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Predictors of somatic symptom persistence in patients with chronic kidney disease (SOMA.CK): study protocol for a mixed-methods cohort study

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ABSTRACT

Introduction Seven of 10 patients with non-dialysis chronic kidney disease (CKD) experience burdensome persistent somatic symptoms (PSS). Despite the high prevalence and relevance for quality of life, disease progression and mortality, the pathogenesis of PSS in CKD remains poorly understood. The SOMA.CK study aims to investigate biopsychosocial predictors and their interactions for PSS in non-dialysis CKD and to develop a multivariate prognostic prediction model for PSS in CKD.

Methods and analysis The study is a mixed-methods cohort study with assessments at baseline, 6 and 12 months. It aims to include 330 patients with CKD stages G2–4 (eGFR=15–89 mL/min/1.73 m^2). Primary outcome is the CKD-specific somatic symptom burden assessed with the CKD Symptom Burden Index. Secondary outcomes include quality of life, general somatic symptom burden and functioning. The interplay of biomedical (eg, biomarkers, epigenetics), treatment-related (eg, therapies and medication) and psychosocial variables (eg, negative affectivity, expectations) will be investigated to develop a prognostic prediction model for PSS. In an embedded mixed-methods approach, an experimental study in 100 patients using an affective picture paradigm will test the effect of negative affect induction on symptom perception. An embedded longitudinal qualitative study in 40–50 newly diagnosed patients will use thematic analysis to explore mechanisms of symptom development after receiving a CKD diagnosis. SOMA.CK is part of the interdisciplinary research unit 'Persistent SOMAtic Symptoms ACROSS Diseases'.

Ethics and dissemination The study was approved by the Ethics Committee of the Hamburg Medical Association (2020-10195-BO-ff). Findings will be disseminated through peer-reviewed publications, scientific conferences, the involvement of our patient advisory board and the lay public. Focusing on subjective symptom burden instead of objective disease markers will fundamentally broaden the understanding of PSS in CKD and pave the path for the development of mechanism-based tailored interventions.

Trial registration number ISRCTN16137374.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The prospective observational design of the SOMA.CK study allows to identify biopsychosocial risk factors and their interactions for the development of persistent somatic symptoms (PSS) in chronic kidney disease (CKD).
⇒ The mixed-methods approach complements the quantitative assessment of risk factors with experimental data on symptom perception and longitudinal qualitative data on symptom development.
⇒ As one project of the interdisciplinary research unit SOMatic symptoms ACROSS diseases, the SOMA.CK study contributes to identify disease-overarching and disease-specific biopsychosocial risk factors and mechanisms for the persistence of somatic symptoms across diseases.
⇒ Whereas the longitudinal design identifies predictors of symptom burden over time, causal conclusions cannot be drawn from this observational study.
⇒ While our focus on non-dialysis CKD stages G2–4 allows a broad view on PSS in mild to moderate CKD, the results cannot be generalised to all stages of renal diseases, patients receiving dialysis and other populations.

INTRODUCTION

Chronic kidney disease

Chronic kidney disease (CKD) is a global health burden, affecting about 8%–16% of the global population.[1 2] The definition of CKD is based on a decrease in renal function or indicators of kidney damage persisting for more than 3 months. According to the Kidney Disease Improving Global Outcomes (KDIGO), CKD is classified into five stages by the glomerular filtration rate with additional subclassification by albuminuria.[3] CKD can cause debilitating harm with progression to end-stage renal disease requiring renal replacement therapy. Disease progression depends on various factors, such as sex, age,

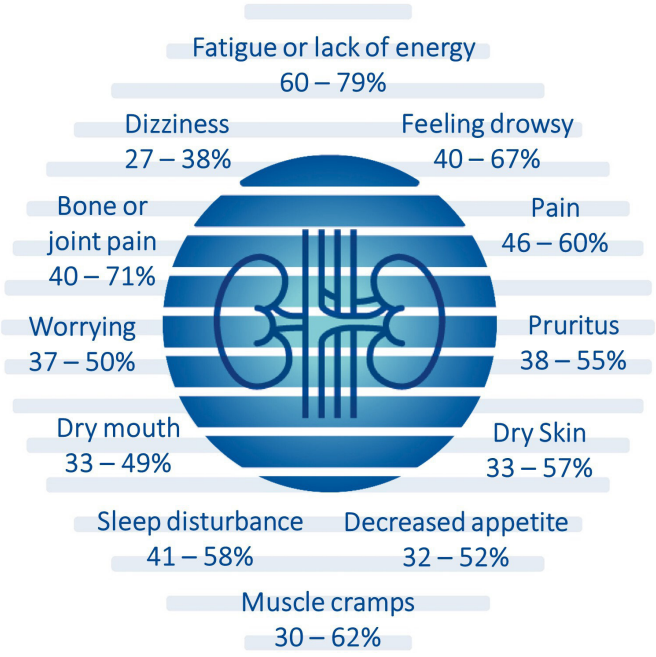

Figure 1 Most prevalent and disabling symptoms in individuals with CKD. CKD, chronic kidney disease.

ethnicity, smoking, obesity, hypertension, hyperglycaemia, cause of CKD, cardiovascular disease and other comorbid conditions.[3 4] Further, CKD strongly increases cardiovascular risk and is associated with premature mortality and poor quality of life (QoL).[5]

Somatic symptom burden in CKD

CKD is largely considered asymptomatic until later stages of renal dysfunction. However, recent evidence suggests that individuals with CKD already experience burdensome persistent somatic symptoms (PSS) in early stages, long before requiring renal replacement therapy.[4 6] The most prevalent and disabling symptoms are fatigue, sleep disturbance, bone or joint pain, frailty and pruritus (figure 1).[4 6–9] The mean number of symptoms per individual ranges from 6 to 20 across studies.[7] Patients often report disabling somatic symptoms to be the core disease burden in their lives.[10] Thus, PSS strongly predict health-related QoL, and both PSS and QoL independently predict progression to end-stage renal disease and mortality. PSS and QoL often impact the decision to start renal replacement therapy.[3 11 12] Notably, symptom burden and impairment in QoL in CKD are comparable to terminal malignant conditions.[13]

Persistent somatic symptoms

PSSs describe subjectively distressing somatic complaints, irrespective of their aetiology, that are present on most days for at least several months.[14] Somatic symptoms are highly frequent, with 80% of the general population experiencing at least one symptom during the past month.[15] PSSs are not only common in patients with CKD but frequently occur across many chronic diseases.[14]

The interdisciplinary research unit Persistent SOMAtic symptoms ACROSS diseases

The SOMA.CK study is part of the interdisciplinary research unit 'Persistent SOMAtic symptoms ACROSS diseases — from risk factors to modification' (SOMACROSS). SOMACROSS aims to identify disease-overarching and disease-specific biopsychosocial risk factors and mechanisms for the persistence of somatic symptoms across diseases.[14] Seven individual research projects investigate PSS in a variety of medical conditions, including liver disease, gastrointestinal diseases, CKD, skin diseases and somatic symptom disorder. SOMACROSS proposes a biopsychosocial 'PSS working model' as a starting point for the investigation of risk factors and aetiological mechanisms, based on the model by Henningsen *et al*.[16] All studies of SOMACROSS share a prospective design with common assessment points, core instruments and outcome variables to allow comparison and validation of results across projects and conditions.[14]

Broadening the aetiological perspective on PSS in CKD: a biopsychosocial model

The pathogenesis of PSS in CKD is still poorly understood and largely understudied. It is reasonable to assume that symptom burden is related to specific renal disease markers. However, most studies failed to show a consistent relationship,[10 17] or found only small relations between symptoms and renal disease markers in non-dialysis CKD.[4] It is only at stage 5 CKD with severely impaired kidney function that symptoms such as vomiting, pruritus or oedema clearly correlate with renal function.[17] In contrast, symptom burden seems to be high even across earlier stages of CKD,[4 10 18] with few apparent differences regarding specific symptoms between stages.[10]

Overall, the lack of a consistent relationship between disease severity and symptoms highlights the difficulty of predicting symptomatology from kidney function alone. This leads to the central question of this study: Why do some individuals with CKD experience more burdensome symptoms than others? A growing body of research across medical diseases and in somatoform or functional disorders indicates that the pathogenesis of PSS can be best explained by a biopsychosocial model.[16] Applying this perspective to CKD implies that beyond disease severity, other biomedical, treatment-related and psychosocial factors act and interact in the development of PSS. The SOMA.CK study proposes a biopsychosocial working model for somatic symptom persistence in CKD (figure 2), based on the generic working model of SOMACROSS.[14] Assuming that relations between somatic symptoms and contributing factors are complex, dynamic and unique in each individual, our model considers the following risk factors and putative mechanisms to explain how PSS evoke in CKD.

Biomedical factors: In addition to established renal disease markers, comorbid medical conditions might add up to overall symptom burden.[19] Further, two novel biomedical aspects warrant investigation as potential links

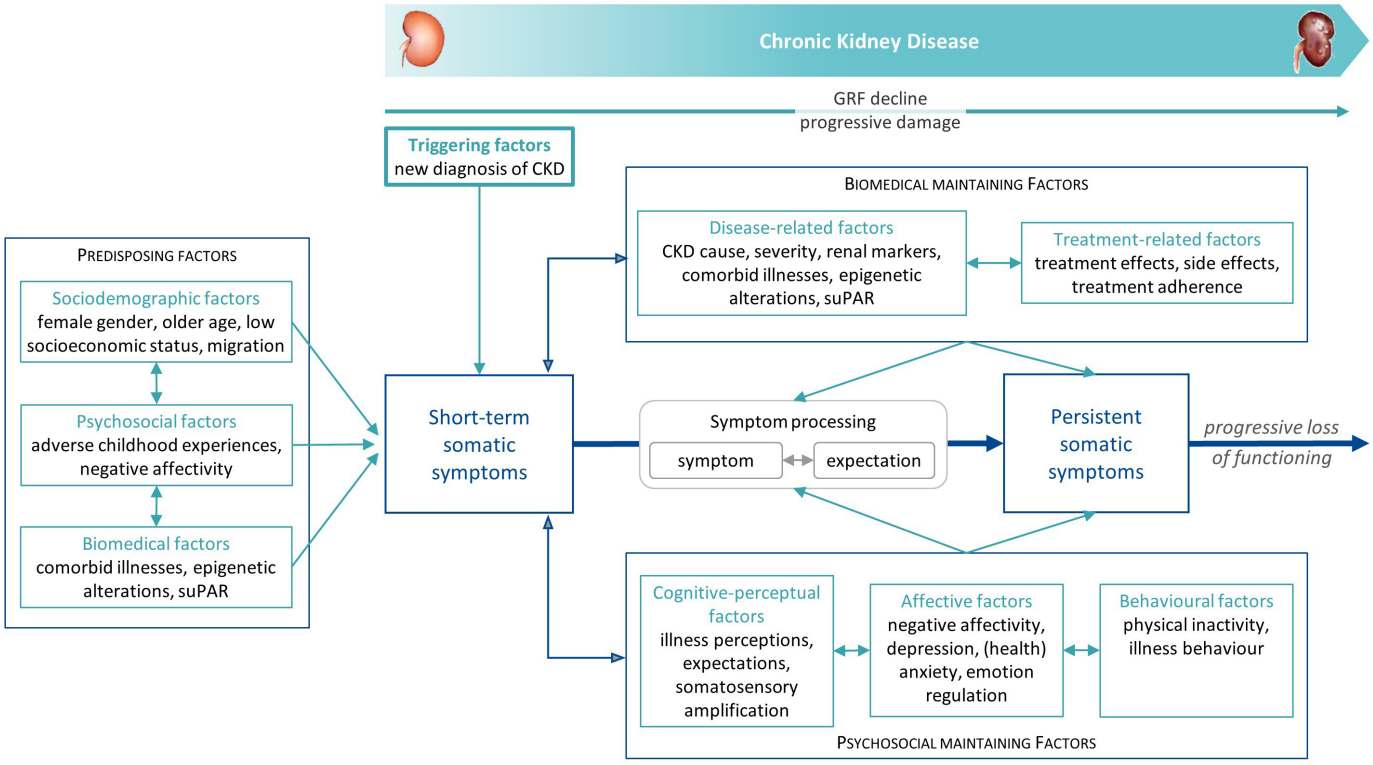

Figure 2 Biopsychosocial working model for somatic symptom persistence in chronic kidney disease (CKD). This model is based on the working model of SOMACROSS and CKD-specific evidence and assumptions. SOMACROSS, Persistent SOMAtic symptoms ACROSS diseases; suPAR, soluble urokinase-type plasminogen activator receptor.

between CKD and PSS. Epigenetic mechanisms have been proposed to determine renal programming, the development and progression of CKD.[20 21] Of note for PSS, altered DNA methylation in inflammation-related genes is associated with symptoms such as chronic pain conditions and predicts chronic postoperative pain.[22] Epigenetic mechanisms have recently been understood as 'scars' of psychosocial stress, shaping the future stress response.[23]

Recently, elevated soluble urokinase-type plasminogen activator receptor (suPAR) levels have emerged as a possible predictor of incidence, progression and mortality in CKD.[24] Given the association of suPAR with cardiovascular disease, CKD and inflammatory diseases, as well as its association with different symptoms like pain[25] or dyspnoea[26] we speculate on its contribution as a predictor of symptom burden in CKD.

Psychosocial factors are major contributors to PSS.[16] There is promising initial evidence that these factors also play a role for PSS in CKD. Potential affective factors include depression, which is consistently associated with elevated somatic symptom burden and adverse outcomes in CKD.[10 27] Negative affectivity is related to elevated symptom reporting,[28 29] and can be understood as the common denominator of (health) anxiety,[16] distress[30] and deficits in emotion regulation.[29] Illness perceptions have been related to higher symptom burden, reduced QoL and greater disease progression in CKD.[31 32] Patients' expectations regarding the anticipated course of symptoms and treatment shape symptom perception from their onset and influence treatment success through complex interactions with biological, medical and social factors.[33] Concerning behavioural factors in CKD, physical inactivity is a major contributor to reduced QoL, morbidity and mortality.[34 35] It is also a risk factor for the development of PSS[36] and might interact with renal pathophysiology and comorbid conditions in aggravating symptom burden in CKD.[34]

Of note, none of the outlined factors alone, but rather their complex biopsychosocial interaction determines individual symptom burden in CKD, as illustrated by the following two examples. First, regarding treatment-related factors,[37] burdensome side effects of drug treatments are often difficult to disentangle from general symptom burden and are fuelled by nocebo effects through negative expectations and increased interoceptive awareness.[38] Second, according to the predictive processing model,[39] symptom perception can be understood as the result of an inferential process in which the brain interprets somatosensory input in the light of 'predictions' (priors). The model suggests that the relationship between physiological dysfunction and symptom experience can be highly variable between and within individuals. Thus, symptom perception in individuals with PSS might be more influenced by priors rather than by actual somatosensory input.[28] For CKD, this could mean that symptom expectations have larger impact in early stages while kidney function and comorbidity might rather determine symptom

burden in more advanced CKD. These interactions are yet to be operationalised and investigated.

Novelty and innovation

Taken together, research on PSS in CKD has predominantly focused on symptom burden in end-stage renal disease or on single symptoms such as fatigue. It has fallen short of assessing even major psychological risk factors. Thus, PSS in CKD are largely under-recognised and understudied.[7] Despite being a major impairment for QoL, patients rarely report their symptom burden to their nephrologists.[40] Thus, physicians dramatically underestimate their patients' symptom burden.[41] Consequently, PSS in CKD are not adequately assessed and treated,[12] with focus placed on single symptoms rather than overall symptom burden.[30] These shortcomings have prompted the recent KDIGO Controversies Conference to advocate for more resources to address the complexity of somatic symptoms in CKD.[42] Only an integrated prospective investigation of biomedical, treatment-related and psychosocial factors will unravel aetiological mechanisms and identify modifiable predictors of somatic symptom persistence in early stages of CKD.

Objectives and hypotheses

The overall objective of the SOMA.CK study is to improve our understanding of how PSS in CKD develop and persist over time. We aim to achieve this goal by means of the following four objectives:

1. To investigate biopsychosocial predictors and their interactions for the development of PSS in CKD in a multivariate prognostic prediction model.
2. To identify unfavourable symptom trajectories and unravel the direction of relations between symptoms and biopsychosocial predictors over time.
3. To test in an embedded experimental study whether symptom perception in patients with CKD can be influenced by inducing negative affect through an affective picture viewing paradigm.
4. To explore mechanisms of symptom development after receiving a new CKD diagnosis with specific focus on illness and symptom perceptions, causal attributions and expectations in an embedded longitudinal qualitative study.

The following hypotheses result from the first three objectives:

Hypothesis 1: Somatic symptom burden in CKD at 12 months is predicted as a function of biomedical factors (eg, renal function, altered DNA methylation, suPAR levels), treatment-related factors (eg, side effects), psychosocial factors (eg, negative affectivity, anxiety, illness perceptions, symptom and treatment expectations, emotion regulation) and their interplay.

Hypothesis 2: Unfavourable symptom trajectories over a 12-month course are predicted by biomedical, biopsychosocial variables and their interplay.

Hypothesis 3: Inducing negative affect increases symptom perception in patients with CKD, particularly in patients with high baseline symptom burden, high trait negative affectivity, deficits in emotion regulation and low CKD disease severity.

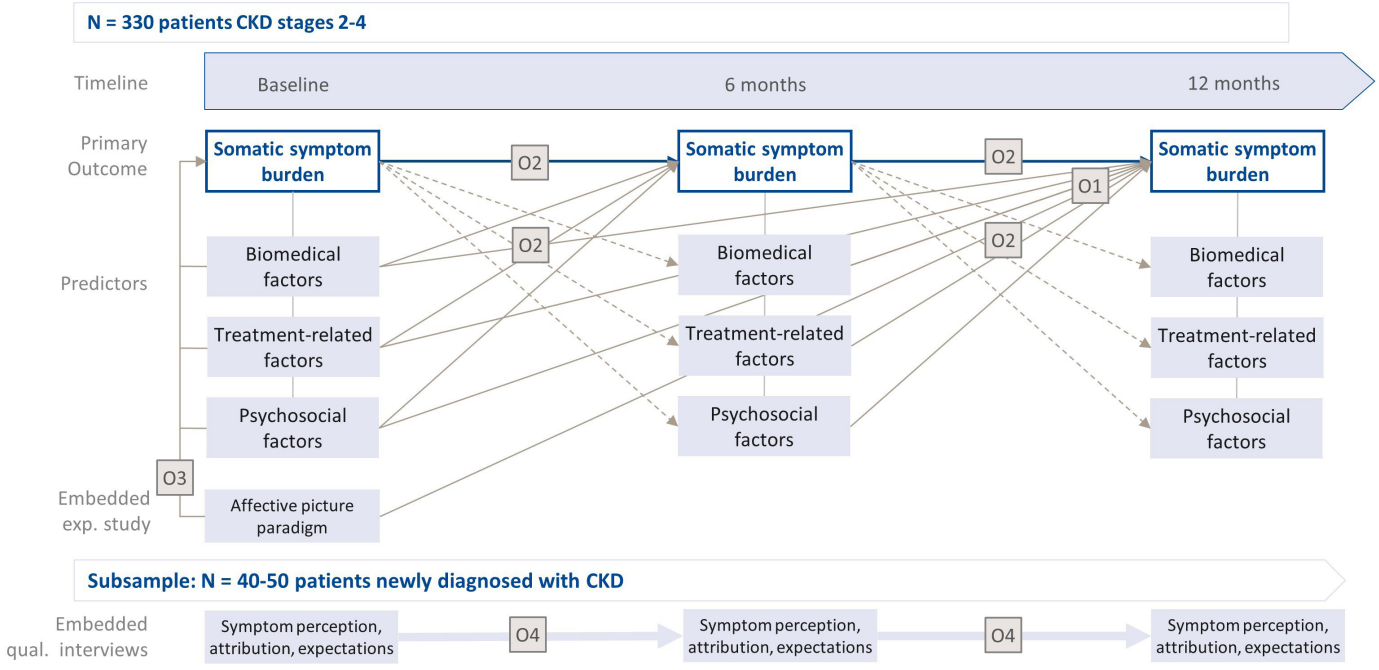

Figure 3 Study design of the prospective mixed-methods cohort study. O1: multivariate prediction of symptom burden at 12 months; O2: identification of symptom trajectories and their baseline predictors as well as relations between symptoms and biopsychosocial predictors over 6 months; O3: effect of inducing negative affect on symptom perception; O4: longitudinal qualitative exploration of mechanisms. CKD, chronic kidney disease.

METHODS AND ANALYSIS

Study design

This is a prospective mixed-methods cohort study with three assessment points at baseline, 6 and 12 months (see figure 3). The SOMA.CK study is one project of the SOMACROSS research unit (FOR 5211),[14] funded for 4 years by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG). Results will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[43] The study was prospectively registered at the ISRTCN registry (ISRCTN16137374).

Quantitative methods will be applied to answer the central research questions (objectives 1 and 2). We will embed an experimental design to investigate mechanisms of symptom perception (objective 3). In a subsample of patients newly diagnosed with CKD, a longitudinal qualitative study will deepen insights into somatic symptom development (objective 4). This mixed-methods approach allows evaluating known, quantitively assessed risk factors, while integrating new potential unknown risk factors and mechanisms from the qualitative approach.

Participants

A total of 330 adult patients with CKD stages 2–4 (estimated glomerular filtration rate (eGFR) 15–89 mL/min/1.73 m^2)[3] will be included in the study. As a subsample, 40–50 patients newly diagnosed with CKD in the past 3 months will be recruited, as the early adjustment process is particularly valuable to understand how symptoms develop.[31] Further inclusion criteria are sufficient oral and written German language proficiency to complete self-report questionnaires and interviews, and written informed consent.

Exclusion criteria are dialysis or kidney transplantation planned within the next 6 months, previous kidney transplantation, previous dialysis for more than 3 months, cognitive impairment (measured with the Mini-Mental-Status-Test),[44] life expectancy lower than 6 months, serious illness requiring immediate intervention, acute psychosis or substance abuse disorder, and acute suicidality.

Setting and study procedure

The study will be carried out at Medical School Hamburg and the III. Department of Medicine at the University Medical Center Hamburg-Eppendorf, Germany. Individuals will be recruited at four collaborating outpatient clinics in Hamburg (Nephrocare Hamburg-Altona and Hamburg-Süderelbe, Diaverum Alter Teichweg and Diaverum Schlankreye).

Eligible patients will be approached by their attending nephrologists during regular visits. The nephrologists will refer potential participants to the study staff, who will check eligibility, provide further oral and written information on the study's objectives, and obtain written informed consent. All patients will receive a financial compensation of €15–€30 for the time expenditure at each assessment point. The study staff individually coordinates all further assessments. Enrolment for the study is planned to be carried out over 12 months.

Patient and public involvement

Relevant patient organisations, namely the 'Nieren Selbsthilfe Hamburg' of the 'Bundesverband Niere e.V.' and 'PKD Cure Familiäre Zystenniere e. V.', are involved in the study. A patient advisory board has been installed consisting of 8 representatives of the patient organisations and the outpatient clinics. The patient advisory board has already been involved in the study design and development of the interview guide for the qualitative study. It will meet at least twice yearly to discuss the study's progress, results and conclusions.

Assessment and study outcomes (for objectives 1 and 2)

Assessments are carried out at baseline, after 6 and 12 months. Table 1 provides an overview of the biomedical and psychosocial predictors and the outcomes. Data will be assessed via self-report or will be extracted from the medical reports. In addition to project-specific measures, joint core instruments of SOMACROSS will be applied, including adverse childhood experiences, neuroticism, stigmatisation and diagnosis of somatic symptom disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[14]

Primary outcome

The CKD Symptom Burden Index (CKD-SBI) will be used as primary outcome measure for the CKD-specific symptom burden at 12 months.[45] The CKD-SBI covers the prevalence, distress, severity and frequency of 32 symptoms commonly occurring in CKD during the past 4 weeks on 0–10 Numeric Rating Scales (NRS). The CKD-SBI was specifically developed for non-dialysis CKD and has shown satisfactory psychometric properties.[45 46]

Secondary outcomes

CKD-related QoL will be measured using the Kidney Disease Quality of Life 36-Item Short-Form Survey,[47] which includes the general QoL scale SF-12 as generic core and three kidney disease-specific scales: burden (4 items), symptoms and problems (12 items), and effects of kidney disease (8 items). In accordance with the core outcome measures of SOMACROSS, further secondary outcomes include general somatic symptom burden (Patient Health Questionnaire-15, PHQ-15), symptom intensity and interference (NRS), and symptom-related disability (Pain Disability Index).

Embedded experimental study (objective 3)

To investigate the impact of priors on symptom perception according to the predictive processing model,[28 39] the affective picture paradigm[48] will be used to test whether symptom perception in patients with CKD can be influenced by inducing negative affect. The paradigm uses pictures of varying affective content from the International Affective Picture System.[49] It consistently elicits higher symptom reporting in patients with functional

Table 1 Outcomes and biomedical and psychosocial predictors of the SOMA.CK study, based on the joint core instruments of SOMACROSS[14]

Domain	Construct	Instrument	Assessment months 0	6	12
Outcome variables					
Primary outcome: somatic symptom burden	CKD-specific somatic symptom burden	CKD Symptom Burden Index (CKD-SBI)	X	X	X
Secondary outcomes: functioning and general symptoms	CKD-related quality of life General somatic symptom burden Symptom intensity/interference Symptom related disability Health-related quality of life	Kidney Disease Quality of Life 36 (KDQOL-36) Patient Health Questionnaire-15 (PHQ-15) EURONET-SOMA Numeric Rating Scale Pain Disability Index - adapted (PDI) Short Form Health Survey (SF-12)	X	X	X
Diagnosis of somatic symptom disorder	Diagnostic classification according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)	Structured Clinical Interview for DSM-5 (SCID)	X		X
Predictor variables					
Sociodemographic factors	Gender, age, nationality, marital status, migration status, current housing situation, insurance, education, occupational status, smoking, healthcare utilisation	Single items	X		
Biomedical and disease-related variables					
Renal disease variables	CKD cause, duration, stage Prior and current renal disease Family history of kidney diseases	Patient record	X		X
Comorbidity	(Prior) Comorbid illnesses	Self-Administered Comorbidity Questionnaire (SCQ)	X		X
Biomedical factors	Vitals	Pulse, blood pressure (according to ESC guidelines,[55] respiratory rate, oxygen saturation)	X	X	X
	Body measures	Weight, height, waist size, hip size	X	X	X
	Inflammatory markers	C reactive protein, interleukin 6, tumour necrosis factor α	X		
	General markers	Blood count, albumin, sodium, potassium, calcium, phosphorus, soluble urokinase-type plasminogen activator receptor (suPAR)	X	X	X
	Renal markers	Creatinine, venous blood gas analysis	X	X	X
	Urine analysis	Albuminuria, proteinuria	X	X	X
	Epigenetic analyses	DNA methylation	X		
	Stool analyses	Microbiome analyses	X		
Treatment-related variables					
Concurrent treatments	Treatments and medication	Patient record	X		X
	Treatment experiences	Numeric Rating Scale			
	Side effects	Numeric Rating Scale			
	Treatment Adherence	Medication Adherence Rating Scale (MARS-D)			
Psychosocial variables					
Cognitive-perceptual factors	Somatosensory amplification	Somatosensory Amplification Scale (SSAS)	X	X	X
	Catastrophising	Coping Strategies Questionnaire-Catastrophising Subscale (CSQ-CAT)	X	X	X
	Illness perceptions	Brief Illness Perception Questionnaire (B-IPQ adapt)	X	X	X
	Treatment expectations	Treatment Expectation Questionnaire (TEX-Q)	X	X	X
	Expectations of symptom severity and coping	Numeric Rating Scales	X	X	X
	Illness-related worries	Whiteley-Index (WI-7)	X	X	X
		Somatic Symptom Disorder – B Criteria Scale (SSD-12)	X	X	X
Affective factors	Negative affectivity	Positive and Negative Affect Schedule (PANAS)	X	X	X
	Anxiety	Generalised Anxiety Disorder-7 (GAD-7)	X	X	X
	Health anxiety	SSD-12	X	X	X
	Depression	Patient Health Questionnaire-9 (PHQ-9)	X	X	X
	Alexithymia	Toronto Alexithymia Scale (TAS-20)	X		
	Emotion regulation	Emotion Regulation Questionnaire (ERQ)	X		

Continued

Table 1 Continued

Domain	Construct	Instrument	Assessment months 0	6	12
Behavioural factors	Physical inactivity /avoidance	International Physical Activity Questionnaire (IPAQ-SF)	X	X	X
	Illness behaviour	SSD-12	X	X	X
Psychosocial factors	Adverse childhood experiences	Adverse Childhood Experiences Questionnaire (ACE-D)	X		
	Personality: neuroticism	Big Five Inventory –10 (BFI-10)	X		
	Life stressors	Perceived Stress Scale-10 (PSS-10)	X		
	Perceived stigmatisation	Single items	X		

CKD, chronic kidney disease; SOMACROSS, Persistent SOMAtic Symptoms ACROSS Diseases.

disorders and high habitual symptom reporters compared with healthy controls.[48 50] Furthermore, we will test whether symptom perception is moderated by general symptom burden, negative affectivity, emotion regulation and disease severity.

We aim to include a consecutive subsample of 100 patients, including 25 patients with low and 25 patients with high habitual symptoms (PHQ-15 <5 vs PHQ-15 ≥10, roughly corresponding to the lower and upper quartile). This sample should allow identifying the expected medium-to-large differences between low and high habitual symptom reporters (f=0.30),[48 51] assuming α=0.05 and 1–β =0.95. After reporting baseline symptoms, participants will watch three series of 20 pictures with either neutral, positive, or negative affective content, but similar valence and arousal based on normative data.

After each series, participants will rate their state somatic symptoms as primary outcome, using a validated 10-item symptom checklist.[48 50] As manipulation check, affective state (valence, arousal and control) using the Self-Assessment Manikin system, and state positive and negative affect using the Positive and Negative Affect Schedule will be assessed.

Differences in symptom reporting between high and low symptom groups will be tested by mixed model analyses with picture category as the within-subject factor and group as between-subject factor; moderators will be analysed within the high baseline symptoms group.

Embedded qualitative study (objective 4)

Our aim to investigate individual mechanisms of symptom development after new diagnosis of CKD is best answered by means of a longitudinal qualitative research approach. Longitudinal qualitative research provides a valuable approach for an in-depth exploration of change in symptoms over time, and their causes and consequences.

Newly diagnosed patients will be invited to participate in individual semistructured interviews led by trained researchers at baseline, 6 and 12 months. Topics will include individual perceptions of CKD and its symptoms during the first year of living with CKD, causal attributions of symptoms, perceived coping abilities, stigmatisation, role of the treatment, expectations of symptoms and treatment, fear of disease progression and informational needs. A prior patient focus group conducted with members of the patient advisory board informed the interview guide. A sample of 40–50 newly diagnosed patients will be included, using purposeful sampling to include a diverse and informationally rich sample. The exact sample size will depend on the theoretical saturation of the research question.[52]

The interviews will be audiorecorded and transcribed verbatim. To ensure a high interpretative rigour within our mixed–methods design, we will develop, perform and analyse the qualitative data within an interdisciplinary team of psychosomatic and nephrological experts, critically reflecting our results by seeking feedback from the patient advisory board and external experts. Thematic content analysis,[53] supported by MAXQDA software, will be used deductively to explore the individual relevance of known mechanisms, and also inductively to search for new putative mechanisms. This allows to integrate additional risk factors into existing knowledge and to generate new hypotheses of aetiological mechanisms.

Sample size estimation

As empirical data on the prediction of PSS in CKD is lacking and does not allow for concise power estimation, our estimated sample size is based on considerations of feasibility and statistical considerations of the applied analyses. Regarding feasibility, based on the annual number of approximately 5000 patients of our collaborating outpatient clinics, conservatively assuming a contact rate of 15% and a participation rate of 50%, we aim to include 330 patients (see figure 4). Assuming an attrition of 14%–15% at each assessment point, our target sample with available outcome data at 12 months will be 240 patients. Regarding statistical considerations of our prediction model, 240 patients will provide reliable estimates aiming for a final model with approx. 8 predictors, following the suggested event rate (high somatic symptom burden in 30% of our sample) of ≥10 per variable. The sample size also provides sufficient power for epigenetic and biomarker analyses.[54]

Biomarker and epigenetic analyses

Core laboratory analyses will be performed at the different assessment time points. These include blood count, albumin, creatinine, sodium, potassium, calcium, phosphorus, C reactive protein, interleukin 6, venous

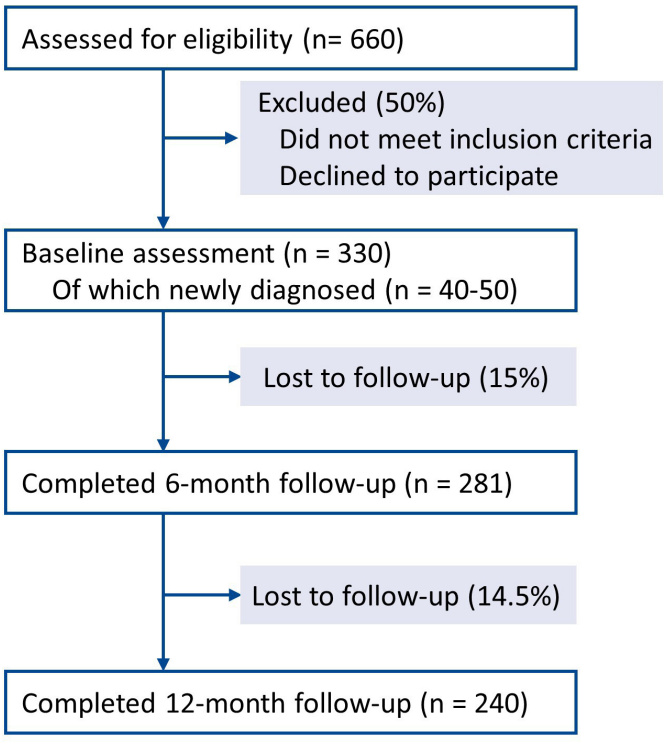

Figure 4 Calculation of patient flow.

blood gas analysis as well as albuminuria and proteinuria. Other core laboratory parameters will be adopted from the patients' charts. Further, whole EDTA-blood, serum, urine and stool will be collected at the different assessment points and stored in the SOMACROSS biobank. Tumour necrosis factor alpha and suPAR will be measured from the stored serum samples.

Epigenetic analyses will be performed on DNA extracted from stored whole EDTA blood. We will primarily analyse epigenetic alterations regarding the prediction of symptom burden. We will focus on DNA methylation and potentially further relevant analyses. Epigenome-wide association studies will be performed using linear mixed models. Moreover, we will analyse and cross-validate epigenetic mechanisms in pilot samples of n=20 patients per diagnosis across SOMACROSS.

The remaining biobank material is intended to investigate other biomarkers or to perform broad analyses such as Omics approaches as indicated.

Data analysis

A longitudinal structural equation model approach will be used to predict change in CKD-specific somatic symptom burden over 12 months (H1), based on biopsychosocial predictors and their interactions. The large number of potential predictor variables will be handled by a priori selection of candidate predictors after redundancy analysis. The analyses will be repeated for the secondary outcomes.

To identify distinct longitudinal trajectories of somatic symptoms (H2), latent class growth analysis will be used to classify intraindividual symptom courses across the three time points into distinct trajectories according to the best model fit. Multiple logistic regression models will be calculated to predict the probability of belonging to a certain symptom trajectory, based on baseline biopsychosocial predictors. The direction of relations between symptom change and biopsychosocial predictors over the 12-month course (H2) will be analysed using cross-lagged panel analysis.

Statistical analyses will be carried out using SPSS, AMOS, Mplus and R software. Missing data will be imputed if more than 5% of the data are missing. The number of imputations will be chosen depending on the proportion of missing data.

The data from the SOMA.CK study will be included in the joint cross-project evaluation of SOMACROSS in order to develop an overarching conceptual model for the persistence of somatic symptoms across diseases.[14]

ETHICS AND DISSEMINATION

Ethical approval

The study was approved by the Ethics Committee of the Medical Chamber Hamburg on 25 January 2021 (reference number 2020-10195-BO-ff). The study will be conducted in accordance with the WMA Helsinki Declaration of Helsinki, the guidelines for Good Clinical Practices, and national and local laws.

Risk evaluation and stopping rules

This is a non-interventional cohort study with minimal adverse event risk due to study participation. Adverse events not related to the study may occur anyhow. Patients may develop severe somatic or psychiatric complications. Referral to immediate medical treatment will be initiated when needed.

Patients at risk to commit suicide may be identified either during the interview or through the PHQ-9 questionnaire. In case suicidal ideation is endorsed, the study staff is trained to follow a pre-defined algorithm defining further steps, that is, the diagnostic assessment of suicide risk, the contact with senior licensed psychotherapists (MCS-M and BJ), suicide prevention hotline numbers, and referral to psychiatric treatment facilities.

The study procedure does not interfere in any way with the usual care provided in the outpatient clinics. In order to avoid influences of the subject under study, no feedback regarding the patients' symptomatology will be provided to the treating physicians during the study. In case that laboratory analyses reveal incidental findings (eg, substantial worsening of kidney function), participants will be immediately informed about the results. Any participant who is contacted by the study team or receives psychosocial support and, thus, receives additional attention, will be omitted from the primary analysis. If study participants do not fulfil the inclusion criteria at the follow-up assessments, for example, due to decline in cognitive function, the participant will be excluded from further assessments and only available data will be analysed.

Dissemination and data sharing

In accordance with the ethics committee approval and the German Research Foundation (DFG) guidelines for the handling of research data, deidentified quantitative individual patient data will be made publicly available. Data sharing will follow the FAIR Data Principles (Findable, Accessible, Interoperable and Reusable). According to the WHO Statement on Public Disclosure of Clinical Trials, the main findings will be submitted for publication in a peer-reviewed journal within 12 months of study completion and will be made publicly available in the clinical trial registry. In addition, we will communicate scientific results in lay language via press releases, social media and patient forums.

CONCLUSION

Recent research suggests the high prevalence and relevance of PSS in non-dialysis CKD.[4 6–9] Yet, the determinants of symptom burden in CKD remain yet to be understood. Therefore, the SOMA.CK study aims to develop a biopsychosocial prediction model for PSS in CKD and to identify predictors of unfavourable symptom trajectories. Applying and adapting the biopsychosocial SOMACROSS working model[14] to predict symptom burden in CKD will allow us to determine the relative impact of risk factors, include promising, yet unexplored variables and investigate putative interactions in the development and maintenance of PSS in CKD. Distinguishing and predicting unfavourable symptom trajectories will identify individuals at risk of PSS who might benefit from early interventions. In sum, focusing on subjective somatic symptom burden instead of objective disease markers in an interdisciplinary team of clinicians, bioscientists and psychometricians will fundamentally broaden our knowledge on PSS in CKD.

The adopted mixed-methods approach, integrating all perspectives of the prospective study and embedded experimental and qualitative exploration of risk factors, will shed light on symptom development after diagnosis and on unexplored aetiological mechanisms. The experimental study will clarify the role of negative affectivity for symptom perception. The results may be relevant for other chronic symptomatic diseases. The longitudinal qualitative study will deepen our understanding of individual symptom development after a new diagnosis, and might identify new putative risk factors.

Taken together, this forms the basis for investigating new mechanisms of symptom development and maintenance in CKD and across other diseases investigated in SOMACROSS. Our improved understanding of (modifiable) risk factors and mechanisms will be the basis for developing mechanism-based, tailored interventions that aim to reduce symptom burden, thus contributing to a higher QoL in individuals with CKD.

With regard to the aims of the SOMACROSS research unit, the SOMA.CK study will contribute to unravelling the relative contribution of generic versus disease-specific mechanisms in the development and maintenance of PSS across diseases.[14] Our specific focus on epigenetic mechanisms across SOMACROSS will provide the basis for further exploration of epigenetic mechanisms in PSS. Thus, the SOMA.CK study will contribute to the overall aim of SOMACROSS to develop a disease-overarching multivariable prediction model for PSS and to inform the development of mechanism-based, tailored interventions in the future.

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REFERENCES

1 Hill NR, Fatoba ST, Oke JL, *et al*. Global prevalence of chronic kidney disease - A systematic review and meta-analysis. *PLoS One* 2016;11:e0158765.
2 Bikbov B, Purcell CA, Levey AS, *et al*. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the global burden of disease study 2017. *Lancet* 2020;395:709–33.
3 KDIGO. Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013;3.
4 Brown SA, Tyrer FC, Clarke AL, *et al*. Symptom burden in patients with chronic kidney disease not requiring renal replacement therapy. *Clin Kidney J* 2017;10:788–96.
5 Go AS, Chertow GM, Fan D, *et al*. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296–305.
6 Fletcher BR, Damery S, Aiyegbusi OL, *et al*. Symptom burden and health-related quality of life in chronic kidney disease: a global systematic review and meta-analysis. *PLoS Med* 2022;19:e1003954.
7 Almutary H, Bonner A, Douglas C. Symptom burden in chronic kidney disease: a review of recent literature. *J Ren Care* 2013;39:140–50.
8 Davison SN, Rathwell S, Ghosh S, *et al*. The prevalence and severity of chronic pain in patients with chronic kidney disease: a systematic review and meta-analysis. *Can J Kidney Health Dis* 2021;8:2054358121993995.
9 Wilkinson TJ, Nixon DGD, Palmer J, *et al*. Differences in physical symptoms between those with and without kidney disease: a comparative study across disease stages in a UK population. *BMC Nephrol* 2021;22:147.
10 Abdel-Kader K, Unruh ML, Weisbord SD. Symptom burden, depression, and quality of life in chronic and end-stage kidney disease. *Clin J Am Soc Nephrol* 2009;4:1057–64.
11 de Goeij MCM, Ocak G, Rotmans JI, *et al*. Course of symptoms and health-related quality of life during specialized pre-dialysis care. *PLoS One* 2014;9:e93069.
12 Yapa HE, Purtell L, Chambers S, *et al*. The relationship between chronic kidney disease, symptoms and health-related quality of life: a systematic review. *J Ren Care* 2020;46:74–84.
13 Jhamb M, Abdel-Kader K, Yabes J, *et al*. Comparison of fatigue, pain, and depression in patients with advanced kidney disease and cancer - symptom burden and clusters. *J Pain Symptom Manage* 2019;57:566–75.
14 Löwe B, Andresen V, Van den Bergh O, *et al*. Persistent SOMAtic symptoms ACROSS diseases - from risk factors to modification: scientific framework and overarching protocol of the interdisciplinary SOMACROSS research unit (RU 5211). *BMJ Open* 2022;12:e057596.
15 Hinz A, Ernst J, Glaesmer H, *et al*. Frequency of somatic symptoms in the general population: normative values for the Patient Health Questionnaire-15 (PHQ-15). *J Psychosom Res* 2017;96:27–31.
16 Henningsen P, Zipfel S, Sattel H, *et al*. Management of functional somatic syndromes and bodily distress. *Psychother Psychosom* 2018;87:12–31.
17 Kumar S, Joshi R, Joge V. Do clinical symptoms and signs predict reduced renal function among hospitalized adults? *Ann Med Health Sci Res* 2013;3:492–7.
18 Almutary H, Bonner A, Douglas C. Which patients with chronic kidney disease have the greatest symptom burden? A comparative study of advanced CKD stage and dialysis modality. *J Ren Care* 2016;42:73–82.
19 Senanayake S, Gunawardena N, Palihawadana P, *et al*. Symptom burden in chronic kidney disease; a population based cross sectional study. *BMC Nephrol* 2017;18:228.
20 Wanner N, Bechtel-Walz W. Epigenetics of kidney disease. *Cell Tissue Res* 2017;369:75–92.
21 Huber TB, Holthofer H. From genetics to personalized nephrology: kidney research at a tipping point. *Cell Tissue Res* 2017;369:1–4.
22 Polli A, Godderis L, Ghosh M, *et al*. Epigenetic and miRNA expression changes in people with pain: a systematic review. *J Pain* 2020;21:763–80.
23 Schiele MA, Gottschalk MG, Domschke K. The applied implications of epigenetics in anxiety, affective and stress-related disorders - A review and synthesis on psychosocial stress, psychotherapy and prevention. *Clin Psychol Rev* 2020;77:101830.
24 Hayek SS, Sever S, Ko Y-A, *et al*. Soluble urokinase receptor and chronic kidney disease. *N Engl J Med* 2015;373:1916–25.
25 Yılmaz N, Yılmaz M, Sirin B, *et al*. The relationship between levels of plasma-soluble urokinase plasminogen activator receptor (suPAR) and presence of migraine attack and aura. *J Recept Signal Transduct Res* 2017;37:447–52.
26 Böcskei RM, Benczúr B, Losonczy G, *et al*. Soluble urokinase-type plasminogen activator receptor and arterial stiffness in patients with COPD. *Lung* 2019;197:189–97.
27 Liu M, Zhang Y, Yang S, *et al*. Bidirectional relations between depression symptoms and chronic kidney disease. *J Affect Disord* 2022;311:224–30.
28 Henningsen P, Gündel H, Kop WJ, *et al*. Persistent physical symptoms as perceptual dysregulation: a neuropsychobehavioral model and its clinical implications. *Psychosom Med* 2018;80:422–31.
29 Rief W, Martin A. How to use the new DSM-5 somatic symptom disorder diagnosis in research and practice: a critical evaluation and a proposal for modifications. *Annu Rev Clin Psychol* 2014;10:339–67.
30 Almutary H, Douglas C, Bonner A. Towards a symptom cluster model in chronic kidney disease: A structural equation approach. *J Adv Nurs* 2017;73:2450–61.
31 Clarke AL, Yates T, Smith AC, *et al*. Patient's perceptions of chronic kidney disease and their association with psychosocial and clinical outcomes: a narrative review. *Clin Kidney J* 2016;9:494–502.
32 Lin C-C, Chen M-C, Hsieh H-F, *et al*. Illness representations and coping processes of Taiwanese patients with early-stage chronic kidney disease. *J Nurs Res* 2013;21:120–8.
33 Laferton JAC, Kube T, Salzmann S, *et al*. Patients' expectations regarding medical treatment: a critical review of concepts and their assessment. *Front Psychol* 2017;8:233.
34 Zelle DM, Klaassen G, van Adrichem E, *et al*. Physical inactivity: a risk factor and target for intervention in renal care. *Nat Rev Nephrol* 2017;13:152–68.
35 Magadi W, Lightfoot CJ, Memory KE, *et al*. Patient activation and its association with symptom burden and quality of life across the spectrum of chronic kidney disease stages in England. *BMC Nephrol* 2022;23:45.
36 Claassen-van Dessel N, van der Wouden JC, Twisk JWR, *et al*. Predicting the course of persistent physical symptoms: development and internal validation of prediction models for symptom severity and functional status during 2 years of follow-up. *J Psychosom Res* 2018;108:1–13.
37 Burnier M, Pruijm M, Wuerzner G, *et al*. Drug adherence in chronic kidney diseases and dialysis. *Nephrol Dial Transplant* 2015;30:39–44.
38 Barsky AJ, Saintfort R, Rogers MP, *et al*. Nonspecific medication side effects and the nocebo phenomenon. *JAMA* 2002;287:622–7.
39 Van den Bergh O, Witthöft M, Petersen S, *et al*. Symptoms and the body: taking the inferential leap. *Neurosci Biobehav Rev* 2017;74:185–203.
40 Pugh-Clarke K, Read SC, Sim J. Symptom experience in non-dialysis-dependent chronic kidney disease: a qualitative descriptive study. *J Ren Care* 2017;43:197–208.
41 Weisbord SD, Fried LF, Mor MK, *et al*. Renal provider recognition of symptoms in patients on maintenance hemodialysis. *Clin J Am Soc Nephrol* 2007;2:960–7.
42 Davison SN, Levin A, Moss AH, *et al*. Executive summary of the KDIGO controversies conference on supportive care in chronic kidney disease: developing a roadmap to improving quality care. *Kidney Int* 2015;88:447–59.
43 von Elm E, Altman DG, Egger M, *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007;147:573–7.
44 Kessler J, Markowitsch H, Denzler P. Mini-Mental-Status-Test. Weinheim: Beltz Deutsche Fassung; 1990.
45 Almutary H, Bonner A, Douglas C. Arabic translation, adaptation and modification of the dialysis symptom index for chronic kidney disease stages four and five. *BMC Nephrol* 2015;16:36.
46 Aiyegbusi OL, Kyte D, Cockwell P, *et al*. Measurement properties of patient-reported outcome measures (PROMs) used in adult patients with chronic kidney disease: a systematic review. *PLoS One* 2017;12:e0179733.
47 RAND. Kidney disease quality of life instrument (KDQOL); 2000.
48 Bogaerts K, Janssens T, De Peuter S, *et al*. Negative affective pictures can elicit physical symptoms in high habitual symptom reporters. *Psychol Health* 2010;25:685–98.
49 Lang P, Bradley MM. The International affective picture system (IAPs) in the study of emotion and attention. *Handbook of emotion elicitation and assessment* 2007;29:70–3.
50 Van Den Houte M, Bogaerts K, Van Diest I, *et al*. Inducing somatic symptoms in functional syndrome patients: effects of manipulating state negative affect. *Psychosom Med* 2017;79:1000–7.
51 Bogaerts K, Rayen L, Lavrysen A, *et al*. Unraveling the relationship between trait negative affectivity and habitual symptom reporting. *PLoS One* 2015;10:e0115748.

52 van Rijnsoever FJ. (I Can't Get No) Saturation: A simulation and guidelines for sample sizes in qualitative research. *PLoS One* 2017;12:e0181689.
53 Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol* 2006;3:77–101.
54 Tsai P-C, Bell JT. Power and sample size estimation for epigenome-wide association scans to detect differential DNA methylation. *Int J Epidemiol* 2015;44:1429–41.
55 Williams B, Mancia G, Spiering W, *et al*. 2018 ESC/ESH guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of cardiology (ESC) and the European Society of hypertension (ESH). *Eur Heart J* 2018;39:3021–104.