**Appendix**

**Does the effect of cognitive behaviour therapy for chronic fatigue syndrome (ME/CFS) vary by patient characteristics?: a systematic review and individual patient data meta-analysis.**

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**Description of intervention**

Cognitive behaviour therapy (CBT) for chronic fatigue syndrome (ME/CFS) (Knoop & Bleijenberg, 2010) is based on the cognitive-behavioural model of fatigue in ME/CFS (Vercoulen et al., 1998) which discerns between factors that trigger fatigue and cognitive-behavioural factors assumed to perpetuate the symptom and associated disability. According to the CBT protocol used by the studies included in this individual patient data (IPD) meta-analysis the maximum attainable goal of CBT is recovery (Knoop, Bleijenberg, Gielissen, van der Meer, & White, 2007), operationalized as no longer being severely fatigued and no longer being limited in functioning by fatigue. CBT is a collaborative process which starts with presenting the rationale of the intervention. The interplay between behaviour, beliefs and physiological mechanisms is discussed. How changing one’s behaviour and beliefs can therefore help reduce fatigue and functional impairments is explained. Patients are invited to formulate treatment goals, i.e. activities they want to resume when less fatigued. Patients are helped to regulate their sleep-wake pattern, i.e. stick to fixed bedtimes and no longer lying down or sleeping during the day. Patients are encouraged to explore their thinking patterns and practice with formulating helpful beliefs with respect to fatigue. Interventions are applied to redirect attention away from symptoms. Activity is targeted in a time contingent graded activity program, which also targets beliefs about the ability to become more active. As the first randomized controlled trial (RCT) testing the efficacy of this protocol (Prins et al., 2001) found that patients with a low physical activity pattern improved less, the protocol was adapted. The revised protocol distinguishes between patients with a low physical activity level and those with a fluctuating activity pattern, assessed with actigraphy or a structured interview (Knoop & Bleijenberg, 2010). Patients with a low level of physical activity are provided guidance on how to immediately start gradually increasing physical activity. Patients with a fluctuating or “boom or bust” pattern of activity are encouraged to spread their activities more evenly before they start to gradually increase their level of physical activity. Further, the patient is helped to also increase mental and social activity gradually and systematically. Patients with more severe pain (i.e. <40 on the Short Form 36 Health Survey (SF-36) (Stewart, Hays, & Ware, 1988) subscale bodily pain) are encouraged to formulate helpful beliefs with respect to pain while increasing their activity level. If patients report an increased ability to become active, they start to attain step by step their personal goals (Worm-Smeitink et al., 2016). The treatment ends by helping the patient with normalization of the experience of fatigue and it addresses relapse prevention. CBT is available in different formats.

For adolescents, an adapted version of the protocol was developed, in which parents are actively involved (Nijhof, Bleijenberg, Uiterwaal, Kimpen, & Putte, 2012). The aims of the therapy take the specific developmental tasks of adolescents into account and return to full-time education is one of the treatment goals.

**Method of identifying studies**

On October 10th 2022, TK and FM systematically searched the literature using MEDLINE, EMBASE, PsycINFO, and Web of Science, for studies satisfying our eligibility criteria. The search was updated on May, 29th 2023. We searched between January 1 1999, the year in which the first study using the Dutch protocol (Prins & Bleijenberg, 1999) was published, and the date of the search or update. Used keywords included terms for chronic fatigue syndrome, cognitive behaviour therapy and randomized controlled trial. We did not include grey literature.

**Full electronic search strategy, exemplary for one database**

 (chronic fatigue syndrome or chronic fatigue or myalg\* encephal\* or asthenia or neurasthenia or post?viral fatigue\* or ME?CFS or systematic exertion intolerance disease).ti,ab.
(cognitive behavio?ral therapy or CBT or cognitive therapy or behavio\* or behavio?ral).ti,ab.
randomized controlled trial.pt.
randomi?ed.ab.
controlled clinical trial.ab.
placebo.ab.
random\*.ab.
trial.ab.
groups.ab.
3 or 4 or 5 or 6 or 7 or 8 or 9
1 and 2 and 10
limit 11 to human
limit 12 to yr="1999 -Current"

**Details of the study selection process**

Authors TK and IC independently screened all titles and abstracts for eligibility. Next, full texts papers were screened by the same authors for studies that met all inclusion criteria.

After removing duplicates, 2386 records were identified. After screening titles and abstracts 1586 records were excluded. A total of 1141 records were excluded because the subject was not (chronic) fatigue. A total of 445 records in which the subject was (chronic) fatigue were excluded, because they did not investigate CBT. This resulted in 61 full texts. Review of these texts led to further exclusion of 53 records. The reasons for excluding the 53 studies are listed below.

* 2 studies were excluded because it was a translation of another record (Prins et al., 2002; Tummers et al., 2011).
* 4 studies were excluded because the study population was not ME/CFS (Breukers et al., 2019; Chisholm et al., 2001; Janse, Wiborg, Bleijenberg, Tummers, & Knoop, 2016; McCrone, Ridsdale, Darbishire, & Seed, 2004).
* 15 studies were excluded because the investigated intervention was not CBT targeting fatigue (Antoni et al., 2014; Antoni et al., 2013; Cox, 2002; Lopez et al., 2011; May et al., 2022; Pinxsterhuis, Sandvik, Strand, Bautz-Holter, & Sveen, 2017; Powell, Bentall, Nye, & Edwards, 2001; Ridsdale, Hurley, King, McCrone, & Donaldson, 2012; Rimes & Wingrove, 2013; Taylor, 2004; Thomas, Sadlier, & Smith, 2006; Thomas, Sadlier, & Smith, 2008; Trondalen et al., 2020; Viner et al., 2004; Wearden et al., 2010).
* 14 studies were excluded because they did not investigate the efficacy of CBT (Adamson, Ali, Santhouse, Wessely, & Chalder, 2020; Albers et al., 2021; Courtney, 2014; Deale, Husain, Chalder, & Wessely, 2001; Meng & Friedberg, 2015, 2017; Quarmby, Rimes, Deale, Wessely, & Chalder, 2007; Severens, Prins, van der Wilt, van der Meer, & Bleijenberg, 2004; Tummers, Knoop, & Bleijenberg, 2010; Tummers, Knoop, van Dam, & Bleijenberg, 2013; van Geelen, Bakker, Kuis, & van de Putte, 2010; Whitehead & Campion, 2002; Wilshire et al., 2018; Worm-Smeitink et al., 2019).
* 5 studies were excluded because they investigated CBT as part of a multidisciplinary treatment or combined with other treatments (Al-Haggar, Al-Naggar, & Abdel-Salam, 2006; Malik et al., 2020; Nunez et al., 2011; Sandler et al., 2015; Stevens, 1999).
* 3 studies were excluded as they were not randomized or controlled (Akagi, Klimes, & Bass, 2001; Bazelmans, Prins, Lulofs, van der Meer, & Bleijenberg, 2005; Burgess & Chalder, 2001).
* 7 studies were excluded because the comparison condition was not a waiting list or care as usual (Baos et al., 2018; Chalder, Deary, Husain, & Walwyn, 2010; Jason et al., 2007; Leone Ridsdale et al., 2001; Stubhaug, Lie, Ursin, & Eriksen, 2008; Vos-Vromans et al., 2016; White et al., 2011).
* 3 studies were identified as an RCT investigating the efficacy of CBT compared to a waiting list or care as usual, but were excluded because they did not use the CIS-fatigue as outcome measure (Gotaas, Stiles, Bjorngaard, Borchgrevink, & Fors, 2021; O'Dowd, Gladwell, Rogers, Hollinghurst, & Gregory, 2006; Strang, 2002).

**Figure A1. Flow diagram of the selection process**



**Study selection and IPD obtained**

Eight studies (Janse, Worm-Smeitink, Bleijenberg, Donders, & Knoop, 2018; Knoop, van der Meer, & Bleijenberg, 2008; Nijhof et al., 2012; Prins et al., 2001; Stulemeijer, de Jong, Fiselier, Hoogveld, & Bleijenberg, 2005; Tummers, Knoop, van Dam, & Bleijenberg, 2012; van der Schaaf et al., 2015; Wiborg, Van Bussel, van Dijk, Bleijenberg, & Knoop, 2015) fulfilled the inclusion criteria. Seven studies were published RCTs investigating the efficacy of CBT for ME/CFS. Of one study, the published study protocol (van der Schaaf et al., 2015) and a paper describing baseline characteristics of patients included in this study (van der Schaaf et al., 2018) were found through our systematic search. The focus of this RCT was on investigating the neurobiological correlates of ME/CFS and its response to CBT in comparison to a waiting list condition. The effects of CBT compared to a waiting list condition in this study have not been published yet. However, the authors provided us full access to all individual patient data of the study to allow us to include the data in our IPD meta-analysis. For all eight studies, IPD were sought and obtained. In our systematic search, we did not identify RCTs on CBT for ME/CFS applying the Dutch protocol with negative results or RCTs with unpublished data, the latter aside from the included study of van der Schaaf et al. (2015).

**Process of requesting, collecting and managing IPD**

For all included studies, anonymized data for each of the pre-specified measurements were requested for each patient randomized. Data were supplied in SPSS or Excel files, were recoded and merged. Missing items were checked and imputations deleted. Data were checked on consistency with published reports and trial protocols.

**Outcomes and putative moderators**

Primary and secondary outcomes were assessed before and after the intervention or control condition.

Primary outcome:

Fatigue severity was assessed with the subscale fatigue severity of the 20-item Checklist Individual Strength (CIS) (Worm-Smeitink et al., 2017). The CIS-fatigue consists of 8 items which are scored from 1 to 7. The total score ranges from 8 to 56, a higher score indicating more severe fatigue (Worm-Smeitink et al., 2017). The CIS is a reliable (Cronbach's α = 0.83–0.92) (Vercoulen et al., 1994; Worm-Smeitink et al., 2017) and valid instrument for the assessment of fatigue in ME/CFS patients (Dittner, Wessely, & Brown, 2004; Vercoulen et al., 1994). The CIS has a validated cut-off score for severe fatigue of ≥ 35 for adults and ≥ 40 for adolescents (Nijhof, Bleijenberg, Uiterwaal, Kimpen, & van de Putte, 2011; Vercoulen et al., 1994; Worm-Smeitink et al., 2017).

Secondary outcomes:

Functional impairment was assessed with the Sickness Impact Profile 8 (SIP8) (Bergner, Bobbitt, Carter, & Gilson, 1981), which assesses overall impairment in eight domains. A higher weighted total score indicates more severe overall impairment. This SIP has good reliability (Cronbach's α = 0.94) (Bergner et al., 1981) and validity (Knoop et al., 2007; Knoop et al., 2008). The cut-off score of < 700 reflects significant functional impairment.

Functional impairment is both an outcome and a putative moderator, because functional impairment is an important criterion in all case definitions of ME/CFS but was also found to be a predictor of the treatment effect of CBT on fatigue severity (Knoop et al., 2008).

Physical functioning was assessed with the subscale physical functioning of the Short Form 36 Health Survey (SF-36) consisting of 10 items (Stewart et al., 1988). The weighted subscale score ranges from 0 (maximum physical limitations) to 100 (ability to do vigorous activity). The SF-36 is a reliable and valid instrument to assess self-reported health status (Scheeres, Wensing, Knoop, & Bleijenberg, 2008; Stewart et al., 1988). The Cronbach's α of the Dutch version is 0.92 (van der Zee & Sanderman, 1993). A cut-off score of > 70 is used to operationalize impaired physical functioning (Tummers et al., 2012).

**Assessments of putative moderators including (1) demographic factors, (2) clinical characteristics, and (3) cognitive-behavioural factors targeted in CBT.**

Demographic factors:

Age was assessed in years and sex as male vs. female, by a questionnaire.

Clinical characteristics:

Self-reported duration of fatigue was assessed in months.

Symptoms were assessed by a questionnaire assessing nine accompanying symptoms of the Centers for Disease Control and Prevention (CDC) criteria for ME/CFS (Fukuda et al., 1994; Reeves et al., 2003). (1) Post-exertional malaise (PEM): “increase of symptoms following exertion”; (2) unrefreshing sleep ; (3) forgetfulness; (4) problems concentrating; (5) muscle pain; (6) joint pain; (7) headaches; (8) tender cervical/axillary lymph nodes, and (9) a sore throat. The frequency of each symptom was assessed using a 4-point Likert scale: (0) not at all; (1) a few times a month; (2) a few times a week; and (3) every day. Duration was assessed with a 3-point scale: (0) not; (1) less than six months, and (2) longer than six months. A symptom was assumed to be present if it occurred at least a few times a week for a period of longer than six months.

Patients met the CDC case definitions if they reported medically unexplained severe fatigue, operationalized as scoring ≥ 35 (Janse et al., 2018; Knoop et al., 2008; Tummers et al., 2012; Wiborg et al., 2015) or ≥ 40 (Nijhof et al., 2012; Prins et al., 2001; Stulemeijer et al., 2005; van der Schaaf et al., 2015) on the CIS-fatigue, lasting for at least six months. Furthermore, patients had to report 4 or more symptoms out of eight additional symptoms (PEM, unrefreshing sleep, cognitive problems, muscle pain, joint pain, headaches, tender cervical/axillary lymph nodes, and a sore throat) and should be functionally impaired. In the studies with adult patients, functional impairment was operationalized as scoring > 700 (Janse et al., 2018; Knoop et al., 2008; van der Schaaf et al., 2015; Wiborg et al., 2015) or > 800 (Prins et al., 2001) on the SIP8 (Bergner et al., 1981), or as scoring ≤ 70 (M. Tummers et al., 2012) on the physical and/or social functioning subscale of the SF-36 (Stewart et al., 1988). In one study with adolescent patients (Nijhof et al., 2012) functional impairment was operationalized as scoring ≤ 85 on the physical functioning subscale of the child health questionnaire (CHQ-CF87) (Raat, Landgraf, Bonsel, Gemke, & Essink-Bot, 2002), or with a school attendance of 85% or less; in the second study with adolescent patients (Stulemeijer et al., 2005), functional impairment was operationalized as scoring ≤ 65 on the physical functioning subscale of the SF-36. The medical status of the patient was assessed by a consultant of the department of internal medicine or general practitioner in the case of adults and by a paediatrician in case of adolescents to rule out medical conditions that could explain the presence of severe fatigue. Trained clinical psychologists or psychiatric nurses (the latter in the study of Tummers et al. (2012)) ruled out psychiatric comorbidity that could explain the presence of the symptoms in unstructured clinical interviews or with a structured interview (Clinical Interview for DSM–III–R (SCID–III–R) (Spitzer, Williams, Gibbon, & First, 1992) or the Mini International Neuropsychiatric Interview (Lecrubier et al., 1997)).

Systemic Exertion Intolerance Disease (SEID) diagnosis / National Institute of Clinical Excellence (NICE) criteria: SEID diagnosis / NICE criteria are fulfilled when patients are severely fatigued and disabled for at least six months (SEID) or three months (NICE) and also report PEM, unrefreshing sleep, and cognitive problems (forgetfulness or problems concentrating) and/or orthostatic intolerance (only SEID). Both severe fatigue and functional impairment were operationalized in the same way as with the CDC case definition. The symptoms unrefreshing sleep, cognitive problems (forgetfulness or problems concentrating) and PEM had to be present for at least several times a week. We did not assess orthostatic intolerance. SEID diagnosis and the NICE criteria overlap regarding symptoms required, a six months delay to diagnosis is built into SEID diagnosis while this is three months in the NICE criteria. Thus, all patients fulfilling SEID diagnosis, also fulfilled NICE criteria.

Depressive symptoms were assessed with the Beck Depression Inventory – Primary Care version (BDI-PC) (Beck, Guth, Steew, & Ball, 1997) in which seven items are scored on a 4-point scale (range 0-3). The total score ranges from 0 to 21, a higher score indicating more depressive symptoms. A cut-off score of ≥ 4 is used as an indication for the presence of clinical relevant depressive symptoms (Steer, Cavalieri, Leonard, & Beck, 1999). The BDI-PC is a reliable (Cronbach's α=0.86) and valid instrument (Beck et al., 1997).

Pain severity and impact was assessed by the subscale bodily pain of the SF-36 (Stewart et al., 1988), which consists of two items. One items assesses pain severity and is scored on a 6-point scale, the second assesses impact of pain on functioning and is scored on a 5-point scale. The weighted subscale score ranges from 0 to 100, higher scores indicating less severe pain and less impact of pain on functioning. A cut-off score of < 40 is used as an indication for more severe (impact of) pain.

Cognitive-behavioural factors:

Self-efficacy was assessed with the Self-Efficacy Scale (SES-28) (Prins et al., 2001) assessing patients’ perceived control over their fatigue. Seven items are scored on a 4-point scale (range 7-28), with a higher score indicating higher self-efficacy with respect to fatigue. The internal consistency of this scale was reported in two studies and was respectively 0.68 and 0.77 (de Vree et al., 2002; Prins et al., 2001).

Focusing on bodily symptoms was assessed with the corresponding subscale of the Illness Management Questionnaire Factor III (IMQ-III) (Ray, Weir, Stewart, Miller, & Hyde, 1993). Nine items are scored on a 6-point scale (range 9-54), with a higher score indicating a stronger focus on bodily symptoms. This questionnaire is specifically designed for ME/CFS patients and has been shown to have good psychometric properties (Ray et al., 1993).

Catastrophizing about fatigue was assessed with the Jacobsen Fatigue Catastrophizing Scale (J-FCS) (Jacobsen, Andrykowski, & Thors, 2004). Ten items are scored on a 5-point scale from 1 to 5. The total score ranges from 10 to 50, with a higher score indicating more catastrophizing. The J-FCS is a reliable instrument (Cronbach's alpha .86) (Heins et al., 2013).

Sleep problems and sleep-wake pattern was assessed with the subscale sleep-rest of the SIP (Bergner et al., 1981). The scale consists of seven items (range 0-499), with a higher score indicating more sleep problems and problems regarding sleep-wake pattern.

Physical activity pattern was assessed with actigraphy, a small device worn at the ankle (van der Werf, Prins, Vercoulen, Van der Meer, & Bleijenberg, 2000) measuring the average physical activity level over 12 days. A low active pattern (at least 11 out of 12 days an average daily activity score below the reference score) and a fluctuating activity pattern (less than 11 days scoring below the reference score) (van der Werf et al., 2000) can be discerned. Research has shown that actigraphy yields highly reliable data and is a valid instrument for measuring physical activity (van der Werf et al., 2000).

**Description of all data that was sought**

The following data for each randomized patient was requested: patient identifier, date of birth (or age at randomization), assigned group after randomization, sex, educational level, school absence (for adolescents), duration of symptoms in months, meeting CDC criteria for ME/CFS, scores on the following questionnaires at baseline: CIS-fatigue, SIP8, physical functioning and bodily pain subscale of the SF-36, CDC symptom questionnaire, BDI-PC, SES-28, IMQ-III, J-FCS, physical activity level and activity pattern assessed with actigraphy. Further, post-treatment scores of the CIS-fatigue, SIP8 and physical functioning subscale of the SF-36 were requested. For all questionnaires, it was checked if the same questionnaire version was used. If this was not the case, the data were not used. Data were not standardized because all studies used identical instruments and measures.

**Process of data checking**

We used standard checks to identify missing data, assess data validity, and consistency. We verified the amount of missing data, checked the order of dates, and assessed data validity and consistency.

**Study characteristics**

For the main study characteristics, see Table 1 in the main manuscript. For additional study characteristics, see the Table A1.

**Table A1: Additional study characteristics**

|  |  |  |
| --- | --- | --- |
| **First author (year)** | **Funding source** | **Unavailability of outcomes or putative moderators** |
| Prins et al. (2001)  | Health Insurance Council | SF-36, JFCS, IMQ-III, SES-28,  |
| Stulemeijer et al. (2005) | Foundation for Children’s Welfare Stamps Netherlands | SIP8, BDI-PC (partly), J-FCS, IMQ, SES-28  |
| Knoop et al. (2008) | n/a | J-FCS, IMQ |
| Tummers et al. (2012) | Netherlands Organisation for Health Research and Development | Actigraphy, SIP8, J-FCS |
| Nijhof et al. (2012) | Netherlands Organisation for Health Research and Development | CDC symptom questionnaire, RAND-36, SIP8, BDI-PC, J-FCS, IMQ-III  |
| Wiborg et al. (2015) | n/a | n/a |
| van der Schaaf et al. (2016) | Funder wants to stay anonymous  | n/a |
| Janse et al. (2018) | n/a | n/a |

BDI-PC Brief Depression Inventory for Primary Care (Beck et al., 1997), CDC Centres for Disease Control and Prevention, IMQ-III Illness Management Questionnaire Factor III (Ray et al., 1993), J-FCS Jacobsen Fatigue Catastrophizing Scale (Jacobsen et al., 2004), SES-28 Self-Efficacy Scale (Prins et al., 2001), SF-36 Short Form Health Survey (Stewart et al., 1988), SIP8 Sickness Impact Profile 8 (Bergner et al., 1981), n/anot applicable.

**IPD integrity**

No important issues were identified when checking IPD of the eight studies.

**Risk of bias**

Four studies were classified as having “some concerns”, three as “high risk of bias”, and one study could not be assessed (van der Schaaf et al., 2015) because its main results were not published yet (see Figure 1 and 2). For a description of the concerns, see Table A2 in this appendix. All studies were penalized because the outcome assessor (the patient) was aware of the intervention received. However, this limitation is inherent to the evaluation of psychological treatments using a subjective outcome measure. Three studies were penalized because data were missing for more than 5 percent of participants. Further, two studies were penalized because no study protocol was published or no trial registration was available, which was not obligatory at the time the trials commenced. Despite these penalizations, we thought these studies provided valuable data and found it appropriate to include them.

**Figure A2: Risk of bias domains of the included studies**



Note: One study could not be assessed (van der Schaaf et al., 2015) because its main results were not published yet.

**Figure A3: Risk of bias domains**



Assessment of studies: Prins et al. (2001), Knoop et al. (2008), Tummers et al. (2012), Nijhof et al. (2012), Wiborg et al. (2015) and Janse et al. (2018). One study could not be assessed because its main results were not published yet (van der Schaaf et al., 2015).

**Table A2: Description of concerns**

|  |  |  |
| --- | --- | --- |
| Study | Domain | Concern |
| Prins et al. (2001)  | 3 | Data are missing for a relatively large number of participants (> 5%) |
| 5 | No published protocol or trial register. Hence, no information available whether analyses were conducted in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis**.**  |
| Stulemeijer et al. (2005)  | 3 | Data are missing for a relatively large number of participants (> 5%), with more missing’s in the CBT group than in the control group; carried forward last observations in cases of missing data. |
| 5 | No published protocol or trial register. Hence, no information available regarding whether analyses were conducted in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis. |
| Tummers et al. (2012)  | 3 | Data are missing for a relatively large number of participants (> 5%), with more missing’s in the CBT group than in the control group; carried forward last observations in cases of missing data. |
| All studies  | 4 | The outcome was a participant-reported measure; i.e. the outcome assessors were aware of the intervention received.  |

**Sensitivity analyses**

For the effect sizes, a sensitivity analysis was conducted excluding studies with a high risk of bias. We also conducted a sensitivity analysis including only studies with a waiting list control group (6 out of the 8 studies, excluding the studies of Nijhof et al. (2012) and Prins et al. (2001) with care as usual as comparison.

In the main analysis, the effect size of CBT vs. control on the CIS-fatigue was 0.84 (Cohen’s d). The effect size of CBT on functional impairment (SIP total score) was 0.63. The effect size of CBT on physical functioning was 0.41.

The sensitivity analysis only including studies with “some concerns” with respect to risk of bias showed similar effect sizes as compared to the main analyses (Cohen’s d = 0.88, 0.71 and 0.43, respectively).

The sensitivity analysis excluding studies with a care as usual comparison condition also showed similar effect sizes as compared to the main analyses (Cohen’s d = 0.86, 0.72 and 0.41, respectively).

**Two-way meta-analysis**

A two-way meta-analysis was conducted as a sensitivity analysis to check the robustness of the model of the effects of CBT on fatigue severity, functional impairment and physical functioning. Intervention effects on the outcomes were calculated per individual RCT, by subtracting the average post-intervention value of the outcome of the control group from that of the intervention group, and dividing the result by the pooled standard deviation. Effect sizes were pooled with a random effects model. The percentage of total variance that can be explained by heterogeneity (I2) was calculated, 25% is considered low, 50% moderate, and 75% high heterogeneity.

In the two-way meta-analysis, the overall effect size on fatigue severity was 0.92, on functional impairment 0.67 and on physical functioning 0.42. Outcomes showed moderate heterogeneity for fatigue severity (I2 = 71%), functional impairment (I2 = 68%) and physical functioning (I2 = 63%).

**Figure A4: Forest plots of the two-way meta-analysis on outcomes fatigue severity, functional impairment and physical functioning.**







**Subgroup analyses PEM and NICE/SEID criteria**

To rule out that clinically relevant differences in outcomes between patients with and without PEM, and meeting and not meeting NICE/SEID criteria exist without being statistically significant because of insufficient power, we conducted sensitivity analyses comparing the treatment response of patients with and without PEM, and patients meeting and not meeting NICE/SEID criteria.

**Effect of CBT vs. control in subgroups**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome**  | **Group** | **N** | **Mean difference (95% CI) between CBT and control post CBT** |
| Fatigue severity  | No PEM  | 153 | -10.81 (-16.55 to -5.07) |
|  | PEM | 903 | -10.62 (-14.06 to -7.19) |
| Functional impairment  | No PEM  | 124 | -500.75 (-711.96 to -289.55) |
|  | PEM | 752 | -437.23 (-610.74 to -263.73) |
| Physical functioning  | No PEM | 137 | 5.72 (-5.57 to 17.02) |
|  | PEM | 673 | 10.06 (4.39 to 15.74) |

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome**  | **Group** | **N** | **Mean difference (95% CI) between CBT and control post CBT** |
| Fatigue severity  | No NICE / SEID | 301 | -9.81 (-14.52 to -5.09) |
|  | NICE / SEID | 755 | -10.76 (-14.25 to -7.28) |
| Functional impairment  | No NICE / SEID | 238 | -424.83 (-569.17 to -280.48) |
|  | NICE / SEID | 638 | -448.34 (-651.89 to -244.80) |
| Physical functioning  | No NICE / SEID | 244 | 6.02 (-0.79 to 12.84) |
|  | NICE / SEID | 566 | 10.93 (4.26 to 17.59) |

CBT cognitive behaviour therapy, CI confidence interval

The difference in outcomes between CBT and control were in the same direction in all subgroups and the differences between subgroups were small and not clinically relevant, perhaps with the exception of the physical functioning score but there the patients who reported PEM or met the NICE criteria improved more and not less. There is no indication that patients with PEM and/or patients meeting NICE/SEID criteria benefit less from CBT compared to patients without PEM and/or patients not meeting NICE/SEID criteria.

**R code**

#main effect:

lmer (post-assessment-outcome ~ condition + pre-assessment-outcome + (1 + condition | Study), dataframe)

Moderation analyses:

# model without interaction term:

lmer (post-assessment-outcome ~condition + pre-assessment-outcome + moderator + (1 + condition | Study), dataframe)

# model with interaction term:

lmer (post-assessment-outcome ~ condition + pre-assessment-outcome + moderator\*condition + (1 + condition |Study), dataframe)

anova (model without interaction term, model with interaction term)

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