The relationship between chronic kidney disease, symptoms and health-related quality of life: A systematic review

Introduction

Chronic kidney disease (CKD) is a growing health problem characterised by progressive and irreversible loss of kidney function (Webster et al. 2017). Globally, it affects about 10 to 15% of the adult population (Hill et al. 2016) with the disease classified into five stages (Webster et al. 2017). Due to reduced kidney function, people with CKD experience a wide range of symptoms. Findings of two previous reviews highlight that the most common physical symptoms experienced are fatigue, pain, drowsiness and pruritus (Murtagh et al. 2007; Almutary et al. 2013). Fatigue, for example, has been reported by 70%–97% of people with CKD (Almutary et al. 2016a). These physical problems are associated with limitations in physical, psychological and social wellbeing. Functional impairment, which is also a common ramification of CKD, can lead to increased dependency on carers and health services (Bowling et al. 2011) and the development or exacerbation of psychological symptoms such as anxiety and depression (Kittiskulnam et al. 2016). As the disease progresses, these problems become more burdensome and often affect the health-related quality of life (HRQoL) of those with CKD (Almutary et al. 2016a).

Health-related quality of life refers to the physical, psychological, social and spiritual aspects of quality of life that are influenced by health and health-related events such as diseases and their treatments (Ferrans et al. 2005; Karimi & Brazier 2016). It is well documented that advanced stages of CKD (i.e. 4 and 5) coupled with dialysis (i.e. haemodialysis or peritoneal dialysis) impact negatively on the HRQoL of people who have CKD (Picariello et al. 2016; Ju et al. 2018). More importantly, due to the slow and unpredictable nature of this disease’s
trajectory, earlier stages of CKD (i.e. 3a and 3b) could also impact on HRQoL of those with CKD (Rosansky 2012). However, studies that examine the impact of early stages of CKD on HRQoL are limited.

Previous systematic reviews collectively reported the symptom burden experienced by people with CKD (Almutary et al. 2013) and how dialysis modality influences their HRQoL (Boateng & East 2011; Ho & Li 2016). To date, no reviews have examined how symptoms and HRQoL change over time and what relationship exists between symptoms and HRQoL in the CKD trajectory; there is also a paucity of reviews in people not receiving kidney replacement therapy (KRT). Therefore, this review examines the current evidence of symptoms and HRQoL in CKD across stages and the relationships between symptoms and HRQoL in these stages.

Methods
The aim of this systematic review is to investigate the recent evidence of symptoms and HRQoL and the relationship between those two concepts in people with CKD who were not receiving KRT. This review follows the Joanna Briggs Institute (JBI) guidelines for quantitative systematic reviews (Moola et al. 2017; Tufanaru et al. 2017). The systematic review protocol was prospectively registered in PROSPERO (CRD42018106784).

Inclusion Criteria
Original studies that were published in English and examined both symptoms and HRQoL of adults (>18 years) with CKD (stage 1–5) were included. Exclusion criteria were participants receiving kidney replacement therapy (KRT; haemodialysis, peritoneal dialysis or kidney transplant), and/or those with acute kidney injury. Self-reported symptoms and HRQoL were
the primary outcomes. Original intervention studies (randomised controlled trials and quasi-
experimental studies) and observational studies (cohort studies, case-control studies and
cross-sectional studies) were included. Mixed methods designs were also included if the
quantitative results were presented. Qualitative designs, case-studies, editorials, opinion
papers and conference abstracts were excluded from this review.

Search Strategy

Six electronic databases (PubMed, MEDLINE, CINAHL, PsycINFO, Cochrane Library and
JBI library) were searched. The keywords included in the search strategy were chronic kidney
disease, end stage kidney disease, chronic renal insufficiency, conservative management,
non-dialysis care, symptoms, health-related quality of life and health status. Keywords were
combined using Boolean phrases (i.e. ‘and’, ‘or’) (see Table 1). The search was limited to
studies published between 1 January 2008 and 31 July 2018. This 10-year period was
determined in order to examine the most recent evidence. Reference lists of selected studies
were also checked for additional eligible papers.

Inclusion and Evaluation Process

The identification and screening process are presented in Figure 1. Following removal of
duplicates, titles (n=869) were screened twice to eliminate the risk of premature exclusion. Of
the 18 studies selected for full-text review, five were excluded due to the inclusion of patients
who received KRT (n=4) and one was a conference abstract. Using appropriate JBI critical
appraisal tools (e.g. for randomised control trials, quasi-experimental studies, cohort studies
and cross-sectional studies; Moola et al. 2017; Tufanaru et al. 2017), the remaining 13
studies were each independently appraised by the principal author and one of the other co-
authors. Any discrepancies in the quality assessments were resolved via discussion between
the author team. Methodological quality of included studies was classified based on predetermined cut-off score (low: <50%, moderate: 50–70% and high: >70%). Any study with low methodological quality was excluded from the review.

**Data Extraction**

The data extracted were participant characteristics (age, gender and eGFR), prevalence and severity symptom scores, physical component summary (PCS) and mental component summary (MCS) scores of HRQoL and results of the relationship between symptoms and HRQoL. Additional details of instruments used were also extracted (see Supplementary Table S2).

**Data Synthesis**

Data synthesis was carried out according to the JBI guidelines for quantitative reviews (Moola et al. 2017; Tufanaru et al. 2017). A meta-analysis was not conducted due to the heterogeneity of studies, therefore a narrative synthesis was undertaken.

**Results**

**Characteristics of Included Studies**

Among the 13 studies included, there were six cohort, four cross-sectional and three intervention studies (see Table 2). The studies were conducted in the United States (n=4), Australia (n=3), Netherlands (n=2), and one in the United Kingdom, China, Singapore and Korea involving a total of 7,741 participants. Sample sizes ranged from 15 (Salmean et al. 2013) to 3,837 (Porter et al. 2016). Across the studies, the majority of participants were male (58%), and the mean age ranged from 51 to 73 years. All studies used validated instruments to assess symptoms and HRQoL. Most of the studies rated moderate methodological quality
(n=9) with only 3 rated as high methodological quality. No study was excluded due to low methodological quality.

Three intervention studies sought to improve symptoms and HRQoL were included in this review. Two of these studies employed nutrition-related interventions (Campbell et al. 2008; Salmean et al. 2013) and the other study used an exercise intervention (Kosmadakis et al. 2012). In terms of intervention designs, Salmean et al. (2013) used a 6-week, pre-post design, Campbell et al. (2008) employed a 12-week RCT and Kosmadakis et al. (2012) used a 6-month quasi-experimental design.

**Chronic Kidney Disease Symptoms**

Ten studies reported a symptom score. The majority (n=6) used the kidney disease quality of life short form (KDQOL-SF) or kidney disease quality of life-36 (KDQOL-36) questionnaires to assess symptoms (see Supplementary Table S1). However, one study used only the sleep-related quality of life questions from the KDQOL-36 (Kumar et al. 2010). One study compared mean symptom scores of people in CKD stages 3a and 3b and found that those in stage 3b had slightly lower symptom scores (Peng et al. 2017). Another study (Gyamlani et al. 2011) used the Center for Epidemiological Studies Depression Scale (CES-D; 0–60 scale; >16 indicates positive for depression) and the Patient Health Questionnaire-2 (PHQ-2; which includes dichotomous responses to two questions; responding 'yes' to either question indicates that the participant suffers from depression) to examine depression. This study found a significant relationship between the two scores (p<0.05).

Six studies reported the occurrence of individual symptoms; however, three of these examined the occurrence of only depression/anxiety-related symptoms (Gyamlani et al. 2011;
Of the studies that reported both physical and psychological symptoms, feeling washed out (Kumar et al. 2010), fatigue (de Goeij et al. 2014) and drowsiness (Lee & Jeon 2015) were the most prevalent symptoms. For studies that did not report a total symptom score and/or symptom prevalence (excluding Salmean et al. 2013), corresponding authors were contacted although no necessary data were provided for this review. Symptom severity was only reported by one study; difficulty in sleeping, constipation and poor appetite were the three most severe and overwhelming symptoms experienced (Lee & Jeon 2015).

Of the included longitudinal studies (n=6), only one study reported a decline in symptom scores over time (de Goeij et al. 2014). The remaining five studies reported baseline symptom scores only. Of these studies, Brown et al. (2015) categorised change in symptom scores as ‘stable’, ‘improved’ or ‘worse’ and compared the scores of people in the pre-dialysis group to those in the non-dialysis group. In this study, the non-dialysis group had more people shift into the ‘improved’ category over time (i.e. from baseline to six months → baseline to 12 months: 42 → 57%). On studying symptom occurrence longitudinally (n=2), de Goeij et al. (2014) found an increase of symptom occurrence over time and Feng et al. (2013) reported a slight reduction in depression occurrence in their follow-up measurements.

Studies involving nutritional and exercise interventions demonstrated significant improvements in some symptoms. (Campbell et al. 2008; Kosmadakis et al. 2012; Salmean et al. 2013). For example, Salmean et al. (2013) and Kosmadakis et al. (2012) reported significant improvements in sleep-related problems and uraemic symptoms, respectively. Two studies (Campbell et al. 2008; Kosmadakis et al. 2012) demonstrated comparisons between intervention and control groups graphically and did not report values.
Health-related Quality of Life in Chronic Kidney Disease

Most of the studies used the KDQOL-SF/KDQOL-36 (n=6) and short form-36 (SF-36; n=5) to assess HRQoL (possible range of scores: 0-100; higher score relates to better HRQoL; see Supplementary Table S3). One study did not report PCS and MCS scores numerically (Kosmadakis et al. 2012). The mean PCS and scores ranged from 31±7.7 (Salmean et al. 2013) to 54.6±22.2 (Meuleman et al. 2017), and the MCS scores from 45.3±12.5 (Campbell et al. 2008) to 67.9±20.4 (Meuleman et al. 2017). McKercher et al. (2013) used the European quality of life-five dimension-three level (EQ5D3L) instrument, finding that pain and mobility problems impacted on HRQoL more than self-care deficits, impairment of usual activities and psychological problems.

Only four longitudinal studies reported a change in HRQoL over time (Feng et al. 2013; de Goeij et al. 2014; Brown et al. 2015; Meuleman et al. 2017). The majority of studies reported a decline in PCS (de Goeij et al. 2014; Brown et al. 2015; Meuleman et al. 2017) and an increase in MCS (Feng et al. 2013; Brown et al. 2015) over time. Brown et al. (2015) found, on comparing the change in PCS and MCS over a 12 month period between the pre-dialysis and the non-dialysis groups, the PCS in the majority of participants in both groups (i.e. pre-dialysis: 55% and non-dialysis: 63%) worsened over time. In contrast, the majority of participants in both groups (i.e. pre-dialysis: 53% and non-dialysis: 53.1%) showed improved MCS over time (Brown et al. 2015). Meuleman et al. (2017) classified PCS and MCS scores into health trajectories. Accordingly, PCS comprised of “low-stable” (i.e. low levels of physical HRQoL that remained stable over time), “medium-declining” (i.e. moderate levels of physical HRQoL that decrease over time), and “high increasing” (i.e. high levels of physical HRQoL that increased over time) trajectories and each contained approximately one third of the sample. MCS was classified by Meuleman et al. (2017) as “low-stable” (i.e. low
levels of mental HRQoL that remained stable over time) and “high-stable” (i.e. high levels of mental HRQoL that remained stable over time) trajectories, and these contained 38.7% and 61.3% participants, respectively. In this study, participants who were in the “medium declining” trajectory had significantly deteriorating PCS (p<0.01) and those in the “high increasing” trajectory showed significant improvements in PCS (p<0.05) over an 18-month period (Meuleman et al. 2017).

All intervention studies demonstrated improvements in physical aspects of HRQoL associated with the nutritional and exercise interventions (Campbell et al. 2008; Kosmadakis et al. 2012; Salmean et al. 2013). Of these, only one study showed a significant improvement in PCS (p<0.05) in the intervention group over the control group (Salmean et al. 2013). Findings related to mental aspects of HRQoL were inconsistent across studies. In the intervention groups, Campbell et al. (2008) found improvements in MCS while Salmean et al. (2013) reported a significant decline in MCS (p<0.05). Notably, Campbell et al. (2008) and Kosmadakis et al. (2012) only presented these comparisons graphically.

Relationship between Symptoms and Health-related Quality of Life in Chronic Kidney Disease

Four studies examined the relationship between symptoms and HRQoL (Gyamlani et al. 2011; McKercher et al. 2013; Lee & Jeon 2015; Meuleman et al. 2017; see Table 3). Of these, three reported a negative relationship between symptoms and HRQoL (i.e. PCS and MCS scores decreased as symptom scores increased; Gyamlani et al. 2011; McKercher et al. 2013; Lee & Jeon 2015). The remaining study found that higher symptom scores had increased odds for “medium declining: physical” and “low stable: physical and mental”
trajectories (Meuleman et al. 2017). Lastly, Kumar et al. (2010) reported that a lower sleep quality score was significantly correlated with lower PCS (r=0.3) and MCS (r=0.31) scores.

Four studies reported the relationship between eGFR and HRQoL (McKercher et al. 2013; Lee & Jeon 2015; Porter et al. 2016; Peng et al. 2017). Of these, three reported that PCS decreased as eGFR decreased (Lee & Jeon 2015; Porter et al. 2016; Peng et al. 2017). However, only two studies reported stable or decreased MCS with decreasing eGFR (Porter et al. 2016; Peng et al. 2017). Porter et al. (2016) reported that unlike MCS, 10mL/min/1.73m² decrements of eGFR had significantly increased odds of a lower PCS. In this study, a score greater than one standard deviation below the mean sub-scale score for the cohort was referred to as “low HRQoL” (Porter et al. 2016). Peng et al. (2017) examined the relationship between CKD 3a and 3b (based on eGFR), finding that those in CKD stage 3b had significantly lower PCS (p<0.05) and MCS (p<0.05) than those in stage 3a.

Overall, all intervention studies demonstrated improvements in PCS and reduction in symptom scores (Campbell et al. 2008; Kosmadakis et al. 2012; Salmean et al. 2013). In terms of MCS, only one study showed improvement when symptoms decreased due to the nutritional intervention (Campbell et al. 2008).

Discussion

This systematic review examined the recent evidence of the symptom experience and HRQoL and the relationship between those two concepts in adults with CKD who were not receiving dialysis. However, only 13 studies assessing symptoms and HRQoL together in people with CKD were found. While the methodological quality of included studies where moderate to high, there were very few interventional studies. Evidence from these studies should be
treated cautiously due to the heterogeneity of studies and inconsistencies in measuring symptoms and HRQoL that prevented meta-analyses being conducted analyses.

By considering symptom experience and HRQoL together, this review highlighted that HRQoL decreases when symptoms increase in people with CKD. This reinforces a negative relationship between symptoms and HRQoL in CKD. This is consistent with a recent study, which demonstrated that the high symptom burden associated with CKD negatively influenced HRQoL of those with CKD (Almutary et al. 2017). This negative relationship could be mediated by an additive effect of symptoms. For instance, fatigue, a common symptom experienced by people with CKD may exacerbate other symptoms (e.g. sleep disturbance, poor appetite and depression), which may collectively cause impairments in physical and social functioning of individuals with CKD (Almutary et al. 2016b).

Feeling washed out, fatigue and drowsiness were the most common symptoms reported by people with CKD in this review. These particular symptoms have been previously reported in other reviews (Murtagh et al. 2007; Almutary et al. 2013), however both of these reviews only included studies assessing people with CKD stages 4 and 5 whereas this current review included all CKD stages. We found only two studies which measured fatigue as a symptom of CKD (de Goeij et al. 2014; Meuleman et al. 2017). As a result, the actual symptom burden experienced by participants across these studies could not be ascertained comprehensively. Surprisingly, only one study compared symptoms across CKD stages (Peng et al. 2017). This study was also limited in scope, only comparing symptoms between CKD stage 3a and 3b. Due to a lack of high quality studies in this area, it is difficult to evaluate which symptoms occur more frequently across the CKD trajectory. Therefore, studies that examine symptoms
across CKD stages are needed to inform the development of care pathways and guidelines that target the relief of symptoms based on the person’s stage of CKD.

In terms of how symptoms change over time, only two studies (Feng et al. 2013; de Goeij et al. 2014) reported follow-up measurements (either as symptom scores or symptom occurrence) although six studies looked at the change of symptoms over time (the other longitudinal studies reported baseline data only). In addition, none of the longitudinal studies examined change of symptoms over time across the different stages of CKD. Therefore, due to inadequate evidence, it is difficult to determine how the symptoms experienced by people with CKD change over time.

When examining how HRQoL changes over time in people with CKD, findings of the current review suggest that physical HRQoL declines and mental HRQoL improves over time. Reduced physical HRQoL could be due to functional impairments as a result of deteriorating kidney function whereas adapting to new life circumstances or changing prospects and expectations over time to align with the contextual changes could explain improvements in mental HRQoL (Ferrans 2007). This is consistent to some extent with, Bonner et al. (2018), who reported that, regardless of the treatment modality (i.e. dialysis or conservative management), those who were potentially in their last 12 months of life had relatively stable HRQoL over time. This could be explained by adaptation to lower HRQoL state due to change of living standards over time.

The exercise and nutritional intervention studies included in this review reported improvements in symptom experience and physical HRQoL as study outcomes. These findings are supported by a previous systematic review that examined the impact of exercise...
interventions on physical functioning and quality of life in those with CKD (Afsar et al. 2018). These improvements suggest that exercise and nutritional interventions contribute to increasing muscle strength, improving cardio-respiratory functioning and reducing kidney deterioration in those with CKD. Despite use of small sample sizes, attrition bias and inconsistent reporting methods, these interventions seemed to be instrumental in ameliorating HRQoL in people living with CKD. However, more intervention studies with large representative samples are warranted before these interventions may be incorporated into routine renal care.

This systematic review has several strengths. It adhered with the steps of the JBI guidelines for systematic reviews such as conducting an extensive literature search to eliminate the risk of premature exclusion of studies and using multiple reviewers to critically appraise studies and to extract data. Nevertheless, this review does have some limitations. First, it only included studies that examined symptoms and HRQoL in people who do not receive KRT. Second, due to a dearth of research that measured symptoms and HRQoL in the same study, evidence of the relationships between these in CKD is not strong. Third, the comparison of symptoms across studies was difficult due to the inconsistent use of instruments which resulted in the occurrence of symptoms being captured and reported in a variety of ways. Fourth, it was difficult to ascertain the true impact of symptoms on people with CKD because, in addition to symptom occurrence, only one study reported severity of symptoms. Given the multi-dimensional nature of symptoms (Almutary et al. 2016a), it is essential to examine the occurrence, severity and frequency of symptoms as well as the distress caused by them to determine symptom burden. Lastly, this review was unable to report how symptoms and HRQoL change over time due to the unavailability of follow up data of longitudinal studies.
Conclusion

This systematic review found few studies about the relationship between symptoms and HRQoL of those with CKD who are not on dialysis. Of these, in view of symptom experience and HRQoL together, the review suggests that HRQoL decreases when symptoms increase in people with CKD. The evidence on how and which symptoms change over time was inconclusive as only one longitudinal study reported change of symptom scores over time. In terms of HRQoL, a decline in PCS and increase in MCS over time was found. No studies were found that assessed how symptoms and HRQoL change when CKD progresses from early stages to advanced stages. Nutritional and exercise interventions could be useful in improving the symptom experience and HRQoL of people with CKD although further research is needed. In addition, longitudinal studies that assess symptoms and HRQoL along the CKD trajectory are warranted.

Implications for Clinical Practice

Chronic kidney disease negatively affects the lives of those people afflicted; understanding their symptom experience and HRQoL and the relationship between these is of utmost importance so that appropriate and timely care can be proactively planned and provided. Regardless of CKD stage, it is important to track individuals’ symptom experiences and HRQoL over time using validated instruments at regular intervals, ideally as part of routine clinical assessments (e.g. every 6 or 12 months due to the protracted CKD trajectory). Results of such assessments could then be used to trigger appropriate interventions and referrals to alleviate suffering and distress. Thus, findings from this review may inform the development of appropriate interventions and care pathways designed to improve both the symptom experience and HRQoL of those with CKD.
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Records identified through database searching (n=1575)
PubMed (n=586); MEDLINE (n=661); CINAHL (n=129); PsycINFO (n=145); JBI (n=26); Cochrane Library (n=28)

Additional records identified through other sources (n=0)

Duplicates removed (n=706)

Records screened (n=869)

Records excluded (n=851)

Full-text articles assessed for eligibility (n=18)

Reasons for exclusion of articles on full text review (n=5)
- Inclusion of patients who receive kidney replacement therapy (n=4)
- Conference abstract (n=1)

Studies included in quantitative synthesis (n=13)

Figure 1: Study selection flow chart. From Moher et al. (2009).
| Search strategy used for PubMed using MeSH and keywords | Hits |
|----------------------------------------------------------|------|
| #1 ((("renal insufficiency, chronic"[MeSH Terms] OR "kidney diseases"[MeSH Terms] OR "kidney failure, chronic"[MeSH Terms] OR "renal insufficiency" [MeSH Terms] OR Chronic kidney disease>Title/Abstract] OR Kidney disease>Title/Abstract] OR End stage kidney disease>Title/Abstract] OR End stage renal disease>Title/Abstract] OR Chronic kidney failure>Title/Abstract] OR Kidney failure>Title/Abstract] OR End stage kidney failure>Title/Abstract] OR Chronic renal failure>Title/Abstract] OR Renal failure>Title/Abstract] OR End stage renal failure>Title/Abstract] OR Chronic renal insufficiency>Title/Abstract] OR Renal insufficiency>Title/Abstract] OR CKD>Title/Abstract] OR ESKD>Title/Abstract] OR ESRD>Title/Abstract] OR CRF>Title/Abstract] OR Conservative management>Title/Abstract] OR Conservative care>Title/Abstract] OR Non-dialysis care>Title/Abstract]))) Limiters: Publication date from 2008/01/01 to 2018/07/31; Humans; English; Adult: 18+ years Search mode: Boolean/Phrase | 84,531 |
| #2 ((Symptom>Title/Abstract] OR Clinical feature>Title/Abstract] OR Clinical manifestation* [Title/Abstract])) Limiters: Publication date from 2008/01/01 to 2018/07/31; Humans; English; Adult: 18+ years Search mode: Boolean/Phrase | 2,54,573 |
| #3 ((Health-related quality of life>Title/Abstract] OR Quality of life>Title/Abstract] OR Health status>Title/Abstract] OR Health status indicator* [Title/Abstract] OR Health status outcome* [Title/Abstract] OR QOL>Title/Abstract] OR HRQOL>Title/Abstract] OR HRQL>Title/Abstract] OR QL>Title/Abstract])) Limiters: Publication date from 2008/01/01 to 2018/07/31; Humans; English; Adult: 18+ years Search mode: Boolean/Phrase | 83,400 |
| #4 #1 AND #2 AND #3 | 586 |
| Author(s), Year, Country | Study design | Sample | Participant characteristics (Age [years; mean±SD or median (IQR)]; Male [%]; eGFR [mL/min/1.73m²]) | Strengths/ Limitations | Quality appraisal |
|--------------------------|-------------|--------|---------------------------------------------------------------------------------|------------------------|------------------|
| Campbell et al. 2008 Australia | Randomised control trial (Baseline & 12 weeks) | CKD stage 4 & 5 (n=47; Intervention group: 24; Control group: 23) | Intervention group: Age: 71±12.3 Male: 60.9 eGFR: 21.9±6.3 | • Confounding factors were controlled <br> • Small sample size <br> • 12-week follow-up data related to symptoms and HRQoL were not reported | Moderate |
| Kumar et al. 2010 United States | Prospective cohort (3 years: Baseline & annually) | CKD stage 3, 4 & 5 (n=673) | Age: 60.4±15.2 Male: 55 eGFR: 25.3±10.4 | • Large sample size <br> • Confounding factors were controlled <br> • Correlation between symptoms and HRQoL was examined <br> • Only baseline symptom scores and PCS/MCS comparisons were reported for those who were not on dialysis | Moderate |
| Gyamlani et al. 2011 United States | Cross-sectional | CKD stage 3, 4 & 5 (n=71) | Age: 61.5±12.3 Male: 98.6 eGFR: Not reported | • Confounding factors were controlled <br> • Correlation between symptoms (depression score) and HRQoL was examined <br> • Small sample size | Moderate |
| Kosmadakis et al. 2011 United Kingdom | Quasi-experimental (Baseline, 1 & 6 months) | CKD stage 4 & 5 (n=40; 1:1- Exercise group: Non-exercise group) | Intervention group: Age: 61.5 Male: 40 eGFR: 25.3 | • Confounding factors were controlled <br> • Small sample size <br> • Actual figures comparing intervention and control group were not reported (only graphs were presented) | High |
| Feng et al. 2013 Singapore | Prospective cohort (4 years: Baseline & every 2 years) | CKD stage 3 & 4 (n=362) | Age: 70.3±7.8 Male: 42.4 eGFR: 51±8.3 | • Confounding factors were controlled <br> • Relationship between symptoms and HRQoL was not examined | Moderate |
| Author(s), Year, Country | Study design | Sample | Participant characteristics (Age [years; mean±SD or median (IQR)]; Male [%]; eGFR [mL/min/1.73m²]) | Strengths/ Limitations | Quality appraisal |
|------------------------|-------------|--------|---------------------------------------------------------------------------------|------------------------|------------------|
| McKercher et al. 2013 Australia | Cross-sectional | CKD stage 4 (n=49) | Age: 72.6±10.2  
Male: 63  
eGFR: 22.2±4.9 | • Confounding factors were controlled  
• Correlation between symptoms and HRQoL was examined  
• Small sample size  
• Only cross-sectional data reported although this was a longitudinal study | Moderate |
| Salmean et al. 2013 United States | Pre-post design (6 weeks) | CKD stage 3, 4 & 5 (n=15) | Age: 66±15  
Male: 40  
eGFR: Not reported | • Confounding factors were controlled  
• Comparison of symptoms and HRQoL between intervention and control group was reported  
• Small sample size | High |
| de Goeij et al. 2014 Netherlands | Prospective cohort (7 years: Baseline & every 6 months [4 time points until reach the endpoint]) | CKD stage 4 & 5 (n=436) | Age: 69 (20)  
Male: 66  
eGFR: 16.9±6.1 | • Confounding factors were controlled  
• Relationship between symptoms and HRQoL was not examined | Moderate |
| Brown et al. 2015 Australia | Prospective cohort (1 year: Baseline, 6 months & 12 months) | CKD stage 4 & 5 (n=395; Pre-dialysis: 273; Non-dialysis: 122) | **Pre-dialysis group**  
Age: 67±14  
Male: Not reported  
eGFR: 16±7  
**Non-dialysis group**  
Age: 82±9  
Male: Not reported  
eGFR: 16±9 | • Confounding factors were controlled  
• Relative change of symptoms and HRQoL over 12 months was examined  
• Relationship between symptoms and HRQoL was not examined | Moderate |
| Lee & Jeon 2015 Korea | Cross-sectional | CKD stage 2, 3 & 4 (n=143) | Age: 66.3±14.29  
Male: 62.2  
eGFR: 41.2±16.25 | • Relationship between symptoms and HRQoL was examined  
• Severity of symptoms examined  
• Confounding factors were identified but not controlled  
• Participants selected from one hospital | Moderate |
| Author(s), Year, Country | Study design | Sample | Participant characteristics (Age [years; mean±SD or median (IQR)]; Male [%]; eGFR [mL/min/1.73m²]) | Strengths/ Limitations | Quality appraisal |
|--------------------------|-------------|--------|------------------------------------------------------------------------------------------------|------------------------|-------------------|
| Porter et al. 2016 United States | Prospective cohort (4 years: Baseline & every 12 months) | CKD stage 2, 3 & 4 (n=3837) | Age: 57.6±11  
Male: 55  
eGFR: 45±16.9 | • Large sample size  
• Confounding factors were controlled  
• Only cross-sectional analysis was reported  
• Relationship between symptoms and HRQoL was not examined | Moderate |
| Meuleman, et al. 2017 Netherlands | Prospective cohort (7 years: Baseline & every 6 months [4 time points until reach the endpoint]) | CKD stage 4 & 5 (n=396) | Age: 64.4±14  
Male: 65.9  
eGFR: 16.8±6.1 | • Confounding factors were controlled  
• Relationship between symptoms and HRQoL was examined; however, complete relationship data were not reported | Moderate |
| Peng et al. 2017 China | Cross-sectional¹ | CKD stage 3a & 3b (n=1277) | Age: 51.68±12.81  
Male: 60.9  
eGFR:  
3a: 51.61±4.24  
3b: 37.13±4.33 | • Large sample size was used  
• Confounding factors were controlled  
• Relationship between stage of CKD and HRQoL was examined  
• Relationship between symptoms and HRQoL was not examined | High |

Note: Validated instruments were used in all studies; ¹Compared symptoms and HRQoL based on stage of CKD; SD: Standard deviation; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; HRQoL: Health-related quality of life; PCS: Physical component score; MCS: Mental component score
| Author(s), Year      | Relationship | Symptoms and HRQoL                          | eGFR/Stage of CKD and HRQoL |
|---------------------|--------------|---------------------------------------------|-----------------------------|
| Campbell et al. 2008| -            | -                                           | -                           |
| Kumar et al. 2010   | -            | -                                           | -                           |
| Gyamli et al. 2011  | Spearman correlation | CES-D and PCS: -0.165  | Spearman correlation | CES-D and MCS: -0.747*  |
|                     |              | PHQ-2 and PCS: -0.165  |                            | PHQ-2 and MCS: -0.528*  |
| Kosmadakis et al. 2011 | -   | -                                           | -                           |
| Feng et al. 2013    | -            | -                                           | -                           |
| McKercher et al. 2013 | Spearman correlation | PHQ-9 and PCS: -0.48*  | Spearman correlation | PHQ-9 and MCS: -0.61*  |
|                     |              | BAI and PCS: -0.61*  |                            | BAI and MCS: -0.58*  |
| Salmean et al. 2013 | -            | -                                           | -                           |
| de Goeij et al. 2014 | -           | -                                           | -                           |
| Brown et al. 2015   | -            | -                                           | -                           |
| Lee & Jeon 2015     | Pearson correlation | PCS: -0.492*   | Pearson correlation | PCS: 0.16                |
|                     |              | MCS: -0.547*   |                            | MCS: -0.123            |
| Porter et al. 2016  | -            | -                                           | Odds ratios                 |
|                     |              | Low ratios     | Low PCS: 1.09*             |
|                     |              | Odds ratios     | Low MCS: 0.98              |
|                     |              | (Ref: high increasing) |                         |
|                     |              | Low stable PCS: 1.31* |                         |
|                     |              | Medium-declining PCS: 1.18*                |                            |
| Meuleman et al. 2017 | Odds ratios (Ref: high stable) | Low stable MCS: 1.24* |                            |
| Peng et al. 2017    | -            | -                                           | Regression coefficient#    |
|                     |              | PCS: -1.12*   |                            |
|                     |              | MCS: -1.00    |                            |
*Significant relationship (p<0.05); # Relationship between stage of CKD and HRQoL; CKD: Chronic kidney disease; eGFR: estimated glomerular filtration rate; HRQoL: Health-related quality of life; PCS: Physical component score; MCS: Mental component score; CES-D: Center for Epidemiological Studies Depression Scale; PHQ-2: Patient health questionnaire-2; PHQ-9: Patient health questionnaire-9; BAI: Beck anxiety inventory
| Author(s), Year | Instrument(s) used                                                                 | Total symptom score (minimum to maximum; mean±SD) | Prevalence: most frequent symptoms (mean±SD or %) | Severity of symptoms* (%) |
|-----------------|-----------------------------------------------------------------------------------|----------------------------------------------------|--------------------------------------------------|---------------------------|
| Campbell et al. 2008 | • KDQOL SF 1.3                                                                    | #                                                  | -                                                | -                         |
| Kumar et al. 2010   | • KDQOL-36                                                                         | • KDQOL-36 Sleep Quality [0-100; <60 indicates poor sleep quality]: 59.4±23.6 | 1. Washed out 34.8±29.3 2. Dry skin 34.6±30.2 3. Muscle soreness 33.8±27.9 4. Pain 33.7±26.9 5. Itchy skin 27.0±29.0 | -                         |
| Gyamblani et al. 2011 | • Center for Epidemiological Studies Depression Scale (CES-D)                      | • CES-D [0-60; >16 indicates depression]: 10.3±8.4 | CES-D; Depression (30%) PHQ-2; Depression (24%) | -                         |
| Kosmadakis et al. 2011 | • Leicester Uraemic Symptom Scale (LUSS)                                           | #                                                  | -                                                | -                         |
| Feng et al. 2013    | • Geriatric Depression Scale (GDS)                                                 | • GDS [0-15; >5 indicates depression]: 7.8±7.8    | Baseline: Depression (12.8%)                      | Follow-up: Depression (11.2%) | -                         |
| McKercher et al. 2013 | • Patient health questionnaire (PHQ-9; for depression)                             | • PHQ-9 [0-27; >10 indicates major depression]: 4.4±5.8 | PHQ-9; Depression (10%) BAI; Anxiety (9.3%)     | -                         |
| Author(s), Year          | Instrument(s) used                                                                                                                                                                                                 | Total symptom score (minimum to maximum; mean±SD)                                                                 | Prevalence: most frequent symptoms (mean±SD or %)                                                                 | Severity of symptoms (%) |
|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|--------------------------|
| Salmean et al. 2013     | • KDQOL-36  
• Simplified Nutritional Appetite Questionnaire (SNAQ)  
• Epworth Sleepiness Scale (ESS)  
• Gastrointestinal Symptom Rating Scale (GSRS)                                                                                                         | Pre-test: no fibre diet  
• KDQOL-36 symptom scale [0-100; 0 = no symptoms to 100 = worst possible symptom experience]: 78±11.6  
• SNAQ [4-20; <14 indicates poor appetite]: 14±3.9  
• ESS [0-24; 10-12 indicates borderline risk of day time sleepiness]: 10±3.9  
• GSRS [15-105]: 23±3.9                                                                 | Post-test: with fibre diet  
• KDQOL-36 symptom scale [0-100; 0 = no symptoms to 100 = worst possible symptom experience]: 80±11.6  
• SNAQ [4-20; <14 indicates poor appetite]: 14±3.9  
• ESS [0-24; 10-12 indicates borderline risk of day time sleepiness]: 8±3.9  
• GSRS [15-105]: 22±3.9                                                                 | -                                                                                                                  | -                                                                     |
| de Goeij et al. 2014    | • Revised illness perception questionnaire (IPQ-R)                                                                                                                                                                | Baseline:  
IPQ-R- Illness identity scale [0-12; 0 = no symptoms to 12 = worst possible symptom experience]: 4.8±2.1 | End point:  
IPQ-R- Illness identity scale [0-12]: 6.7±4.2                                                                  | Baseline:  
1. Fatigue (82.5%)  
2. Loss of strength (61.1%)  
3. Stiff joints (51.3%)  
4. Weight loss (38.7%)  
5. Sleep difficulties (37.9%)                                                                 | End point:  
(94%)  
(82.8%)  
(67.9%)  
(54.5%)  
(55.3%)                                                                 | -                                                                     |
| Author(s), Year | Instrument(s) used | Total symptom score (minimum to maximum; mean±SD) | Prevalence: most frequent symptoms (mean±SD or %) | Severity of symptoms (%) |
|----------------|-------------------|-----------------------------------------------|------------------------------------------------|--------------------------|
| Brown et al. 2015 | • Memorial Symptom Assessment Scale-Short Form (MSAS-SF)  
• Palliative care Outcome Scale-Symptoms-Renal (POS-S Renal; used only for non-dialysis group) | Baseline  
MSAS-SF [0-32; 0 = no symptoms to 32 = worst possible symptom experience]  
Pre-dialysis group: 9.1±5.3  
Non-dialysis group: 12.2±5.6  
POS-S Renal [0-68; 0 = no symptoms to 68 = worst possible symptom experience]: Not reported | | |
| Lee & Jeon 2015 | • Palliative care Outcome Scale | | 1. Drowsiness (58.7%)  
2. Weakness (53.1%)  
3. Pain (46.9%)  
4. Constipation (45.5%)  
5. Difficulty sleeping (41.3%) | 1. Difficulty sleeping (18.2%)  
2. Constipation (11.9%)  
3. Poor appetite (11.9%)  
4. Pain (10.5%)  
5. Poor mobility (10.5%) |
| Porter et al. 2016 | • KDQOL-36 | KDQOL-36 symptom scale [0-100; 0 = no symptoms to 100 = worst possible symptom experience]: 83.4±14.9 | | |
| Meuleman et al. 2017 | • Revised illness perception questionnaire (IPQ-R) | IPQ-R- Illness identity scale [0-14; 0 = no symptoms to 14 = worst possible symptom experience]: 3.1±2.5 | | |
| Peng et al. 2017 | • KDQOL-36 | KDQOL-36 symptom scale [0-100; 0 = no symptoms to 100 = worst possible symptom experience]:  
Stage 3a: 90.9±11.05  
Stage 3b: 89.3±11.52 | | |

*% of people who experienced severe/overwhelming symptoms; SD: Standard deviation; KDQOL SF: Kidney disease quality of life-short form; KDQOL-36: Kidney disease quality of life-36
### Supplementary Table 2: Instruments used to evaluate symptoms

| Author(s), Year | Instrument(s) used | Number of items | Recalling period of symptoms |
|-----------------|-------------------|-----------------|-----------------------------|
| Campbell et al. 2008 | KDQOLSF 1.3 | KDQOLSF 1.3 Symptom scale: 11 | KDQOLSF 1.3 Symptom scale: Past four weeks |
| Kumar et al. 2010 | KDQOL-36 | • KDQOL-36 Symptom scale: 11 <br> • KDQOL-36 Sleep quality (SQ) related questions: 4 | KDQOL-36 Symptom scale and SQ related questions: Past four weeks |
| Gyamalani et al. 2011 | • Center for Epidemiological Studies Depression Scale (CES-D) <br> • Patient health questionnaire (PHQ-2; for depression) | • CES-D: 20 <br> • PHQ-2: 2 | • CES-D: Past one week <br> • PHQ-2: Past two weeks |
| Kosmadakis et al. 2011 | Leicester Uraemic Symptom Scale (LUSS) | 11 | Not specified |
| Feng et al. 2013 | Geriatric Depression Scale (GDS) | 15 | GDS: Past one week |
| McKercher et al. 2013 | • KDQOLSF 1.3 <br> • Patient health questionnaire (PHQ-9; for depression) <br> • Beck Anxiety Inventory (BAI) | • KDQOLSF 1.3: Symptom scale: 11 <br> • PHQ: 9 <br> • BAI: 21 | • KDQOLSF 1.3 Symptom scale: Past four weeks <br> • PHQ-9: Past two weeks <br> • BAI: Past one month |
| Salmean et al. 2013 | • KDQOL-36 <br> • Simplified Nutritional Appetite Questionnaire (SNAQ) <br> • Epworth Sleepiness Scale (ESS) <br> • Gastrointestinal Symptom Rating Scale (GSRS) | • KDQOL-36: Symptom scale: 11 <br> • SNAQ: 4 <br> • ESS: 8 <br> • GSRS: 15 | • KDQOL-36 Symptom scale: Past four weeks <br> • SNAQ: Not specified <br> • ESS: Not specified <br> • GSRS: Past one week |
| de Goeij et al. 2014 | Revised illness perception questionnaire (IPQ-R) | IPQ-R Illness identity scale: 12 out of 14 symptoms | Not specified |
| Brown et al. 2015 | • Memorial Symptom Assessment Scale-Short Form (MSAS-SF) <br> • Palliative Outcome Scale-S-renal (POS-S renal) | • MSAS-SF: 32 <br> • POS-S renal: 17 | • MSAS-SF: Past one week <br> • POS-S renal: Past one week |
| Lee & Jeon 2015 | Palliative Outcome Scale (POS) | 17 | POS: Past three days |
| Author(s), Year       | Instrument(s) used                  | Number of items                  | Recalling period of symptoms                      |
|----------------------|-------------------------------------|----------------------------------|--------------------------------------------------|
| Porter et al. 2016   | KDQOL-36                            | KDQOL-36 Symptom scale: 11       | KDQOL-36 Symptom scale: Past four weeks          |
| Meuleman et al. 2017 | Revised illness perception questionnaire (IPQ-R) | IPQ-R Illness identity scale: 14 | Not specified                                    |
| Peng et al. 2017     | KDQOL-36                            | KDQOL-36 Symptom scale: 11       | KDQOL-36 Symptom scale: Past four weeks          |

KDQOL SF 1.3: Kidney disease quality of life-short form; KDQOL-36: Kidney disease quality of life-36
## Supplementary Table 3: Evaluation of HRQoL of included studies

| Author(s), Year          | Instrument(s) used | Physical component score (minimum to maximum; mean±SD) | Mental component score (minimum to maximum; mean±SD) | Reporting problems prevalence (%) |
|--------------------------|-------------------|---------------------------------------------------------|------------------------------------------------------|----------------------------------|
| Campbell et al. 2008     | KDQOL SF 1.3      | Baseline Intervention group: 33.8±10.2                   | Baseline Intervention group: 48.5±11.9               | -                                |
|                          |                   | Control group: 34.7±10                                   | Control group: 45.3±12.5                             |                                  |
| Kumar et al. 2010        | KDQOL-36          | 37.5±11.7                                               | 50.2±10.4                                            | -                                |
| Gyamli et al. 2011       | SF-36             | 36.3±10.7                                               | 52.0±8.4                                             | -                                |
| Kosmadakis et al. 2011   | FACIT-Sp          | #                                                       | #                                                    | -                                |
| Feng et al. 2013         | SF-12             | Baseline 46.9±7.9                                        | Follow-up 49.2±6.6                                   | -                                |
| McKercher et al. 2013    | • KDQOL SF 1.3    | 37.7±10.1                                               | 50.7±9.4                                             | EQSD3L reporting problems:       |
|                          | • EQSD3L          |                                                         |                                                      | • Pain (61.2%)                    |
|                          |                   |                                                         |                                                      | • Mobility (51%)                  |
|                          |                   |                                                         |                                                      | • Usual activities (49%)          |
|                          |                   |                                                         |                                                      | • Anxiety (26.5%)                 |
|                          |                   |                                                         |                                                      | • Self-care (12%)                 |
| Salmean et al. 2013      | KDQOL-36          | Pre-test: No fibre diet 31±7.7                           | Post-test: With fibre diet 35±11.6                    | -                                |
|                          |                   | End point 47±27.1                                        |                                                      |                                  |
| de Goej et al. 2014      | SF-36             | Baseline 54.4±23                                         | End point 47±27.1                                    | -                                |
|                          |                   | End point 67.8±20.9                                       |                                                      |                                  |
| Brown et al. 2015        | SF-36             | Baseline Pre-dialysis group: 38±11                       | Baseline Pre-dialysis group: 50±10                   | -                                |
|                          |                   | Non-dialysis group: 29±8                                 | Non-dialysis group: 46±12                             |                                  |
| Lee & Jeon 2015          | SF-36v2           | 47.9±8.92                                               | 50.9±10.47                                           | -                                |
| Author(s), Year | Instrument(s) used | Physical component score (minimum to maximum; mean±SD) | Mental component score (minimum to maximum; mean±SD) | Reporting problems prevalence (%) |
|----------------|-------------------|------------------------------------------------------|------------------------------------------------------|-----------------------------------|
| Porter et al. 2016 | KDQOL-36          | 41.3±11.5                                            | 50.4±10.5                                            | -                                 |
| Meuleman et al. 2017 | SF-36             | 54.6±22.2                                            | 67.9±20.4                                            | -                                 |
| Peng et al. 2017 | KDQOL-36          | Stage 3a: 46.6±8.2                                    | Stage 3a: 51.2±8.4                                    | -                                 |
|                 |                   | Stage 3b: 44.5±9.2                                    | Stage 3b: 50.2±9.2                                    | -                                 |

*PCS/MCS score was not reported; HRQoL: Health-related quality of life; SD: Standard deviation; KDQOL SF: Kidney disease quality of life-short form; KDQOL-36: Kidney disease quality of life-36; SF-36: Short form-36; SF-12: Short form-12; SF-36v2: Short form-36 version 2; EQ5D3L: European quality of life-five dimension-three level questionnaire; FACIT-Sp: Functional Assessment of Chronic Illness Therapy-Spiritual Wellbeing; CES-D: Center for Epidemiological Studies Depression Scale; PHQ-2: Patient health questionnaire-2; PCS: Physical component score; MCS: Mental component score