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Reducing fatigue in kidney patients: evaluation of a computer-based cognitive bias modification treatment

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Abstract

Background: The number of people with chronic kidney disease (CKD) is growing annually with many receiving hemodialysis to treat their condition. Among kidney patients fatigue is a highly prevalent symptom affecting 60-97% who receive hemodialysis. Despite the high prevalence of fatigue, there is no targeted medical treatment available. However, cognitive biases, such as attentional and self-identity bias, seem to play a role in the development and perpetuation of fatigue. Hence, cognitive bias modification (CBM) can be used to modify those biases. A modified version of the Implicit Association Task (IAT) was used to target self-identity bias and the Visual Probe Task (VPT) was used to target attentional bias. Since the role of CBM in treating fatigue in renal patients is not yet researched, the aim of this study was to investigate the role of CBM on cognitive biases, as well as on secondary outcomes such as fatigue and all-or-nothing behaviour. Moreover, the conditions under which CBM is most effective, such as the treatment dose, were analysed.

Methods: In a single-case series experimental design the hypotheses were examined. A sample of 24 dialysis and pre-dialysis patients participated in the 14-days CBM training and answered questionnaires that measured cognitive biases as well as symptoms and behaviour before, during and after treatment.

Results: The results indicate significant reductions in attentional as well as self-identity biases after participating in CBM training. Analyses examining the optimal dose, effects of bias strength at baseline measure, symptom change and correlation of bias with all-or-nothing and avoidance behaviours at baseline measure were all found to be non-significant. Therefore, the results provide evidence for the effectiveness of CBM in modifying cognitive biases but cannot yet support the role of CBM in targeting secondary outcomes, such as fatigue.

Conclusion: Renal patients who undergo CBM treatment show significantly reduced attentional and self-identity bias. However, the role of cognitive biases remains unclear since the treatment did not seem to influence subjective levels of fatigue or fatigue-related behaviours. Hence, further research is needed to investigate the role of cognitive biases in renal patients. Future research should be directed at interventions that include a larger sample size, a longer follow-up period and a placebo group.

Keywords: cognitive biases, CBM, fatigue, renal patients, hemodialysis

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Introduction

"I am too tired to do that!" This is something the majority of people may think from time to time, for instance after a night without much sleep or when having the flu and therefore feeling low in energy. However, a small part of the population feels like that every day. Approximately 70% of patients with renal disease, namely 3 million people globally, are receiving hemodialysis to treat their condition with an annual growth of 5-6% (Ravani et al., 2017; Salehi et al., 2020). Fatigue is a highly prevalent symptom among kidney patients affecting 60-97% who receive hemodialysis (Ju et al., 2018) and persists even in pre-dialysis patients (Picariello et al., 2016). It is characterized by feeling tired, low in energy and weak (Salehi et al., 2020). Hemodialysis patients who suffer from fatigue report a decreased quality of life due to not being able to work or participate in social or leisure activities. As a consequence, they experience symptoms of depression and a decreased mental health (Ju et al., 2018; Picariello et al., 2016). Next to the psychological effects, fatigue in hemodialysis patients is associated with several somatic symptoms, such as muscle, bone or joint pain, sleep disturbances and shortness of breath (Bossola et al., 2018).

Despite the high prevalence of fatigue in renal patients, there is no targeted medical treatment available and patients are left with complementary non-pharmacological interventions (Karadag & Samancioglu Baglama, 2019). Examples are interventions targeting behaviour, such as scheduling regular exercise for the patients (Salehi et al., 2020) or Cognitive Behavioural Therapy (CBT), which shows promising evidence but has a low uptake due to the already high treatment burden of hemodialysis patients (Picariello et al., 2020). The aforementioned interventions are mainly targeting cognitions and behaviour. However, there is a growing body of evidence that unconscious or automatic processes play an important part in perpetuating fatigue. Patients with a chronic fatigue syndrome (CFS) often show an attentional bias for fatigue-related words (Hughes et al., 2017). This increased focusing on symptoms has been shown to maintain them (Hughes et al., 2016). Next to the attentional bias, CFS patients were also found to have an interpretive bias towards interpreting ambiguous information in a somatic way (Hughes et al., 2017). These biases start a vicious cycle of always attending to bodily symptoms and interpreting them as sign of fatigue, perceiving oneself as very fatigued and consequently checking oneself even more for fatigue symptoms. Therefore, interpretation and attention are two crucial factors in the development and maintenance of CFS (Hughes et al., 2016).

This study aims to investigate whether computer-mediated techniques, such as Cognitive Bias Modification (CBM), can modify automatic cognitive processes such as fatigue-related biases and thereby decrease fatigue in renal patients. The effectiveness of the new CBM intervention, 'VitalMe', in reducing cognitive biases as well as reducing all-or-nothing and avoidance behaviour and subjective fatigue will be assessed. Based on previous research it is assumed that a CBM intervention can reduce the attentional as well as the self-identity bias renal patients have with regard to fatigue. As a consequence of a CBM intervention and its supposed influence on cognitive biases, it is assumed that patients will report a reduced feeling of fatigue and reduced behavioural patterns, such as avoidance and all-or-nothing behaviour. Hence, the results of this study might offer new insights into an alternative treatment method than medical or traditional psychosocial interventions that also takes the psychosomatic component of fatigue in renal patients at an implicit level into account. In the following, the most important variables for this study are defined.

Cognitive biases

In order to decrease fatigue-related complaints in kidney patients, it is crucial to understand what contributes to the development and especially the perpetuation of fatigue symptoms. Previous research found that people process information not only consciously (explicit), but also unconsciously or automatic (implicit) (Back et al., 2009). According to the reflective-impulsive model (RIM), impulsive processes are triggered by outside cues that lead to the automatic activation of schemata in an associative network (Back et al., 2009). According to the multifactorial cognitive behavioural model of Harvey & Wessely (2009), the development of fatigue is linked to several predisposing, precipitating and perpetuating factors. Hughes et al. (2016) state that a crucial predisposing and perpetuating factor of fatigue are cognitive biases, which lead for instance to symptom focusing, what perpetuates fatigue.

There seem to be two important cognitive biases in kidney patients suffering from fatigue: First, an attentional bias where patients are unconsciously preoccupied with symptoms of fatigue and fatigue-related cues. Second, it is suspected that kidney patients who suffer from fatigue developed a self-identity bias what entails that patients start to perceive fatigue as a part of their identity. Consequently, this might unconsciously provoke fatigue-related behaviour, what worsens fatigue as a symptom. Hence, cognitive biases in fatigue might play a dual role: First, directly, by altering the experience of fatigue by increasing perceived severity and frequency. Second, indirectly, by mitigating behaviours that contribute to the experience of fatigue, resulting in self-imposed limitations and an actual decrease of physical capacity (Wolbers et al., 2021). In case of fatigue, this may include avoidance or 'all-or-nothing' behaviour (Chilcot et al., 2016). These maladaptive behaviour patterns can ultimately result in a vicious cycle that may even increase the severity of symptoms (Chilcot et al., 2016). For instance, in a study with chronic pain patients it was found that the self-concept is linked to pain severity, as seeing pain as part of the self was linked to more severe pain (Reed et al., 2021).

According to Cunningham & Turk (2017) the attention directed at fatigue-related cues increases even more since signals that are considered as relevant to the self are attended with priority. Therefore, individuals show a quicker response to fatigue-cues when they identify oneself with fatigue (Cunningham & Turk, 2017). Hence, the development of a self-identity bias towards fatigue is likely to increase the attentional bias towards fatigue-related cues even more. This raises the question to what extent the concept of an attentional and a self-identity bias overlap since literature suggests that both result in a heightened attention and altered behaviour.

Cognitive bias modification

CBM focuses on the modification of target cognitive bias by exposing participants to a task where they have to respond in a repetitive manner contrary to their own initial tendencies, leading to an implicit manifestation of the favoured response (Cristea et al., 2015). In order to target attentional biases, the visual probe task (VPT), which is a form of CBM, is often used to modify the individuals' selective attention. Originally, the VPT is used to measure attentional biases. Here, a visual probe (e.g. a dot or a fixation cross) appears on the screen for a pre-determined period of time. Afterwards, two stimuli, whereby one is the threatening (in this case a fatigue-related stimulus) and one a neutral stimulus, are presented simultaneously for a pre-determined time. Lastly, the visual probe appears either at the location of the threatening or the neutral stimulus (50-50 distribution). Individuals are then asked to indicate the location of the probe as quickly as possible. The faster individuals respond to the probe that appears at the location of the threatening stimulus, the stronger the attentional bias (Schoth et al., 2012).

In order to retrain attentional biases a modified version of the VPT is used. Participants are trained to direct their attention away from the health-threat cue, in this case a fatigue stimulus, by letting the dot appear under a positive stimulus, in this case vitality, in 90% of trials (Kemps et al., 2014). As a consequence of this task, the patients practice to shift their attention away from the threatening and towards the positive stimulus (Meissner et al., 2019).

In order to measure self-identity bias, a form of CBM called Implicit Association Task (IAT) is used. It directly targets individual's associations with certain stimuli (Hughes et al., 2017). For the IAT, the first step is to distinguish the target-concept. The target concept consists of a health-threat stimulus and a positive stimulus that should be attended by the individual instead, for example ‘fatigue’ and ‘vitality’. One category is assigned to a response of pressing a key with the right hand, while the other is assigned to a response with the left hand. Second, the attribute dimension is introduced, for example ‘self’ and ‘other’. Afterwards, the different categories are paired with the attribute dimension. In a second round, they are paired in a reversed manner (Greenwald et al., 1998). For instance, first ‘fatigue’ is paired with ‘self’ and ‘vitality’ with ‘other’. In the second round ‘fatigue’ is paired with ‘other’ and ‘vitality’ with ‘self’. The performance difference implicitly measures the association of the categories with each other (Greenwald et al., 1998). It is assumed that participants are faster in accomplishing the compatible than incompatible task (Schimmack, 2019). Hence, someone who already associates himself with fatigue will show shorter response times in the first round. In order to retrain this self-identity bias patients are trained to categorize words of one category with a certain stimuli. For example, attribute ‘vitality’ and ‘self’ stimuli to each other and ‘fatigue’ and ‘other’ stimuli. By executing this task quickly for a number of times, novel automatic links are established in the memory between the category ‘vitality’ and ‘self’, letting the self-identity of an individual becoming more vitality-congruent.

According to a meta-analysis of Jones & Sharpe (2017) CBM was successfully used as a treatment method to decrease anxiety complaints. Stronger attentional biases at baseline measures were found to correlate with stronger bias changes after training. Moreover, two studies that were included reported a significant positive correlation between change in attentional bias and change in symptoms. Hence, there is evidence that successfully changing attentional bias in renal patients might reduce their fatigue symptoms. A study of Kemps et al. (2014) investigated the influence of CBM on chocolate cravings and found that after attentional retraining with the modified VPT the ‘avoid chocolate’ group demonstrated less craving for chocolate whereas the ‘attend chocolate’ group demonstrated more cravings. Hence, CBM in retraining attentional bias was highly effective in this study. Targeting fatigue in renal patients has not been investigated yet, however, the variety of fields where it did show successful results is promising evidence for this study since the concept of changing attentional bias is in line with this study.

All-or-nothing & Avoidance behaviour

Kidney patients suffering from fatigue are often observed to show two predominant activity patterns that contribute to the perpetuation of fatigue: All-or-nothing behaviour and activity limitation, also called avoidance behaviour (Chilcot et al., 2016). All-or-nothing behaviour is characterized by periods where the patient feels rather well and therefore engages in intense activities, followed by extended rest periods in response to occurring fatigue symptoms (Band et al., 2017). A reduction in all-or-nothing behaviour has been identified as a mediator in the relationship between CBT and fatigue. Therefore, it is desired to decrease all-or-nothing behaviours in order to also reduce fatigue (Band et al., 2017). The authors also linked the avoidance of activity to the patients' beliefs about the physical origin of their symptoms. Moreover, there is evidence that the avoidance of activity is linked to the maintenance of fatigue symptoms and the increase of activity can lead to a reduction of them (Band et al., 2017).

Next to the reduction of symptoms, the goal of a successful CBM intervention would be to tackle these all-or-nothing and avoidance behaviours since they play an important role in the maintenance of fatigue (Chilcot et al., 2016). As stated earlier, cognitive biases might aggravate fatigue by mitigating behaviours such as avoidance and all-or nothing behaviour (Wolbers et al., 2021). Based on this, it can be assumed that a high bias score at baseline measure correlates with a high score on avoidance and all-or-nothing behaviour at baseline measure. Hence, next to investigating whether these behaviours can be modified by CBM interventions, it might be interesting to investigate whether the strength of all-or-nothing and avoidance behaviours in renal patients depends on the strength of self-identity bias before receiving CBM treatment. This might give more insight into how these behaviours are related to a self-identity bias and in the potential effectiveness of a CBM intervention on them in this target group.

Hypotheses

The primary objective of this study is to investigate whether CBM can target fatigue-related cognitive biases and thereby decrease fatigue in renal patients. For the secondary outcomes the effects of the CBM intervention on subjective fatigue and vitality and avoidance and 'all-or-nothing' behaviour are investigated. Hence, the following hypotheses arise:

H_1: Attentional bias is significantly reduced after the CBM intervention.

H_2: Self-identity bias towards fatigue is significantly reduced after the CBM intervention.

H_3: The effectiveness of the CBM intervention increases if participants are getting exposed to a higher dose of CBM trainings.

H_4: There is a significant difference in subjective fatigue levels between pre- and post-test measures. Mean values tend towards a decreased fatigue in post-test measures. Effects are stronger for patients with higher self-identity bias at baseline scores.

H_5: A self-identity bias towards fatigue is positively correlated with an attentional bias.
H_6: Self-identity bias towards fatigue at baseline measure correlates with baseline avoidance behaviour.
H_7: Self-identity bias towards fatigue at baseline measure correlates with baseline all-or-nothing behaviour.

Methods

Study design

In this study a single-case series experimental design (SCED) was implemented (Barlow & Hersen, 1973) with (A) one to two weeks varying baseline, (B) seven daily single CBM sessions, (B') seven days of combined CBMs, and (A') three weeks post-treatment follow-up. Participants were randomly assigned to one of four conditions (seven days vs. 14 days baseline X single attentional bias modification (A-CBM) vs. self-identity bias modification (SI-CBM) to start in the first treatment week).

Participants

A total of 30 adult patients (n_{Isala}=16, n_{ZGT} = 14) with a CKD 4-5 or D5 were included in this study. Potential candidates of the participating centres ZGT Almelo and Isala Zwolle were identified by trained nurse-specialists in cooperation with the researcher. In order to fulfil the inclusion criteria for this study they were required to be able to read and write Dutch, have adequate vision to operate a computer, report moderate to severe fatigue, and have basic internet skills. Participants were excluded if they were scheduled for receiving transplantation within three months or had any somatic or psychiatric comorbidity that might impede the patients' adherence to the CBM treatment or study protocol. Six patients stopped the intervention because of (a combination of) health issues (n=4), not agreeing with the framing of this study (n=1), being busy (n=1) and limited skills to use the borrowed laptop (n=2). Hence, 24 participants remained to complete the study (12 "predialysis", 8 haemodialysis, 4 peritoneal).

Table 1

General Biographical Characteristics of the Participants (N=24)

Item	Category	Frequency	Percentage
Gender	Female	12	50
	Male	12	50
Age	Range	26-84	
	Mean	61.59	
	Standard Deviation	13.67	
Nationality	Dutch	22	100
Stage kidney disease	CKD 4-5	12	50
	D 5	12	50

Materials

Measurement

In order to assess the effect of the CBM treatment on primary outcomes, the full and brief version of the Visual Probe Task (VPT & B-VPT) and the full and brief version of the Self-identity Implicit Association Task (SI-IAT & SI-BIAT) were used. To investigate the secondary outcomes, the Checklist Individual Strength (CIS), the Visual Analogue Scale for Fatigue and Vitality (VAS-F & VAS-V), the Subjective Vitality Scale (SVS), as well as the behavioural subscales of the Cognitive and Behavioural Responses (CBRQ) were used.

The Visual Probe Task (VPT) is used to measure attentional bias in this study (MacLeod et al., 1986). The VPT comprises 160 trials that start with a fixation cross that is presented in the centre of the screen for 500 milliseconds (ms). Afterwards, word pairs (each pair containing a fatigue and vitality synonym) appear for 500 ms. Words appear randomized below or above the fixation cross. Next, a target probe (letter E or F) appears in the location of either the fatigue or vitality synonym and remains until the patient responds by pressing the correct designated key. The location of the probe is varied between both categories in a 50/50% ratio. The full VPT was conducted at first baseline, post-treatment, and follow-up. The B-VPT is used to enable more frequent measurements at the intermediate time points (see Table 2). It contains a total of 80 responses and 16 practice trials. VPT scores were calculated by subtracting the fatigue mean from the vitality mean for every meeting. Hence, a positive score means that it took the participant longer to respond to the vitality cue than to the fatigue cue, indicating a bias towards fatigue.

The Self-Identity Implicit Association Task is used to measure self-identity bias in this study (Greenwald et al., 1998). Participants have to categorize stimuli representing two target categories (‘Fatigue’ and ‘Vitality’) and two attitude categories (‘Self’ and ‘Other’) with each other. In the first condition (*Fatigue congruent*), they categorize ‘Fatigue’ and ‘Self’ words together by pressing one response key and ‘Vitality’ and ‘Other’ words by pressing another key. In the second condition (*Vitality congruent*) they group ‘Vitality’ and ‘Self’ together by pressing one response key and ‘Fatigue’ and ‘Other’ by pressing the other key. Examples of words are ‘Tired’, ‘Energy’, ‘I’, and ‘She’ (see Table 3). Words belonging to both conditions were generated in several preliminary studies (Klaus, 2016). The average response latency between conditions is seen as an indicator of association strength. This so-called D-score was calculated by subtracting the mean of the fatigue-congruent from the incongruent trials and dividing it by the standard deviation of all trials (Greenwald et al., 2003). *D* has a theoretical minimum of -2 and a theoretical maximum of +2, with a higher (or more positive) score indicating a more implicit bias towards fatigue (Nosek et al., 2014). In order to enable more measurement points (see Table 2), a brief version of the IAT is developed (SI-BIAT) that has been validated in a preliminary study (Sriram & Greenwald, 2009). The psychometric quality of the IAT is still debated. Bar-Anan & Nosek (2014) report that the IAT shows high internal consistency (α = .88) and good relationships with other attitude measures. However, there is no evidence of discriminant validity. Schimmack (2019) confirmed in a recent study that there is still lacking evidence of discriminant validity for the IAT. Hence, it is debatable whether the IAT is an appropriate measurement instrument for implicit cognitions.

The Visual Analogue Scale for Fatigue (VAS-F) consists of a single item asking about the subjective experience of fatigue (*"How tired do you feel at this moment?"*) (Nicklin et al., 2010). It is measured at seven time points during the intervention, four times at baseline level and three times during and after the training. The item requires respondents to indicate their current state along a visual analogue line that ranges between two extremes, for example from "not at all tired" to "extremely tired". Scores can range between 0 and 10, with VAS-F scores ≥ 5 indicating fatigue (Nicklin et al., 2010). According to a study of Nicklin et al. (2010), the VAS shows good criterion and construct validity and is therefore suited to measure subjective fatigue.

The behavioural subscales of the Cognitive and Behavioural Responses Questionnaire (CBRQ) were used to measure avoidance and all-or-nothing behaviour (Ryan et al., 2018). Both variables were measured twice at baseline and three times at post-test measure. The scale comprises five items measuring avoidance behaviour (e.g. *"I stay in bed to control my symptoms"*) and eight items measuring all-or-nothing behaviour (e.g. *"I tend to overdo things when I feel energetic"*). The items can be answered using a five-point Likert scale (1 = "Never" to 5 = "All the time") with higher scores indicating a stronger performance of avoidance and/ or all-or-nothing behaviour. The CBRQ showed high internal consistency (α = .91) and satisfactory construct validity, however, only with a weak association with fatigue (Loades et al., 2020).

Table 2

Time Schedule of the Single-Case Series Design, including the Planned Outcome Measures

Week	1	2	3	4	5	6	7
Phase	A Baseline	A Baseline	B CBM	B' CBM	A' Post	A' Post	A' F-up
Group							
I			A-CBM	A+SI			
2 week B-line II			A-CBM	A+SI			
III			SI-CBM	SI+A			
2 week B-line IV			SI-CBM	SI+A			
Measures[a]	Mon-Sun[b]	Mon-Sun	Mon-Sun	Mon-Sun	Mon-Sun	Mon-Sun	Mon-Sun
Brief measures							
SI-BIAT+B-VPT VAS-F+VAS-V	■□■□□□■	□■□■□■□	■□□□■□□	■□□■□□□	■□□□□□□	■□□□□□□	■□□□□□■
Full measures							
SI-IAT+VPT+CIS+SVS Behaviors	■□□□□□□	■□□□□□□	□□□□□□□	□□□□□□□	■□□□□□□	□□□□□□□	□□□□□□■

Note.a. The baseline repeated measurements in week 1 only apply to Groups II and IV. Groups I and III will start with measurements in week 2, according to the variable baseline SCED design.
b. The days at which repeated measurements are planned of the brief biases (SI-BIAT, B-VPT), Visual Analogue Scale for Fatigue and Vitality (VAS-F, VAS-V), are highlighted in red; full measurements of biases and fatigue and vitality (IAT, VPT, CIS, SVS) are highlighted in blue.

Table 3

IAT Blocks

Blocks	Categories		Examples
	Left side	Right side	
1 = Practice block	Fatigue	Vitality	Exhausted, awake, weary
2 = Practice block	Self	Other	Mine, their, she
3 = Practice block	Self	Other	Tired, me, strong, their
	Fatigue	Vitality	
4 = Test block	Self	Other	Tired, me, strong, their
	Fatigue	Vitality	
5 = Practice block	Self	Other	Mine, their, she
6 = Practice block	Self	Other	Sleepy, he, attentive, me
	Vitality	Fatigue	
7 = Test block	Self	Other	Sleepy, he, attentive, me
	Vitality	Fatigue	

Training

During the training phase of the intervention, a modified version of the VPT was used to retrain the attentional bias, referred to as A-CBM. In A-CBM the patients learn to resist the urge to direct their attention to fatigue stimuli by letting the letters E and F appear at the location of the vitality cue. By directing the patients' attention to the vitality cue in 90% of the trials, patients' attentional bias will change away from fatigue towards vitality (Schoenmakers et al., 2007).

In order to retrain the self-identity bias, a modified version of the IAT was used to retrain self-identity bias, referred to as the SI-CBM. Instead of only measuring an implicit bias towards fatigue, the SI-CBM aims to modify this bias. It is assumed that by only linking 'self' and 'vitality' stimuli, and 'others' and 'fatigue' stimuli with each other, patients will develop an implicit bias towards vitality and attenuate the I-fatigue bias. Hence, during the IAT the task would be to categorise words like 'Strong' and 'I' as well as 'Tired' and 'Others' together in order to strengthen the association of oneself with the concept of vitality.

Procedure

In this study, participants were recruited from the participating centres ZGT Almelo and Isala Zwolle, where data collection took place between January and March 2020. Prior to the study, participants were asked for their informed consent. Therefore, they were shortly informed about the topic of this study. They were informed about the confidentiality and anonymity of this study and that they have the right to withdraw at any time without any consequences.

In total, the intervention comprised four groups of participants that completed a seven-week intervention. The study entailed three phases: two weeks of baseline measures, two weeks of treatment phase, and three weeks post-measures or follow-up (see Table 2 for the detailed measurement points). In week one, group II and IV participated in baseline measures, group I and III only started in the second week. In the treatment phase, participants of group I and II received daily a single A-CBM in week three and an additional SI-CBM in week four. Group III and IV received daily a single SI-CBM for the third week and an additional A-CBM during the fourth week. In week five to seven the post-treatment and follow-up phase started where participants completed different brief and full measures to assess cognitive biases and secondary outcomes, such as subjective fatigue and vitality.

Data analysis

In order to assess the collected data, various quantitative analyses were performed using IBM SPSS Statistics 24. The first step was to bring the data from the long into the wide format and to recode reversed items if applicable. Next, general descriptives were calculated. Skewness and kurtosis were computed to determine the normality of the data, whereby +1 and -1 were set as cut off scores, since values close to zero indicate a normal distribution (Field, 2013).

To answer the first and second hypotheses, whether there is a reduction in attentional as well as self-identity biases towards fatigue after the CBM intervention, results of the SI-IAT *D*-scores and the VPT scores at baseline and post-measures were compared. The aggregate of all baseline measures into a single variable had to be computed by calculating the mean out of the first six measurement points while excluding missing data points. The same was done for post and follow-up measures by calculating the mean of measurement points nine to twelve. For short-term changes the mean of measurement points nine and ten, and for long-term changes the mean of measurement points eleven and twelve was calculated. Next, a paired t-test was used in order to compare means across both variables from baseline and post-measures. Bootstrapping sample size was set to 1000 and a 95% confidence interval was used.

A General Linear Model was applied to test the hypothesis that the effectiveness of the CBM intervention increases with a higher dose of treatments. The repeated *D*-score was taken as a within-factor (i.e. 'effect of time') and a high versus low dose variable (starting in the first week with A-CBM/ SI-CBM vs. starting in the second week) was created that interacted with the within-factor.

In order to investigate whether subjective fatigue levels changed after the intervention and whether this is also related to the strength of self-identity bias at baseline (H_4), a General Linear Model was used to determine whether the strength of self-identity bias was functioning as a moderator in the relationship between baseline and post-test fatigue measures. Before that, a paired t-test was used to compare the means of subjective fatigue at baseline and at post-test measure. For the GLM, subjective fatigue was taken as a within-factor and a strong versus weak bias at baseline variable was created that interacted with the within-factor. A dichotomous variable was created with a median split procedure, after which half of the sample was categorized as having a high self-identity bias at baseline measure whereas the other half was categorised as having a low self-identity bias at baseline measure.

To investigate whether the presence of a self-identity bias towards fatigue increases the attentional bias, the biases baseline measures were compared by calculating Pearson's correlation coefficient. The statistical significance was set at $p < .05$. However, if the assumptions for parametric testing were not met, Spearman's rho was used.

In order to test whether self-identity bias scores (*D*-scores) correlate with avoidance and all-or-nothing behaviour scores at baseline measure (H_6 & H_7), Pearson correlation scores or Spearman's rho were calculated between the variables self-identity bias at baseline level and avoidance behaviour scores at baseline level, as well as between the variables self-identity bias at baseline level and all-or-nothing behaviour scores at baseline level. In addition to that, a paired t-test was conducted to measure the change of avoidance and all-or-nothing behaviour from baseline to post-test measures.

Results

In the following results section, results of the analyses that answer the study hypotheses are presented. First, general descriptives with means and standard deviations of the scales are presented. Second, the results of analyses that answer hypothesis one until seven are displayed.

Descriptive Statistics

In Table 4 means and standard deviations for each scale are displayed. Baseline measures were taken during the first two weeks of the intervention. Short-term measures include measurements taken in week five and six. Long-term measures include the follow-up testing in week seven. In post & follow-up all measurements were combined. As Table 4 displays only attentional and self-identity bias changed during the intervention while fatigue and all-or-nothing and avoidance behaviour stayed almost at the same level.

Table 4

Means and Standard Deviations for the VPT (Attentional Bias), IAT (Self-Identity Bias), VAS-F (Fatigue) and CBRQ (All-or-nothing and Avoidance Behaviour)

Scale	Mean	Std. Deviation
VPT		
baseline	23.56	70.33
post & follow-up	-20.26	27.66
short-term	-54.90	134.84
long-term	23.27	149.90
IAT		
baseline	-.04	.22
post & follow-up	-.25	.17
short-term	-.25	.23
long-term	-.27	.17
VAS-F		
baseline	4.72	1.65
post & follow-up	4.81	1.90
CBRQ		
All-or-nothing		
baseline	13.48	4.45
post & follow-up	12.54	3.27
Avoidance		
baseline	19.07	6.14
post & follow-up	19.65	4.94

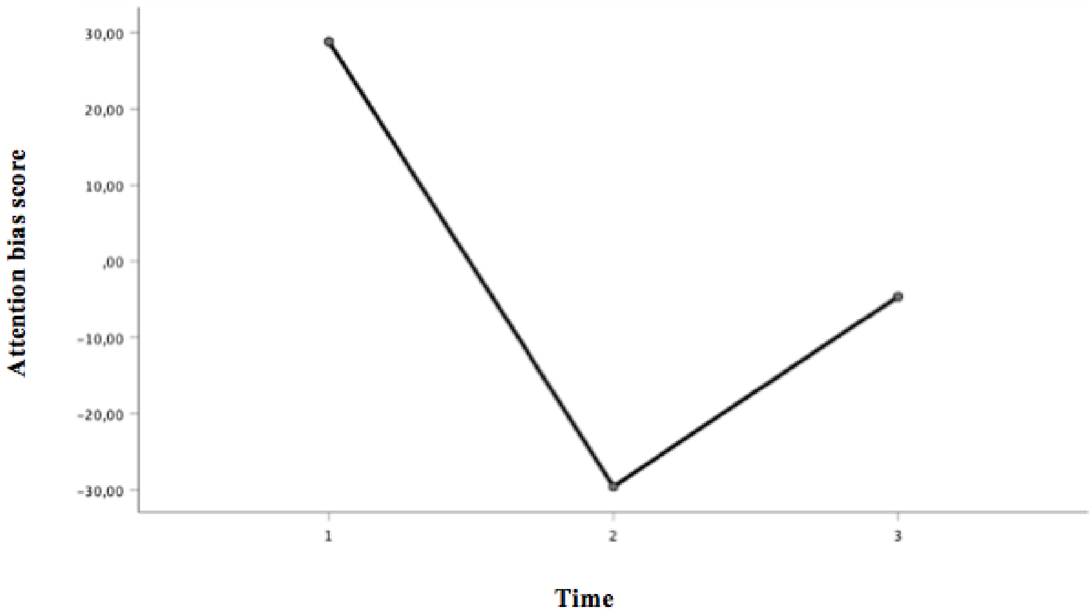
CBM Effects

Hypothesis 1

After testing whether there is a significant reduction in *attentional bias* scores towards fatigue after CBM, results demonstrated a significant average difference between baseline and post as well as follow-up measures with medium effect sizes (see Table 5). Since a higher (or positive) score indicates a stronger implicit bias towards fatigue, a higher baseline than post-test score indicates a change in attentional bias from fatigue to vitality (see Figure 1). Hence, the hypothesis that CBM reduces attentional bias scores towards fatigue can be accepted.

Figure 1

Changes in Attentional Bias Between Baseline (First Two Weeks), Post-test (Week Five and Six) and Follow-up (Week Seven) Measures (N=10)

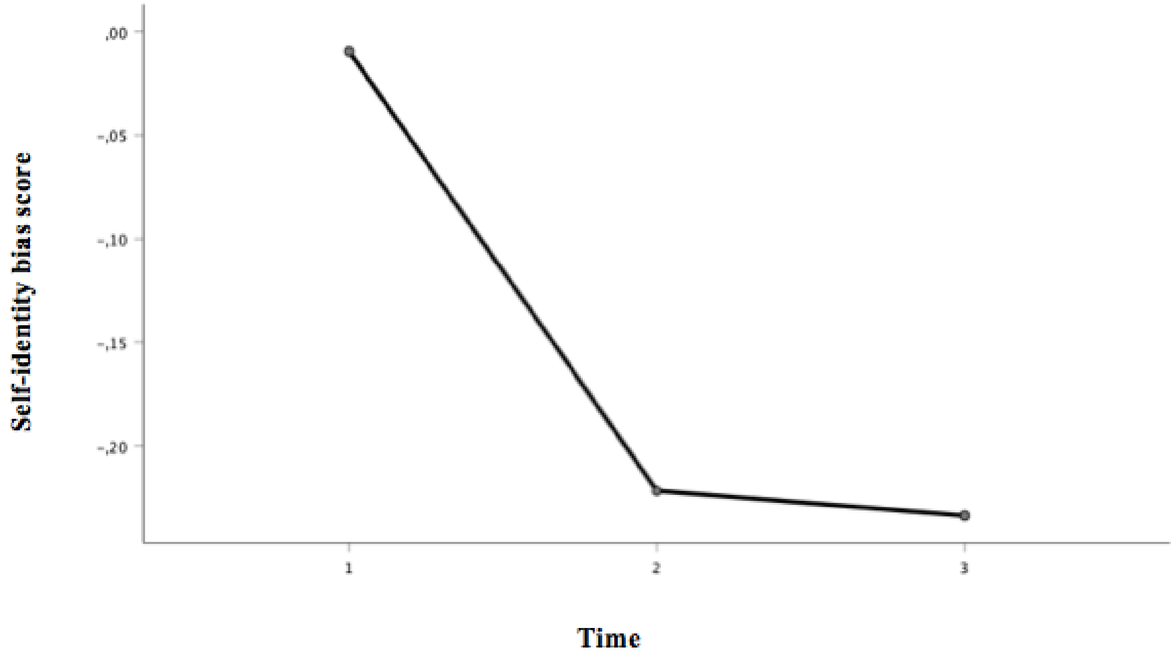


Hypothesis 2

For the second hypothesis, whether there is a significant reduction in *self-identity bias* scores towards fatigue after CBM, results demonstrated a significant average difference between baseline and post as well as follow-up measures with large effect sizes (see Table 5). Since a higher (or more positive) score indicates a stronger implicit bias towards fatigue, a higher baseline than post-test score indicates a change in self-identity bias from fatigue to vitality (see Figure 2). Hence, the hypothesis that CBM reduces self-identity bias scores towards fatigue can be accepted.

Figure 2

Changes in Self-Identity Bias Between Baseline (First Two Weeks), Post-test (Week Five and Six) and Follow-up (Week Eight) Measures (N=10)



Hypothesis 3

For the third hypothesis, it was investigated whether the effectiveness of CBM increases if participants are getting exposed to a higher dose of treatments. The results demonstrate a significant decrease in self-identity bias towards fatigue from pre- to post-test, as it was confirmed in Hypothesis 2 (see Table 5). However, they also show a non-significant interaction between the covariate, treatment dose, with a main effect of .01 and the change in bias towards fatigue over time, $F(1)=.01$, $p=.91$.

The results from the General Linear Model on attentional bias demonstrate a non-significant decrease in bias towards fatigue over time, $F(1)=3.63$, $p=.08$. They also show a non-significant interaction between the covariate, treatment dose with a main effect of .001, and the change in bias towards fatigue over time, $F(1)=.11$, $p=.74$. Since the results do not indicate a significant difference on a high- and a low-dose treatment condition, the hypothesis can be rejected.

Hypothesis 4

Additionally, it was tested whether there is a significant reduction in *subjective fatigue* levels between pre- and post-test measures with a stronger effect for patients with higher *self-*

identity bias at baseline measure. The results demonstrated no main effect of time on subjective fatigue, $F(1)=.24$, $p=.64$. Moreover, the results did not indicate a significant difference between a strong and a weak bias with a main effect of 1.43, $F(1)=.004$, $p=.95$. Hence, the hypothesis that the treatment demonstrates greater effects on patients with a higher self-identity bias at baseline measure can be rejected.

Table 5

Paired Samples T-Tests Including Effect Size Estimates

	Mean	Std. Deviation	Cohen's d	Std. Error Mean	95% CI Lower	95% CI Upper	t	df	Sig. (2-tailed)
Attentional bias	44.17	78.81	.56	20.35	.53	87.81	2.17	14	.048
short-term	52.71	93.02	.56	24.86	-.99	106.42	2.12	13	.05
long-term	33.69	84.00	.40	25.33	-22.74	90.12	1.33	10	.21
Self-identity bias	.22	.27	.81	.07	.07	.36	3.13	14	.01
short-term	.19	.31	.61	.08	.01	.36	2.24	13	.04
long-term	.26	.30	.87	.09	.05	.46	2.79	10	.02
Fatigue	-.08	1.46	-.50	.38	-.89	.72	-.22	14	.83
All-or-nothing behaviour	.33	1.63	.20	.42	-.57	1.24	.79	14	.44
Avoidance behaviour	-.12	2.30	-.50	.59	-1.40	1.15	-.21	14	.84

Note. This table demonstrates the change in variables during the intervention. Since the measurement points for bias measures were taken more frequent during the study, the change in bias is demonstrated as a whole (first row: all post and follow-up measures), in the short-term (second row: two post-test measures), and in the long-term (third row: two follow-up measures). For fatigue, all-or-nothing and avoidance behaviour only changes as a whole are displayed.

Cognitive Bias as a Predictor

Hypothesis 5

For the fifth hypothesis it was tested whether the presence of a *self-identity bias* towards fatigue at baseline level is associated with the *attentional bias* at baseline level. Since the data does not fulfil the assumptions for parametric testing, Spearman's rho instead of Person's correlation coefficient was used for all correlations that were tested. Results revealed the expected positive but non-significant correlation (see Table 6). Hence, the hypothesis that the presence of a self-identity bias towards fatigue at baseline level increases the attentional bias at baseline level can be rejected.

Hypothesis 6

Furthermore, it was tested whether *self-identity bias* correlates with *avoidance behaviour* at baseline measure. Results demonstrated a weak positive correlation between both variables, however, the results were not significant (see Table 6). A positive correlation was expected in this case. Therefore, the hypothesis that self-identity bias correlates with avoidance behaviour can be rejected.

Hypothesis 7

Lastly, it was tested whether *self-identity bias* correlates with *all-or-nothing behaviour* at baseline measure. Results revealed a strong negative correlation between both variables, however, the results were only marginally significant (see Table 6). A negative correlation contradicts the expected positive correlation. Hence, the hypothesis that self-identity bias correlates with all-or-nothing behaviour can be rejected.

In conclusion, the results cannot confirm all hypotheses. Hypothesis 1 and 2 can be confirmed since a significant reduction in attentional and self-identity bias scores towards fatigue were found after undergoing the CBM intervention. The remaining hypotheses (H_3 – H_7) must be rejected because they were all found to be not significant. However, for Hypothesis 7 the effect was marginally significant and might therefore be worth to be viewed as partially confirmed.

Table 6

Correlations of Self-Identity and Attentional Bias at Baseline Measure and Self-Identity Bias and Avoidance as well as All-Or-Nothing Behaviour at Baseline Measure.

	Attentional bias	Avoidance Behaviour	All-or-nothing Behaviour
Self-identity bias	.32 (*p*=.21)	.28 (*p*=.33)	-.50 (*p*=.07)

Note. Correlation is significant at the .05 level (2-tailed).

Discussion

In order to gain a deeper understanding of the effects of a cognitive bias modification treatment for reducing fatigue in renal patients, the aim of this study was to explore the effects of CBM on attentional and self-identity biases towards fatigue as well as on subjective fatigue. By reducing or modifying the identification with fatigue and the increased attention that is directed at fatigue-cues, the CBM intervention aimed to provide a new treatment approach for fatigue in renal patients. The CBM training was expected to reduce fatigue by decreasing cognitive biases. The study is the first that offers an overview of the possibilities when using CBM in treating renal patients with chronic fatigue. It was conducted with a sample of 24 renal patients in a single-case series experimental design.

The results demonstrated that attentional bias and self-identity bias were reduced after the CBM intervention, whereby seven vs. 14 days of daily training sessions did not have an effect on the results. However, the study could neither find significant changes in subjective fatigue, nor an association of cognitive biases on avoidance or all-or-nothing behaviours. First of all, the study aimed to assess the effects of CBM on attentional and self-identity bias towards fatigue. On average, self-identity bias as well as attentional bias decreased after training (H_1 & H_2). For attentional bias the results demonstrate a medium effect size, while for self-identity bias the effect size was large. Hence, there was a larger change for self-identity bias than for attentional bias after CBM training. The review of meta-analyses of Jones & Sharpe (2017) already assessed the effectiveness of CBM and found a successful change in attentional bias in ten out of ten studies, whereby they included mood disorders as well as appetitive stimuli, such as eating disorders or alcohol use. Since there are no studies up to this point that investigate the effects of CBM on self-identity bias, the present study provides first results on this.

This study also made an attempt to show the development of biases after the training. In order to achieve that, the development of cognitive bias score in the short-term (post-test measures, or week five and six) and long-term (follow-up measures, or week seven) were assessed. For attentional bias, only the aggregated score of post- and follow-up measures yielded significant results and demonstrated a decrease in attentional bias. When looking at post- and follow-up measures separately, hence, the short-and long-term measures after the CBM intervention, results were non-significant. This might be caused by more subjects having all missing values on two measurements, resulting in a lower sample size. However, when looking at the mean it still suggests that effects of CBM training are fading during the three weeks after the training. The indication that A-CBM effects are not long lasting is in line with other studies. In a meta-analysis of Heeren et al. (2015) they compared studies that examined the effects of A-CBM for social anxiety. The compared studies included follow-up measures up to four months, finding non-significant results. This is in line with the findings that Jones & Sharpe (2017) report in their review of meta-analyses. The follow-up measures ranged between one and six months and could not show any significant results for emotional outcomes. However, small significant effects for addiction treatment outcomes might indicate that CBM can have long-term effects in some cases. Since this study did not statistically test the change from post- to follow-up measure, this would need further investigation. Assuming CBM effects may wear down over time (Jones & Sharpe, 2017), this study suggests that it requires an interval of more than three weeks post treatment to assess long-term effects.

Moreover, the present study aimed to explore the effects of a higher dose of CBM treatment. For this, a seven vs. 14 days of daily training sessions condition was tested (H_3). In contrast to our expectation, results revealed no difference in bias decrease for both conditions. Jones & Sharpe (2017) report in their review of meta-analyses that dose, number of trainings and time between sessions does not influence the effectiveness of CBM trainings. However, for instance in the meta-analysis of Hakamata et al. (2010) that a higher number of sessions has beneficial effects on attentional bias. Consequently, there is again mixed-evidence on the question whether a higher dose positively influences the treatment outcomes. Nevertheless, the results show that there is no difference in prolonging the treatment for seven days. Hence, it would be interesting to test other options, for instance whether a higher number of sessions a day would increase treatment success or also whether reducing the treatment moments even further is equally successful. The latter option would be interesting in order to avoid adding to the already high treatment burden of renal patients.

Another question this research aimed to investigate was whether higher baseline bias scores may amplify the effect of CBM treatment in reducing subjective fatigue (H_4). Research indicated that patients were able to reduce their symptoms even more when they started the treatment with higher bias scores at baseline measure (Price et al., 2016). Hence, this study aimed to investigate the strength of bias as a moderator. The analysis did not reveal a significant difference between a weak and a strong bias, meaning that strength of bias is not influencing the treatment outcome for subjective fatigue. Studies that investigated the effect of bias strength never investigated it as a moderator for symptom change but only for bias change. For instance, the study of Heeren et al. (2015) that did not find any effects that would lead to the conclusion that a higher baseline score leads to more bias change. According to the review of meta-analyses of Jones & Sharpe (2017) was Price et al. (2016) the only one out of three meta-analyses who found this effect. A question that arises in this context is whether the relevant contrast on baseline bias strength was chosen for this study or if other contrasts would have yielded different results. When looking at the average subjective fatigue scores it becomes clear that there are no measurable changes between baseline and post-test measures, indicating that the CBM training did not have any effects on the patient's subjective fatigue levels regardless of their initial bias strength. Hence, it would be advisable to conduct the measure again in a sample where the symptoms were reduced in order to receive more meaningful results.

Since it is hypothesized that CBM improves symptoms by changing biases, the previous finding, that a change in bias does not necessarily also lead to a change in symptom, raises the question whether CBM only changes a cognitive bias while this does not influence the symptoms. The review of meta-analyses of Jones & Sharpe (2017) found mixed-evidence on this question. Mogoaşe et al. (2014) found in her meta-analysis assessing the efficacy of A-CBM a significant reduction in anxiety symptoms. A possible explanation why some studies find a change in symptoms while others only detect a bias change would be that the CBM paradigm might differ in efficacy since especially A-CBM resulted more often in symptom change and approach-avoidance CBM in a change in addictive behaviours (Mogoaşe et al., 2014; Jones & Sharpe, 2017). However, in the present study two types of bias retraining, A-CBM and SI-CBM, were studied from which both were successful in changing bias in the sample while secondary outcomes, such as subjective fatigue, remained at the same level. Moreover, the study did not include a placebo group, therefore, it is not known whether the symptom could have increased in the placebo group due to unknown outside factors that worsened the patient's fatigue since fatigue is a symptom that is not only triggered by their renal disease but also by factors such as quality of life (Pretto et al., 2020).

Another explanation why some studies find significant changes in symptoms could be that CBM training is more effective for some symptoms than for others. Jones & Sharpe (2017) found in their meta-analyses review that eight out of nine meta-analyses found significant reductions in anxiety symptoms. A study of Sharpe et al. (2012) found that A-CBM might be a potential treatment for pain patients, revealing promising results in a sample that reported reduced average pain after receiving A-CBM. In this study it seems as fatigue does not, while the cognitive biases did decrease. A possible explanation might be that biases play a much smaller role in fatigue as it was expected. The result that fatigue did not decrease seems to provide evidence for the argumentation that the disease itself seems to be predictive of fatigue levels. Their fatigue might be attributable more to physical causes, for instance the high variance in blood pressure that is caused by haemodialysis due to the short time in which blood is withdrawn and re-added again. The imbalance in electrolytes in renal patients is also a physical factor that contributes to feelings of tiredness (Soliman, 2015). However, other studies found evidence that, for instance, illness cognitions and fatigue-related behaviour are crucial predictors of fatigue (Chilcot et al., 2016). This contrary evidence calls for further investigation of the concept of fatigue in renal patients.

Next to a change in symptoms, the present study also aimed to investigate behavioural change since all-or-nothing and avoidance behaviours play an important role in the perpetuation of fatigue (Chilcot et al., 2016). It was assumed that the baseline measure of all-or-nothing and avoidance behaviour would correlate with the baseline measure of self-identity bias towards fatigue since patients who see fatigue as part of their identity (reflected in a high self-identity bias score at baseline measure) are assumed to engage more in these behaviours (H_6 & H_7). Results demonstrated a weak positive, however non-significant, correlation between avoidance behaviour and self-identity bias. For all-or-nothing behaviour results revealed a strong negative but only marginally significant correlation. Even though the hypotheses could not be confirmed, it is still interesting to take a closer look at the strong negative correlation between all-or-nothing behaviour and self-identity bias since this stands contrary to the expected positive correlation. It raises the question about the validity of both biases since a negative correlation is not found again in any other studies. Due to the debated psychometric quality of cognitive bias measures, this is an issue that should be investigated in further studies (Bar-Anan & Nosek, 2014; Schimmack, 2019).

Next to this unexpected finding, the results show that CBM was unable to change both types of behaviour (see Table 5). In the review of meta-analyses of Jones & Sharpe (2017) there was mixed-evidence on the question whether CBM could change behaviour. While Mogoaşe et al. (2014) found a decrease in substance use symptomatology, Cristea et al. (2016) were not able to confirm this effect of CBM on addiction or craving outcomes. Lastly, Forscher et al. (2019) summarized that changes in bias measures do not necessarily translate into changes in behaviour. Hence, similar to the symptoms, further research might be needed to look into factors that influence the effectiveness of CBM in influencing behaviours.

Lastly, the study also aimed to investigate whether the presence of a self-identity bias at baseline measure also increases the attentional bias (H_5). The results revealed a moderate positive, however non-significant, correlation. Even though the results were non-significant, the moderate correlation indicates that there is a difference between attentional and self-identity biases and they do not relate to the same concept. Therefore, further research is again needed in order to achieve significant results.

Limitations, Strengths and Practical Implications for Further Research

A big strength of the study is that it is the first that aimed to investigate fatigue in renal patients CKD 4-5. There are no studies up to this point that investigate fatigue in this target group. However, due to the rising numbers of patients receiving dialysis and the high percentage that experiences fatigue, it might investigate a potential treatment that could improve the life of a huge target group. Moreover, it is explorative in nature since it measured various variables. It tested already two types of CBM training, namely A-CBM and SI-CBM. Another strength is that patients were able to perform the training during their dialysis, at home or in another environment of their own choice instead of in a laboratory. Especially patients with chronic diseases wish for a treatment that is short and easily accessible (Wolbers et al., 2021). Hence, this training was beneficial since it did not add much to the high treatment burden of kidney patients.

However, it is appropriate to recognize several potential limitations. The first limitation of this study relates to the strength that participants did not complete the training in a laboratory. Nevertheless, it has been shown that A-CBM is most effectively delivered in a laboratory (Jones & Sharpe, 2017). Since the study could not control whether patients experienced distractions during the training or the measurements, the results may be lacking reliability to some extent.

The second limitation is the time frame where the data was gathered. Since the data was gathered between January and March 2020 it took place when Covid-19 started to spread in the Netherlands. This might affect especially the post and follow-up measures that were taken in February and March. While Covid-19 influenced the mental health of the whole population (Pfefferbaum & North, 2020), it might especially affect patients with a chronic illness. Due to the predicted high risk of Covid-19 for chronically ill patients, renal patients were likely to suffer from a high level of fear in combination with severely strict measures in order to avoid an infection with the virus. Hence, their quality of life is likely to be decreased during that time period. Quality of life, however, is an important factor that influences fatigue levels in patients undergoing haemodialysis (Pretto et al., 2020). In order to investigate the potential influence of Covid-19 on the results, the study would have to be repeated at a time when the pandemic is over.

The third limitation is that no control or placebo group was involved in this study. A control group might have been beneficial in order to give an indication whether an improvement in bias scores would have occurred without the CBM intervention due to a spontaneous recovery or whether outside factors influenced cognitive biases or symptoms. For instance, if Covid-19 had an influence on fatigue levels this would become visible by including a control group. An increase in fatigue within the control group, while fatigue in the CBM group remains the same, could indicate that the CBM intervention indeed did have a positive effect on symptoms and thus unknown outside factor confounded a true effect. By establishing a cause-and-effect relationship the validity of results would be increased.

Lastly, a very important limitation is the questionable psychometric quality of cognitive bias measures. The reliability and validity of the measures is questioned in various studies (Bar-Anan & Nosek, 2014; Schimmack, 2019). Moreover, Forscher et al. (2019) raised the question whether a change in bias measure can be translated into a change in behaviour. Taking these questions into consideration, it is difficult to interpret the given results. The lack in symptom and behaviour change seems to provide evidence for the voiced criticism about the bias measures. However, since this study did not assess the psychometric quality of those measures, this question needs to be further assessed in future research.

Hence, the implications for future research that arise from the limitations are to repeat the testing of hypotheses that were rejected because the results were lacking statistical power due to the low sample size. By that, it might be valuable to rule out potential causes for non-significant results, for example by including a larger sample size and also by measuring biases and symptoms over a longer time span to see if symptoms decrease at a later point. Moreover, a placebo or control group could provide evidence about outside factors influencing the patient's fatigue level. Since this study is the first that investigates the effects of CBM on fatigue in kidney patients further research is undoubtedly needed.

Conclusion

In conclusion, this study is the first that investigates the effects of CBM on fatigue in renal patients. The data confirmed the suspected effect of CBM on self-identity and attentional biases in demonstrating a significant reduction of both cognitive biases. Therefore, CBM could be identified as an effective treatment method for reducing cognitive biases in renal patients. However, fatigue and fatigue-related behaviour, such as avoidance and all-or-nothing behaviour, did not change after treatment. Hence, it is questionable whether cognitive biases play a tremendous role in renal patients suffering from fatigue. Moreover, questions about the working mechanisms of CBM have to be further investigated. This study could not ultimately provide information about the optimal dose for treatment and the role of bias strength at baseline measure. Despite these limitations, the present study enhanced the understanding of CBM in renal patients and provides interesting starting points for further research. Consequently, CBM can be seen as an interesting treatment option that needs further investigation to provide optimal results for patients.

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