains: illness identity, timeline acute/chronic, timeline cyclical, negative consequences, personal control, treatment control, illness coherence, and emotional response), demographic (age and gender) and clinical (BMI, comorbidities, kidney function, time since CKD diagnosis, and levels of albumin and hemoglobin) characteristics. It was hypothesized that distinct HRQOL trajectories would be observed and that the factors would differ across the identified trajectories. Due to lacking or inconsistent evidence, no directional a priori hypotheses were formulated.

Method

Study Design

The PREDialysis PATient REcord-2 (PREPARE-2) study is a prospective follow-up study in 25 specialized nephrology outpatient clinics in the Netherlands. Between July 2004 and June 2011, patients were included at the moment of referral to one of the participating clinics, where they received regular treatment by a multidisciplinary team (consisting of a nephrologist, a nurse practitioner, a dietician, and a social worker) according to the Dutch Federation of Nephrology treatment guidelines (Multidisciplinary guidelines predialysis, 2011; based on Kidney Disease Outcomes Quality Initiative [K/DOQI, 2002] and Kidney Disease Improving Global Outcomes [KDIGO, 2012] guidelines). Patients were followed until initiation of dialysis, kidney transplantation, a recovered kidney function, transferal to non-participating centers, refusal of further participation, death, lost during follow-up, or the end of follow-up (13 May 2015). Approval by

the Medical Ethics Committee or Institutional Review Board of all participating centers was obtained.¹

Patients

Incident predialysis patients (i.e. within the previous six months referred to a specialized predialysis outpatient clinic) with progressive renal failure and an estimated glomerular filtration rate (eGFR) of less than 30 ml/min/1.73m² (i.e. CKD stages 4–5), were eligible for inclusion, if they were at least 18 years of age. Patients with a kidney transplant dysfunction were also included, if patients received a donor kidney transplant at least one year ago. Prior to study inclusion, written informed consent was obtained from all participants.

Data, Definitions, and Measurements

Demographic and clinical data were collected during routine visits at the clinics: at the start of predialysis care, at every subsequent 6-month interval, and at the end of follow-up. All clinical measurements were collected according to the standard care of each clinic, and laboratory measurement were periodically extracted from medical records and electronic hospital information systems. As indicator for kidney function, eGFR was calculated by using the abbreviated Modification of Diet in Renal Disease formula (Levey, Greene, Kusek, & Beck, 2000). Based on information from medical records, comorbidities were classified as follows: diabetes mellitus (DM; type 1 or type 2), and cardiovascular disease (CVD; myocardial infarction, coronary disease, and/or angina pectoris).

¹ Participating centers: Academic Medical Center (Amsterdam), Sint Lucas-Andreas Hospital (Amsterdam), VU Medical Center (Amsterdam), Gelre Hospitals (Apeldoorn), Amphia Hospital (Breda), Reinier de Graaf (Delft), Jeroen Bosch Hospital (Den Bosch), Medical Center Haaglanden (The Hague), Hospital Gelderse Vallei (Ede), Catharina Hospital (Eindhoven), Scheper Hospital (Emmen), Dialysis Clinic North (Beilen), Admiraal de Ruyter Hospital (Goes), Groene Hart Hospital (Gouda), University Medical Center Groningen (Groningen), Kennemer Gasthuis (Haarlem), Medical Center Leeuwarden (Leeuwarden), Leiden University Medical Center (Leiden), Rijnland Hospital (Leiderdorp), Laurentius Hospital (Roermond), Franciscus Hospital (Roosendaal), Franciscus Gasthuis (Rotterdam), Máxima Medical Center (Veldhoven), Zaans Medical Center (Zaandam), Isala Clinics (Zwolle).

Patients were also asked to fill out a questionnaire at home, and return the questionnaire as soon as possible. The questionnaire included the 36-item Short Form Health Survey Questionnaire (SF-36) to assess HRQOL (Ware & Sherbourne, 1992). The SF-36 items were divided into two summary scores: a physical composite score (consisting of four subscales: physical functioning, physical role functioning, bodily pain and general health), and a mental composite score (consisting of four subscales: vitality, social role functioning, emotional role functioning, and mental health). Scores were transformed to a 0–100 score, with higher scores indicating better HRQOL. The SF-36 showed good reliability with Cronbach alpha values of 0.90 and 0.81 for the physical composite score and mental composite score respectively. The questionnaire also contained the Revised Illness Perception Questionnaire to assess illness perceptions (Moss-Morris et al., 2002). Seven domains were derived from 38 items scored on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree): timeline acute/chronic, timeline cyclical, negative consequences, personal control, treatment control, illness coherence, and emotional response. The eighth domain ‘illness identity’ was assessed using a sum-score of 14 items in a yes or no format. Like other studies (e.g. Kim & Evangelista, 2010), illness perception cause was excluded from the analysis due to heterogeneous causes of CKD. Higher scores on domains reflect that patients attribute more physical symptoms to their kidney disease (i.e. illness identity), and that patients believe to a higher extent their kidney disease is chronic and cyclical in nature, has negative consequences upon their life, causes emotional distress, can be effectively controlled by themselves or their treatment, and that they understand their kidney disease (i.e. illness coherence). All domains showed moderate to good reliability with Cronbach alpha values ranging from 0.63 to 0.90 (see Meuleman et al., 2015).

Statistical Analysis

To describe patients’ baseline characteristics, descriptive statistics were computed. Continuous variables are presented as mean (standard deviation [SD]) for normally distributed varia-

bles and as median (interquartile range [IQR]) for skewed variables. Chi-square tests of association and t-tests were conducted to investigate if patients who were included in and excluded from analysis differ with regard to baseline characteristics.

To identify distinct groups of patients that share similar HRQOL trajectories during predialysis care, latent class growth models (LCGM) were used. LCGM is a model based cluster analysis approach in order to determine whether longitudinal changes in an outcome may be best described by a single or multiple distinct trajectories (i.e. classes; see also Nagin & Odgers, 2010). Four time points were included in the analysis (i.e. baseline, and follow-up measurements at 6, 12 and 18 months) to ensure the availability of sufficient HRQOL measurements and fit the models adequately (i.e. LCGM needs at least three time point to fit the models). As suggested by literature (Jung & Wickrama, 2008; Nylund, Asparouhov, & Muthén, 2007), we determined the optimal number of latent trajectory classes by using a combination of several standard fit indices: substantial number of participants in each class (at least 5% of the sample), Bayesian Information Criterion (i.e. lower values indicate a better fit), entropy summary measures (i.e. entropy values range from zero to one, with values closer to one indicating a better quality of the classification), and Vuong-Lo-Mendell-Rubin likelihood test for K-1 vs. K classes (i.e. a p-value less than 0.05 indicates that the current model has a better fit than the model with 1 class less). Linear and non-linear models were evaluated, but in all cases, linear models provided a better fit to the data. To assess the adequacy of the final models, the average posterior probabilities were calculated (i.e. a value of at least 0.70 suggests a good probability that participants belong to the assigned class – there is homogeneity within the class). Labels were assigned to each identified class according to the corresponding class characteristics: the intercept (i.e. the baseline score, for instance: low, medium or high), and the magnitude and direction of the slope (i.e. a statistically significant positive or negative change over time, or the absence of a statistically significant change over time [i.e. a stable trajectory]) (see results). A series of univariate logistic regression analyses were ran to investigate the association between the separate baseline factors (age, gender,

eGFR, BMI, DM, CVD, time since CKD diagnosis, serum albumin, hemoglobin, and illness perceptions) and HRQOL class membership (for details see Jung & Wickrama, 2008). Analyses for illness perceptions were repeated using multinomial logistic regression analysis to adjust for age, eGFR, DM and CVD. For both physical and mental HRQOL models, the reference category was the class representing the highest level of HRQOL (see results), and effects are expressed as odds ratios (ORs) with 95% confidence intervals (CI).

Descriptive statistics, Chi-square tests of association and t-tests were conducted using SPSS version 24.0. LCGM and logistic regression analyses were ran in Mplus version 7.3, and all models used full-information maximum likelihood estimation to addressing missing data (i.e. using all available data under the assumption that data are missing at random) to ensure maximum power and avoided bias estimates (Jung & Wickrama, 2008; Muthén & Muthén, 2015). P-values of <0.05 were considered statistically significant.

Results

Of the 502 included patients, 396 patients (78.9%) completed the baseline SF-36 questionnaire (the physical component was completed by 384 patients and the mental component by 394 patients) and were included in the analysis. No significant differences in baseline characteristics (i.e. illness perceptions, demographic and clinical factors; see Table 1) were observed between patients who were included in and excluded from the analysis, with the exception that excluded patients attributed less physical symptoms to their kidney disease (illness identity; $t = -5.0, p < 0.01$). In the included sample, the mean age (SD) was 64.4 (14.0) years and the mean (SD) scores for physical and mental HRQOL were 54.6 (22.2) and 67.9 (20.4) respectively. All baseline characteristics are shown in Table 1.

During the first 18 months of predialysis care, 20 patients (5.1%) died, 6 patients (1.5%) experienced a recovered kidney function, 21 patients (5.3%) received a kidney transplant, 6 patients (1.5%) were transferred to a non-participating center, 23 patients (5.8%) refused further

participation, and 1 patient (0.3%) was censored for other reasons. Dialysis was initiated in 145 patients (36.6%; 84 patients [57.9%] started on hemodialysis, and 61 patients [42.1%] on peritoneal dialysis), and 174 patients (43.9%) still received predialysis care. The median [IQR] follow-up time in this sample was 16.1 [7.2-32.0] months).

Distinct Physical HRQOL Trajectory Classes

A 3-class solution was found to fit the data adequately (Table 2). The three identified classes of physical HRQOL are summarized in Table 3, and Figure 1a depicts the physical HRQOL trajectories. The first class termed “low-stable” contained 34.1% of the patients, and was characterized by low levels of physical HRQOL that remained stable over time. The second class (32.5% of the sample), termed “medium-declining”, was defined by a moderate level of physical HRQOL, which significantly worsened with time. The final class (33.4% of the patients) was a “high-increasing” class, and was characterized by a high level of physical HRQOL, which significantly increased over time.

Distinct Mental HRQOL Trajectory Classes

A two-class solution was deemed adequate for mental HRQOL (Table 2). The two mental HRQOL classes are shown in Table 3, and Figure 1b depicts the mental HRQOL trajectories. The first class termed “low-stable” contained 38.7% of the patients, and was characterized by low levels of mental HRQOL that remained stable over time. The second class, termed “high-stable” (61.3% of the sample), was defined by high levels of mental HRQOL that remained stable over time.

Factors Associated with Physical HRQOL Class Membership

Of the demographic and clinical factors (age, gender, eGFR, BMI, DM, CVD, time since CKD diagnosis, serum albumin and hemoglobin) only age and CVD were significantly associated

with physical HRQOL class membership: compared to the high-increasing physical HRQOL class (class 3), a one-year increase in age was associated with a 4% increase in the odds of being in the low-stable physical HRQOL class (class 1; OR=1.04, $p<0.01$), and the presence of CVD was associated with a 2.1 times increase in the odds of being in the low-stable physical HRQOL class (class 1; OR=2.1, $p<0.01$). Six out of the eight illness perception domains were also significantly associated with physical HRQOL class membership while adjusting for age, eGFR and comorbidity (see Table 4 for the crude and adjusted odd ratio's). Increased odds for a low-stable physical HRQOL class (class 1) were detected in patients who believed to a lesser extent that they can personally control their kidney disease and that they completely understand their condition, compared to the high-increasing physical HRQOL class (class 3). Put another way, a single point increase in personal control (higher control) reduced the odds of being in the low-stable class by 12% (OR_{adj}=0.88, $p<0.01$) and a single point increase in coherence (higher coherence) was associated with a 15% reduction in the odds of being in the low-stable class (OR_{adj}=0.85, $p<0.01$). Furthermore, compared to the high-increasing physical HRQOL class (class 3), a one-point increase in illness identity, cyclical timeline, negative consequences and emotional response increased the odds of being in the low-stable physical HRQOL class (class 1) by 50%, 36%, 14% and 7% respectively. Similarly, compared to the high-increasing physical HRQOL class (class 3), a one-point increase in illness identity was associated with a 21% increase in the odds of being in the medium-declining physical HRQOL class (class 2). Only trends were found for the odds of being in the medium-declining physical HRQOL class (class 2) with regard to the illness perceptions cyclical timeline (OR=1.13, $p=0.06$) and negative consequences (OR=1.14, $p=0.05$) compared to the high-increasing physical HRQOL class (class 3).

Factors Associated with Mental HRQOL Class Membership

None of the demographic or clinical factors (age, gender, eGFR, BMI, DM, CVD, time since CKD diagnosis, levels of serum albumin and hemoglobin) were significantly associated

with mental HRQOL class membership. Four out of the eight illness perception domains were significantly associated with mental HRQOL class membership while adjusting for age, eGFR and comorbidity (see Table 5 for the crude and adjusted odd ratio's). Compared to the high-stable mental HRQOL class (class 2), a one-point increase in cyclical timeline, negative consequences and emotional response increased the odds of being in the low-stable mental HRQOL class (class 1) by 22%, 14% and 7% respectively. Furthermore, increased odds for a low-stable mental HRQOL trajectory (class 1) were detected in patients who believed to a lesser extent that they completely understand their kidney disease compared to the high-stable mental HRQOL class (class 2). Put another way, a single point increase in coherence (higher coherence) was associated with a 16% reduction in the odds of being in the low-stable class ($OR_{adj} = 0.84, p < 0.01$).

Discussion

To the best of our knowledge this study is the first to examine distinct trajectories of HRQOL in patients receiving predialysis care using LCGM and to investigate which patient characteristics and illness perceptions at the start of predialysis care are associated with these specific HRQOL trajectories during predialysis care.

This study shows that distinct HRQOL trajectories can be detected during the first 18 months of predialysis care. Patients indeed differ to a large extent in their evaluation of HRQOL over time, and hence, underlines the importance of investigating heterogeneity of HRQOL in this population. Three physical HRQOL trajectories were observed, all containing approximately one-third of our sample: a trajectory in which patients report stable levels of low physical HRQOL, a trajectory in which patients report moderate levels of physical HRQOL that worsened over time, and a trajectory in which patients report high levels of physical HRQOL that improved with time. Additionally, two mental HRQOL trajectories were identified: one trajectory containing approximately 60% of our sample in which patients reported stable high levels of mental HRQOL, and a second trajectory in which patients reported stable low levels of mental HRQOL.

These results highlight that a large proportion of our sample has an unfavorable (i.e. stable low or declining) HRQOL trajectory during the first 18 months of predialysis care, which puts them at risk for adverse outcomes such as accelerated progression toward ESRD and mortality (de Goeij et al., 2014; Tsai et al., 2010). Furthermore, the findings that HRQOL remained rather stable in a large proportion of our sample could, to a certain extent, be considered remarkable as the predialysis phase is often considered a dynamic period. The predialysis phase is characterized by an accelerated disease progression, an intensified treatment to treat health complications and prepare patients for renal replacement therapy (i.e. dialysis or transplantation), an increase in overt physical symptoms and drug-related side effects, and many patients perceive this phase as a stressful period during which they experience feelings as helplessness and hopelessness (de Goeij et al., 2014; Ekelund & Andersson, 2007; Iles-Smith, 2005; Sijpkens et al., 2008; Tong et al., 2009). Therefore, one might expect that most patients report decreasing levels of physical and mental HRQOL during predialysis care and this expectation is also in line with previous studies that found decreased mean levels of HRQOL during predialysis care (de Goeij et al., 2014). However, we did not find decreasing levels of physical and mental HRQOL in the majority of our sample and, although speculative, a possible explanation for our findings could be found in the phenomenon ‘response shift’. Response shift refers to a change in individuals’ meaning of HRQOL over time due to changes in their internal standard (e.g. a change in idea what poor health is), values (e.g. reprioritization the importance of certain life domains) and/or reconceptualization of the concept HRQOL (Sprangers & Schwartz, 1999). These cognitive changes reflect patients’ adaptation to new situations, and could perhaps explain why patients’ evaluation of HRQOL did not decline but remained rather stable in a large proportion of our sample despite declining health. Finally, this stability in HRQOL seems particularly applicable to mental HRQOL: mental HRQOL remained rather stable in all patients while physical HRQOL remained stable in only one-third of our sample. A possible explanation for this difference could be that

predialysis care is relatively more focused on the treatment of physical aspects compared to the mental aspects of the disease (Multidisciplinary guidelines predialysis, 2011).

Antecedent factors associated with different HRQOL trajectories were also examined in this study. The results showed that none of the demographic or clinical factors were associated with mental HRQOL class membership, however, age and CVD were associated with physical HRQOL class membership: increased odds for a low-stable physical HRQOL trajectory were detected in older patients and patients diagnosis with CVD. In addition, six out of the eight illness perceptions were associated with HRQOL class membership; increased odds for both a low-stable physical and mental HRQOL trajectory were detected in patients who believed to a higher extent that their kidney disease has an unpredictable cyclical nature, has negative consequences upon their lives, causes emotional distress, and in patients who believed to a lesser extent that they fully understand their kidney disease. Additionally, increased odds for a low-stable physical HRQOL were detected in patients who believed to a lesser extent that they can personally control their disease, and increased odds of a low-stable and medium-declining physical HRQOL trajectory was detected in patients who attributed more physical symptoms to their kidney disease. These findings are in line with and builds on previous studies that found lower mean levels of HRQOL in patients with CKD associated with an older age (Chin et al., 2008), CVD (Chin et al., 2008; Mujais et al., 2009) and stronger negative perceptions of illness, including illness identity, cyclical timeline, negative consequences, personal control, illness coherence and emotional response (Covic et al., 2004, 2006; Fowler & Baas, 2006; Griva et al., 2009; Timmers et al., 2008).

An explanation for the relationship between illness perceptions and HRQOL found in this study can be derived from the Common Sense Model of self-regulation (Leventhal et al., 1980, 1984). This theoretical framework suggests that patients' perceptions of illness shape their cognitive and behavioral adjustment to managing their illness (i.e. coping process and illness related behaviors) and consequently contribute to health outcomes. For our results,

this could mean that patients with stronger negative illness perceptions deal with their kidney disease in more maladaptive ways (e.g. denial, non-adherence to treatment guidelines, and not seeking support), and consequently result in impaired or deteriorating HRQOL. Until now, the evidence for this explanation in patients with CKD is contradictory and limited to only a few cross-sectional studies; Knowles, et al. (2014) found (mal)adaptive coping to mediate the relationship between illness perceptions and psychological well-being, whereas Kim & Evangelista (2010) did not find adherence to treatment guidelines to mediate the relationship between illness perceptions and clinical outcomes. Moreover, a recent meta-analysis also concluded that evidence for coping as a potential mediator in the relationship between illness perceptions and psychological health in people with other conditions was inconsistent (Dempster, Howell, & McCorry, 2015). Therefore, additional research is needed to further explore this potentially mediating role of coping and health behaviors in the relationship between illness perceptions and HRQOL trajectories during predialysis care.

Taken together, the results of this study suggest that in many patients physical and mental HRQOL remained compromised or became impaired during the first 18 months of predialysis care. Hence, implementing additional strategies at the start of predialysis care to support patients at risk for impaired HRQOL is required. Our results also suggest that illness perceptions are, compared to the demographic and clinical factors, most closely related to HRQOL trajectories. This latter finding is especially important because literature shows that unhelpful illness perceptions can be changed by means of psychoeducational interventions, and consequently improve outcomes (Karamanidou, Weinman, & Horne, 2008; Petrie, Cameron, Ellis, Buick, & Weinman, 2002). Based on our results, key aspects of such interventions to optimize HRQOL would be to target unhelpful beliefs about illness identity, cyclical timeline, consequences, personal control, illness coherence and emotional response. Examples of support strategies that could be implemented to target these unhelpful illness perceptions are: education (e.g. enhancing knowledge about kidney disease and how they can personally influence disease

progression by adopting a healthy lifestyle), challenge misconceptions (e.g. about the unpredictable cyclical nature of CKD and related symptoms), and develop action plans (e.g. how to deal with emotional distress and the negative consequences that the disease has upon their lives, for instance by means of reattribution or increasing social support) (Karamanidou et al., 2008; Petrie et al., 2002). However, pilot studies are needed to evaluate if illness perception-based interventions would indeed improve HRQOL trajectories in patients receiving predialysis care.

The main strength of this study is the longitudinal instead of cross-sectional design that provided the opportunity to investigate changes in HRQOL over time. The PREPARE-2 dataset also offers information on a broad range of factors (i.e. HRQOL, illness perceptions, and variety of demographic and clinical factors) in a large sample of patients. A disadvantage of this observational design is that causal interpretation is still limited. Furthermore, a selection bias could have been introduced as not all eligible patients starting predialysis care have been included in this study (i.e. only patients who were asked and willing to participate). Potentially, unidentified confounding could also have led to biased results: i.e. a decreased health status at the start of predialysis care could have caused both stronger negative illness perceptions and impaired HRQOL trajectories. However, we believe that we adequately adjusted for disease severity (i.e. age, kidney function, and comorbidities), and the results from the crude and adjusted analyses were very similar. Besides this, there is missing data as some patients did not (fully) complete the questionnaire (i.e. the questionnaire was not returned or insufficiently filled out), did not visit the predialysis outpatient clinic every six months or reached a study endpoint. However, it is unlikely that our missing data led to biased results, since little differences in baseline characteristics were observed between patients who were included in and excluded from the analyses. Moreover, to ensure maximum power and avoided bias estimates, missing data was treated using full-information maximum likelihood estimation, and there was no evidence that missing data was not random in nature. Finally, additional research is needed to confirm our results, to assess how HRQOL tra-

jectories develop after 18 months of predialysis care, and to investigate if changes in illness perceptions would also lead to changes in HRQOL trajectories in patients receiving predialysis care.

Despite these limitations and the need for future research, this study identified various important markers for unfavorable HRQOL trajectories: an older age and the presence of CVD were associated with unfavorable physical HRQOL trajectories, and stronger negative perceptions of illness at the start of predialysis care were associated with unfavorable physical and mental HRQOL trajectories. Personalized treatment approaches to optimize HRQOL during predialysis care are desired and should take into account illness perceptions.

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Table 1

Baseline characteristics (n=396)

Characteristic	
Demographic	
Age, years, mean \pm SD	64.4 (14.0)
Sex, female, N (%)	135 (34.1)
Clinical	
Time since CKD diagnosis, median (IQR) years \square	12.0 (9.0-20.0)
Diabetes mellitus, N (%)	101 (25.5)
Cardiovascular disease, N (%)	161 (40.7)
Body mass index (kg/m ²), mean \pm SD $\square\square$	26.6 \pm 5.0
eGFR (ml/min/1.73m ²), mean \pm SD $\square\square\square$	16.8 \pm 6.1
Serum albumin (g/l), mean \pm SD \dagger	40.9 \pm 4.6
Hemoglobin (g/dl), mean \pm SD \ddagger	12.3 \pm 1.5
Psychosocial	
Physical HRQOL (range 0-100), mean \pm SD [*] , ^a	54.6 \pm 22.2
Mental HRQOL (range 0-100), mean \pm SD ^{**} , ^a	67.9 \pm 20.4
Illness identity (range 0-14), mean \pm SD ^b	3.1 \pm 2.5
Timeline acute/chronic (range 6-30), mean \pm SD ^b	24.9 \pm 4.2
Cyclical timeline (range 4-20), mean \pm SD ^a	11.3 \pm 3.4
Negative consequences (range 6-30), mean \pm SD ^b	20.6 \pm 4.1
Personal control (range 6-30), mean \pm SD ^b	18.0 \pm 4.1
Treatment control (range 5-25), mean \pm SD ^b	15.2 \pm 3.0
Illness coherence (range 5-25), mean \pm SD ^b	17.4 \pm 4.1
Emotional response (range 6-30), mean \pm SD ^b	16.5 \pm 5.3

Note. Continuous variables are presented as mean \pm SD for normally distributed variables and as median (IQR) for skewed variables.

Abbreviations: HRQOL, Health-related quality of life; eGFR, estimated glomerular filtration rate; SD, standard deviation; IQR, interquartile range.

Complete data available with the exception of the following variables with data available for:

□381 (96.2%), □□388 (98.0%), □□□351 (88.6%), †325 (82.1%), ‡349 (88.1%), *384 (97.0%), **394 (99.5%).

^a Mean scores of the general Dutch population for physical and mental HRQOL are 76.3 and 77.9 respectively (these mean physical and mental HRQOL composite scores were calculated based on unstandardized mean scores of the SF-36 subscales described by Aaronson et al., 1998).

^b Higher scores on illness perception domains reflect that patients attribute more physical symptoms to their kidney disease (i.e. illness identity), and that patients believe to a higher extent their kidney disease is chronic and cyclical in nature, has negative consequences upon their life, causes emotional distress, can be effectively controlled by themselves or their treatment, and that they understand their kidney disease (i.e. illness coherence).

Table 2

Latent class growth model fit specification for physical and mental HRQOL classes

Number of classes:	1	2	3 ^a	4
Physical HRQOL				
Number of free Parameters	6	9	12	15
Log likelihood	-4162.26	-3978.54	-3931.15	-3920.26
Bayesian Information Criterion	8360.54	8011.10	7934.32	7930.55
Entropy	-	0.73	0.67	0.68
Vuong-Lo-Mendell-Rubin likelihood				
test for $K-1$ vs. K classes, p-value	-	<0.01	<0.01	0.09
Number of classes:	1	2 ^b	3	4
Mental HRQOL				
Number of free Parameters	6	9	12	15
Log likelihood	-4111.98	-3961.41	-3929.53	-3913.31
Bayesian Information Criterion	8235.96	7976.94	7931.21	7916.79
Entropy	-	0.76	0.67	0.63
Vuong-Lo-Mendell-Rubin likelihood				
test for $K-1$ vs. K classes, p-value	-	<0.01	0.36	0.03

Abbreviation: HRQOL, Health-related quality of life

^a A three-class solution had the best model fit as determined by the combination of the fit indices, and the average posterior probabilities for each trajectory class were higher than 0.70 (0.85, 0.77, and 0.90 respectively).

^b A two-class solution had the best model fit as determined by the combination of the fit indices, and the average posterior probabilities for each trajectory class were higher than 0.70 (0.91 and 0.94, respectively).

Table 3

Class solutions for physical HRQOL (n=384) and mental HRQOL (n=394)^a

	Trajectory	Intercept	Slope ^b	N (%)
Physical HRQOL				
Class 1	Low-stable	32.45**	-0.86	131 (34.1)
Class 2	Medium-declining	57.10**	-3.91**	125 (32.5)
Class 3	High-increasing	75.28**	1.84*	128 (33.4)
Mental HRQOL				
Class 1	Low-stable	48.86**	-1.41	152 (38.7)
Class 2	High-stable	80.13**	-0.61	242 (61.3)

Abbreviation: HRQOL, Health-related quality of life.

^aThe median (IQR) number of HRQOL measurements was 2 (1–3) during the first 18 months of predialysis care. Physical and mental HRQOL scores available at follow-up were: 260 (67.7%) and 261 (66.2%) at 6 months, 169 (44.0%) and 168 (42.6%) at 12 months, and 102 (26.6%) and 102 (25.9%) at 18 months respectively.

^bChange in HRQOL scores per 6 months during the first 18 months of predialysis care.

* $p < 0.05$, ** $p < 0.01$.

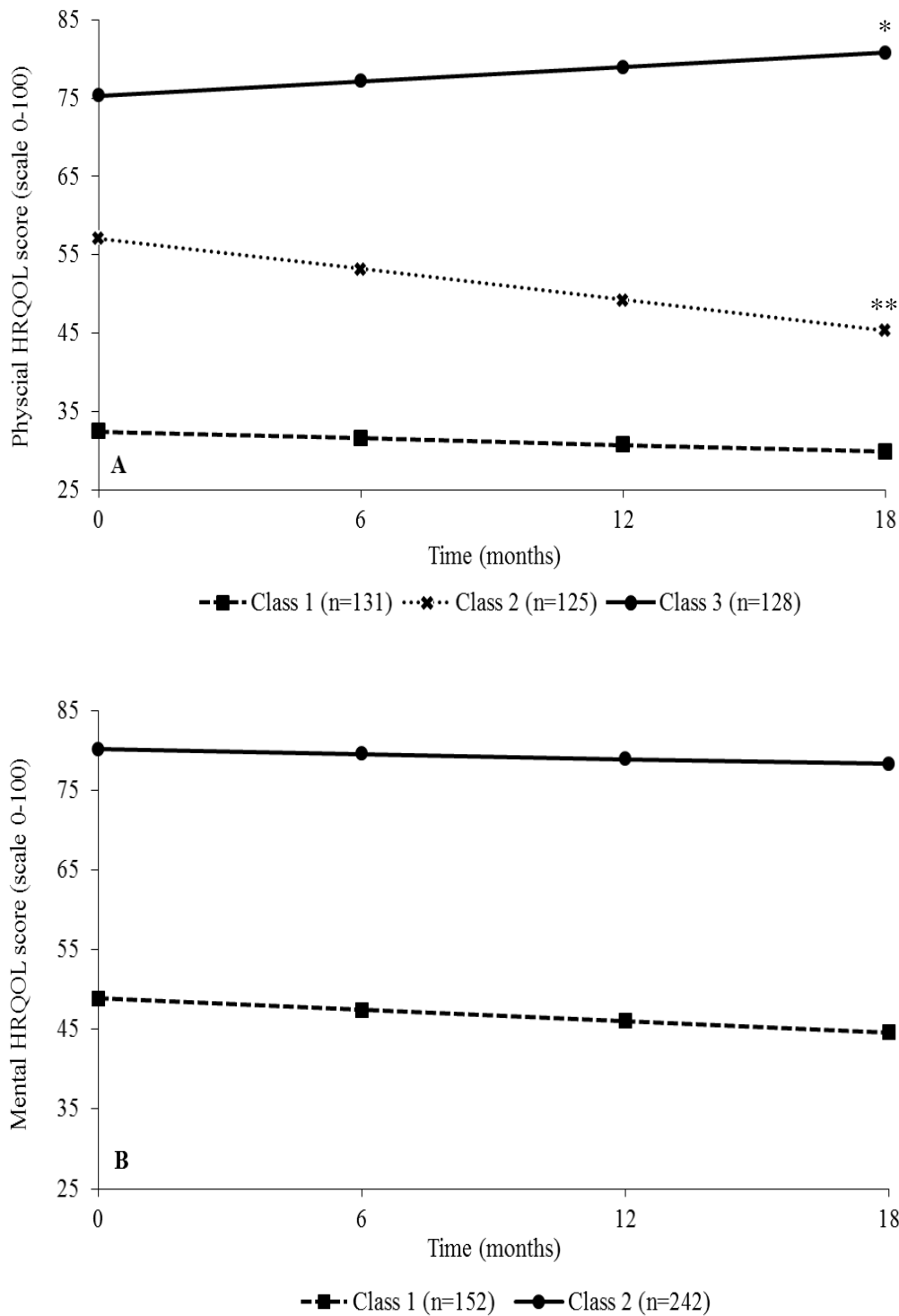


Figure 1. Distinct trajectories of HRQOL during the first 18 months of predialysis care: three physical HRQOL trajectories (A; n=384), and two mental HRQOL trajectories (B; n=394). * $p < 0.05$, ** $p < 0.01$; significant change in HRQOL scores per 6 months during the first 18 months of predialysis care.

Table 4

Factors associated with physical HRQOL class membership (n=384)

	Class 1 ^a		Class 2 ^a	
	Low-stable physical HRQOL		Medium-declining physical HRQOL	
	Unadjusted	Adjusted ^b	Unadjusted	Adjusted ^b
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Illness identity	1.31 (1.18–1.46)**	1.50 (1.26–1.79)**	1.18 (1.03–1.34)*	1.21 (1.02–1.44)*
Timeline acute/chronic	0.98 (0.90–1.06)	0.98 (0.90–1.06)	1.03 (0.93–1.15)	1.05 (0.93–1.18)
Cyclical timeline	1.20 (1.05–1.35)*	1.36 (1.14–1.58)*	1.16 (1.06–1.27)**	1.13 (1.00–1.26)
Negative consequences	1.08 (1.01–1.16)*	1.14 (1.02–1.25)*	1.18 (1.08–1.23)*	1.14 (1.00–1.28)
Personal control	0.90 (0.82–0.98)*	0.88 (0.78–0.97)**	0.97 (0.89–1.06)	0.99 (0.90–1.08)
Treatment control	0.94 (0.77–1.12)	1.11 (0.97–1.24)	0.99 (0.88–1.09)	1.09 (0.96–1.23)
Illness coherence	0.83 (0.65–1.06)	0.85 (0.74–0.95)**	0.95 (0.81–1.12)	0.95 (0.86–1.03)
Emotional response	1.02 (0.97–1.08)	1.07 (1.00–1.15)*	1.05 (0.97–1.13)	1.05 (0.96–1.13)

Abbreviations: OR, Odds ratio; CI, confidence interval.

Note: Higher scores on domains reflect that patients attribute more physical symptoms to their kidney disease (i.e. illness identity), and that patients believe to a higher extent their kidney disease is chronic and cyclical in nature, has negative consequences upon their life, causes emotional distress, can be effectively controlled by themselves or their treatment, and that they understand their kidney disease (i.e. illness coherence).

^a Reference class: high-increasing physical HRQOL (class 3).

^b Adjusted for age, kidney function, and comorbidities.

* $p < 0.05$, ** $p < 0.01$.

Table 5

Factors associated of mental HRQOL class membership (n=394)

	Class 1 ^a	
	Low-stable mental HRQOL	
	Unadjusted	Adjusted ^b
	OR (95% CI)	OR (95% CI)
Illness identity	1.24 (1.08–1.42)**	1.06 (0.80–1.26)
Timeline acute/chronic	0.98 (0.91–1.04)	0.99 (0.92–1.06)
Cyclical timeline	1.18 (1.09–1.28)**	1.22 (1.11–1.32)**
Negative consequences	1.10 (1.04–1.18)**	1.14 (1.05–1.23)**
Personal control	0.94 (0.88–1.00)	0.99 (0.92–1.06)
Treatment control	1.00 (0.93–1.09)	1.02 (0.93–1.10)
Illness coherence	0.86 (0.79–0.93)**	0.84 (0.76–0.93)**
Emotional response	1.06 (0.99–1.12)	1.07 (0.87–0.99)*

Abbreviations: OR, Odds ratio; CI, confidence interval.

Note: Higher scores on domains reflect that patients attribute more physical symptoms to their kidney disease (i.e. illness identity), and that patients believe to a higher extent their kidney disease is chronic and cyclical in nature, has negative consequences upon their life, causes emotional distress, can be effectively controlled by themselves or their treatment, and that they understand their kidney disease (i.e. illness coherence).

^a Reference class: high-stable mental HRQOL (class 2).

^b Adjusted for age, kidney function, and comorbidities.

* $p < 0.05$, ** $p < 0.01$.