Cognitive Behavioural Therapy for Fatigue Reduction in Paediatric Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: A Systematic Review and Meta-Analysis

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Table of Contents

List of Figures

List of Tables

Chapter 3: Results

Abstract

Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) is a condition primarily characterised by severe fatigue. In children and adolescents, the condition can have additional profound negative consequences, including increased school absences, psychiatric comorbidities, and significant family burden. Effective treatment to reduce symptoms and other negative consequences is therefore critical. While a gold standard of treatment does not currently exist, numerous studies have demonstrated cognitive behavioural therapy (CBT) to be effective in reducing fatigue severity. The present study conducted a systematic review and meta-analysis to determine the efficacy of different CBT methods in reducing fatigue severity in paediatric patients diagnosed with CFS/ME. Ten studies with a pooled sample of 363 children and adolescents were identified through a search of the Embase, PsychInfo, and PubMed databases. Reporting quality of the included studies was examined using the QualSyst tool. Using a random-effects model, standardised mean differences in fatigue severity scores between pre- and post-CBT were calculated. Heterogeneity, risk of bias, and subgroup analysis of CBT delivery format (including standard, family-focused, and remote) were also investigated. CBT was found to have a large effect in reducing fatigue severity, and no significant difference was found between different therapy delivery formats. However, significant heterogeneity suggests limitations in drawing conclusions from these results. CBT should be recommended to paediatric CFS/ME patients in the form which is most appropriate for the individual. Determining the aetiology of the condition is crucial in order to further develop and improve treatment options.

Keywords: CFS/ME, CBT, children, adolescents, systematic review, meta-analysis

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma in any University, and, to the best of my knowledge, this thesis contains no material previously published except where due reference is made. I give permission for the digital version of this thesis to be made available on the web, via the University of Adelaide's digital thesis repository, the Library Search and through web search engines, unless permission has been granted by the School to restrict access for a period of time.

Sophie Price

28th September 2020

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Chapter 1

Introduction

1.1 What is CFS/ME?

Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) is a debilitating condition for which there is currently no universally accepted treatment. Although the present study focuses on children and adolescents, symptomology is similar in both adult and paediatric populations. The defining characteristic of the condition is severe, persistent fatigue that is not improved by rest, and cannot be explained by exertion or underlying illness (Gregorowski et al., 2019; Knight et al., 2019). There is no definitive diagnostic test for CFS/ME, so diagnosis is made based on subjective symptoms. In addition to fatigue, symptoms often include: post-exertional malaise, unrefreshing sleep, impaired memory and cognition, tender lymph nodes, muscle weakness, joint pain, headaches, sore throat, and hypersensitivities to light and sound (Carruthers et al., 2003; Daniel et al., 2019; Fukuda et al., 1994; Jason, 2006; National Institute for Health and Care Excellence, 2007; Sharpe et al., 1991). Diagnosis is made when patients present with these symptoms, and fulfil one of the numerous case criteria established over the past several decades (Carruthers et al., 2003; Fukuda et al., 1994; Jason, 2006; National Institute for Health and Care Excellence, 2007; Sharpe et al., 1991). However, as no universal consensus has been established as to which criteria should be used, choice of diagnostic criteria remains at the discretion of the clinician.

Diagnosis based on case criteria rather than clear medical biomarkers means that diagnosis of CFS/ME is often a slow process of exclusion, typically involving extensive and invasive tests. Many patients suffer with their illness for years before a diagnosis is made (Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, 2015). This is partly because the subjective phenomenon of fatigue is notoriously difficult to define. The fatigue associated with CFS/ME has been defined as an overwhelming

lack of energy and feeling of exhaustion, which results in a substantial reduction in previous levels of activity (Fukuda et al., 1994; Worm-Smeitink et al., 2017). However, in medical terminology, fatigue can refer to weakness (associated with neuromuscular conditions), sleepiness (associated with primary sleep disorders), or lack of motivation (associated with mood disorders) (Sandler & Lloyd, 2020; Vercoulen et al., 1994). Misdiagnosis or lack of diagnosis may also occur because many medical professionals are sceptical about the serious nature of the condition, do not receive adequate education regarding it, or believe it to be entirely psychological (Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, 2015). Scepticism surrounding the condition also means patients are often subject to stigma by peers, family, and healthcare providers, and left without the support they require (Daniel et al., 2019). Research by Anderson and Ferrans (1997) found that 77% of adults diagnosed with CFS/ME reported negative experiences with healthcare providers, and other research into the stigma surrounding the condition found that 95% of patients seeking treatment reported feeling estranged from the medical system (Anderson et al., 2014).

1.2 Pathophysiology

CFS/ME has likely existed throughout history under a guise of different names and diagnoses. CFS and ME were the names given to two clusters of similar illnesses in the USA in 1984, and in the UK in 1955 respectively (Rowe et al., 2017). The collection of symptoms that characterise the syndrome were first described clinically in 1987 (David et al., 1988), and since that time numerous studies have attempted to explain the aetiology (Komaroff, 2019). Various environmental, metabolic, infectious, inflammatory, immunologic, hormonal, and psychiatric causes have been put forward to explain the condition (Daniel et al., 2019; Straus, 1991). One persistent hypothesis proposes that certain viral pathogens such as Epstein-Barr virus may be responsible for the development of CFS/ME. While prolonged and disabling

fatigue states are common following viral infection (Hickie et al., 2006), there is no evidence for abnormal persistence of any viable pathogens in patients who developed CFS/ME compared to controls who recovered uneventfully (Sandler & Lloyd, 2020).

CFS/ME is currently recognised by the World Health Organisation (WHO) as a neurological disorder, and is believed to be a complex, multisystem neuroimmune disease (Kim et al., 2020). However, the exact mechanisms of the condition remain poorly understood, and extensive research has not found any significant underlying pathological process in patients (Powell et al., 1999).

1.3 Paediatric CFS/ME

Although one paediatric case definition has been developed (Jason, 2006), most children and adolescents are still diagnosed based on criteria established for adult patients. The primary difference between adult and paediatric diagnoses is that symptoms must be present for six months in adult patients and three months in paediatric patients (Carruthers et al., 2003; Jason, 2006).

Prevalence estimates of CFS/ME in children and adolescents vary greatly between studies, ranging from 0.11% to 4.4% (Crawley, 2017; Geraghty & Adeniji, 2019; Jason, 2006). CFS/ME is equally common in both sexes before puberty, but after puberty it is three to four times more likely to occur in females, suggesting that hormonal changes may trigger the difference in gender prevalence (Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, 2015; Gregorowski et al., 2019; Jason, 2006). The wide range in prevalence estimates is likely due to broad diagnostic criteria and differing methods used to identify cases (Geraghty & Adeniji, 2019). Additionally, in children and adolescents, CFS/ME symptoms may be more easily confounded with those of other conditions, as developmental stage may affect how symptoms are expressed and communicated. For example, cognitive impairments and sleep disruptions may manifest as

increased irritability in younger patients, or disturbed learning and memorisation in older children (Jason, 2006).

Notwithstanding that the prognosis for children or adolescents diagnosed with CFS/ME tends to be optimistic, with most patients who receive treatment recovering over one to five years (Joyce et al., 1997; Sandler & Lloyd, 2020), the impact of the condition is profound. Adolescence is usually characterised by accelerated changes in physical, cognitive, and psychosocial functioning, and is a time of considerable stress (Cicognani, 2011). Therefore, paediatric CFS/ME can have devastating effects on an individual's life, disrupting educational, social, and family life at an especially vulnerable developmental stage (Kennedy et al., 2010). In children and adolescents, CFS/ME is the most common cause of long-term absence from school (Similä et al., 2020), with 62% of patients attending only 40% of school or less (Gregorowski et al., 2019), and an average total absence from school of one year (Norris et al., 2017). Prolonged school absence has been shown to have significant impacts on educational achievement, social development, and future employment (Geraghty & Adeniji, 2019). In addition, chronic illness such as CFS/ME in childhood is associated with increased risk of comorbid mental health conditions such as anxiety and depression (Pao & Bosk, 2011). Loades and Chalder (2017) report that at least 30% of young people with CFS/ME also have depression, and that rates of depression in this population are higher than in children with other chronic illnesses including cystic fibrosis and migraine. A 2010 study by Kennedy, Underwood, and Belch showed similar results, reporting that adolescents with CFS/ME had a significantly lower quality of life when compared to healthy peers, and when compared to children with other health conditions such as type 1 diabetes and asthma.

Studies have also found that paediatric CFS/ME can have significant negative effects on the families of sufferers. Missen et al. (2012) found that the majority of families of children with CFS/ME are impacted financially, experiencing decreased income and

increased expenditure. They further report that mothers of children with CFS/ME experience low mood, high anxiety, and have an increased probability of developing mental health problems. Siblings of sufferers are also impacted, with studies revealing high levels of anxiety in this population when compared to matched controls (Velleman et al., 2016).

1.4 Treatment

Despite the devastating impact CFS/ME can have on young people and their families, the unknown aetiology means there is no gold standard of treatment. Most current treatment methods aim to manage symptoms and reduce disability, and may include bed rest, graded exercise therapy (GET), cognitive behavioural therapy (CBT), complementary therapies, and pharmacological treatments (Knight et al., 2013). A recent systematic review investigated randomised controlled trials (RCTs) for CFS/ME in adult patients (Kim et al., 2020). Of the 55 RCTs reviewed, there were three trials in which pharmacotherapies were effective (two using immunomodulators and one using coenzyme Q10). Of the non-pharmacological therapies reviewed, CBT was effective in five trials, GET in three, and acupuncture, tuina (a Chinese massage therapy) (Li et al., 2017), and integrative rehabilitation (involving exercise, CBT, heart-rate monitoring, and mediation) (Taylor, 2004) effective in one trial respectively. The authors of the systematic review concluded that to date, the overall results of RCTs have been more positive for non-pharmacological interventions than for pharmacological treatments (Kim et al., 2020), and particularly for psychotherapeutic approaches.

Other studies have echoed these conclusions, and have found GET and CBT to most effectively reduce symptoms and disability in patients with CFS/ME (White et al., 2011; Wiborg et al., 2010). As such, these therapies are currently the two first-line treatments recommended for children and adolescents (National Institute for Health and Care Excellence, 2007; Vink, 2019). GET is based on the theory that CFS/ME is perpetuated by a physiological process of deconditioning, as well as the avoidance of physical activity.

Treatment does not aim to directly challenge any illness-related cognitions, but instead focuses solely on increasing physical activity (White et al., 2011). CBT for CFS/ME however, encourages the patient to gradually build up their physical activity, while also addressing dysfunctional illness and fatigue-related beliefs (Wiborg et al., 2012).

1.5 The Cognitive Behavioural Model

The cognitive behavioural formulation of CFS/ME is shown in Figure 1. The model suggests that physical, social, and psychological factors may interact and contribute to the development of the condition, and that beliefs and behaviours may serve to maintain fatigue and disability (Janse et al., 2017; Loades & Chalder, 2017). Cognitive behavioural models propose that CFS/ME begins with a period of intense fatigue, which is attributed by the patient, their family, or their healthcare provider to a physical illness that will improve with rest. Therefore, a period of rest and reduced activity is recommended to aid recovery. This reduced activity leads to physical deconditioning and a worsening of physical symptoms, which results in increased sensitivity and intolerance to fatigue. A heightened focus on physical symptoms, and the belief that symptoms may indicate severe illness serve to increase feelings of worry, helplessness, and loss of control. As a result of these beliefs, the patient may then further reduce their physical activity, or increase it to the point of overexertion (known as ‘boom or bust’), which both exacerbates symptoms, and continues the cycle (Heins et al., 2013; Loades & Chalder, 2017). It is important to note that the cognitive behavioural model has been put forward not as a cause of CFS/ME, but as a system that serves to perpetuate the symptoms of the condition, as well as the extent of the disability it causes.

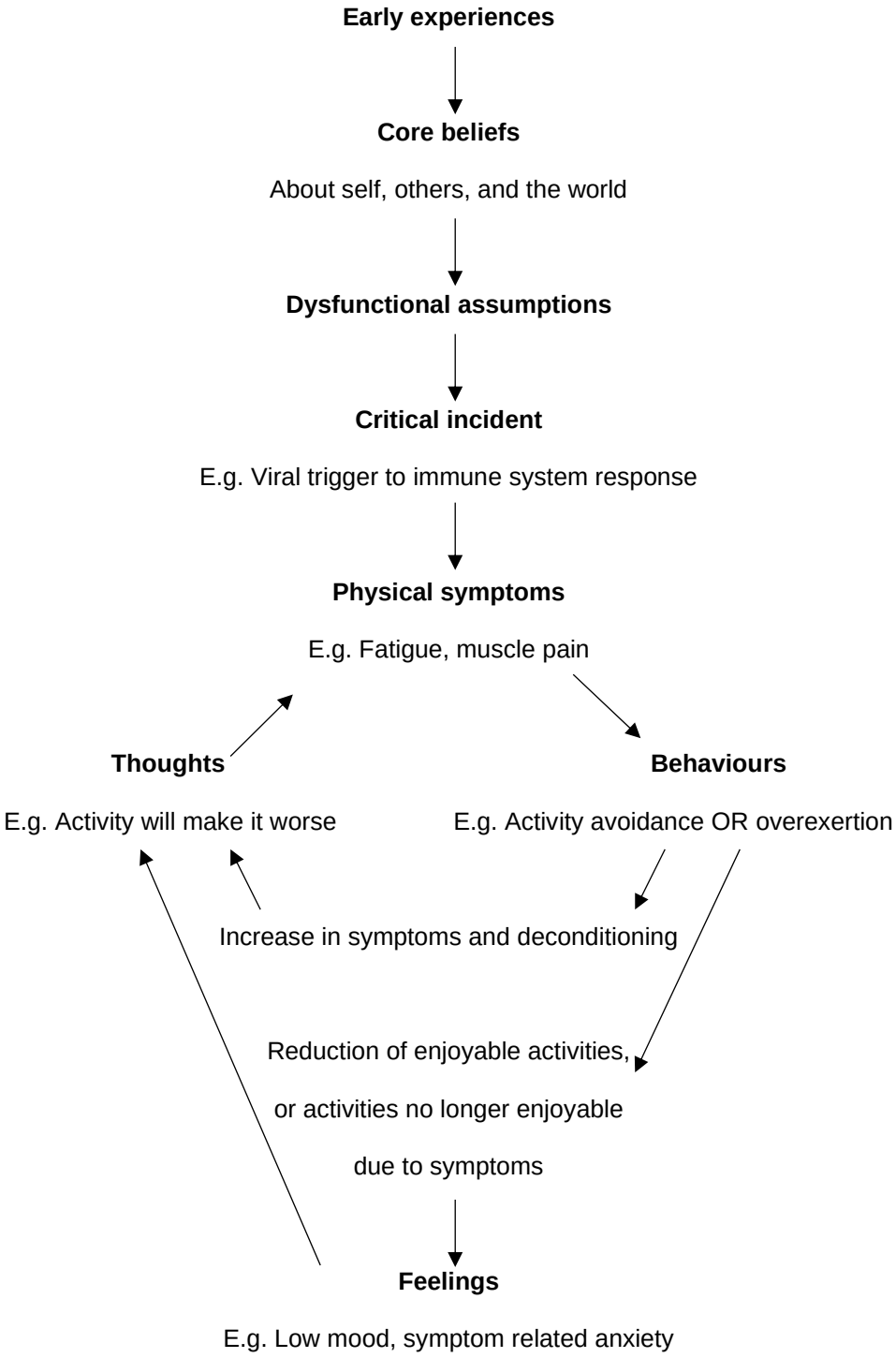

Figure 1

Cognitive Behavioural Formulation of CFS/ME (adapted from Loades and Chalder, 2017)

1.6 CBT for CFS/ME

For any condition for which CBT is used as a treatment, the therapy first involves the identification of biased or dysfunctional cognitions. These are then subject to objective evaluation, with the goal of developing more functional and balanced thoughts and beliefs (Graham & Reynolds, 2013). For young people with CFS/ME, the cognitive component of therapy aims to challenge negative illness and fatigue-related cognitions. For example, misinterpretations related to the cause and meaning of symptoms, or fear regarding physical activity may be focussed on (Burgess & Chalder, 2011). The cognitive component may also address depression and anxiety if these are comorbid conditions, but this is not the primary focus. The behavioural component of CBT aims to monitor and manage activity levels, and work towards a gradual increase (in contrast to the 'boom or bust' cycles which can often occur). Sleep habits are also addressed, with an effort to promote sleep hygiene (e.g. waking up at the same time each morning, avoiding naps, and maintaining optimal environmental conditions for sleep) (Loades & Chalder, 2017).

Despite the successes in using CBT to treat symptoms of paediatric CFS/ME (Knoop, Bleijenberg, et al., 2007), the treatment is not without its criticisms. Some authors claim that the demonstrated reduction in symptom severity is simply a result of the patient adapting to living with a chronic medical condition, and that a true treatment effect does not actually exist (Knoop, Bleijenberg, et al., 2007). Others claim that using CBT to treat CFS/ME-associated fatigue implies the condition is psychological rather than physical in nature, which may therefore be met with frustration and resistance by patients (Dickson et al., 2007).

1.7 CBT Delivery

Even for patients with psychological conditions for which CBT is less controversial, (such as depression, adjustment disorder, and anxiety), studies have shown that only about 20% of those referred for therapy enter treatment (Mohr et al., 2006; Weddington, 1983).

Several barriers have been identified as possible reasons for this, including: long waiting lists; lack of available therapists; inaccessibility of clinics (due to geographical location or lack of transport); high financial costs; perceived stigma of attending a mental health clinic; and family time constraints (Cuijpers et al., 2008; Mohr et al., 2006; Spence et al., 2011). For patients diagnosed with CFS/ME, another level of unique challenges may be added, with some patients being able to sit up only for a few minutes, or requiring the use of a wheelchair as a result of their fatigue (Burgess & Chalder, 2011). A remote CBT delivery format (i.e. consultations with therapists via phone or email) has the potential to remove many of these barriers, allowing accessible options to patients who may otherwise be forced to forego treatment. Previous research investigating telephone-delivered therapy for patients with obsessive compulsive disorder found telephone consultations reduced treatment time by 40% compared to face-to-face sessions, with equal effectiveness (Lovell et al., 2006). Improvements in technology in more recent years have brought the development of online CBT modules that the patient is able to work through in their own time, either on their own or with family. This method of CBT delivery has been shown to be appealing to an adolescent population, with many young people preferring email or online counselling rather than in-person or phone-based therapy (King et al., 2006). Further, these methods have also been shown to be successful, with internet-delivered CBT proving effective in reducing symptoms of obsessive-compulsive disorder in adolescents (Lenhard et al., 2014), and symptoms of CFS/ME in adults (Janse et al., 2018).

A family-focused format of CBT delivery may also be beneficial in the context of paediatric CFS/ME. As the condition impacts not only the young person affected, but also their parents and siblings, therapy that can take into account illness-specific demands (e.g. managing sleep and exercise regimens), as well as issues relating to education, finances, and the maintenance of social and family relationships is important (Smith et al., 2020). In a

review of family-focused interventions for families affected by long-term health conditions, Smith et al. (2020) write that family involvement in psychotherapy has a positive impact on the individual, helping to empower them to self-manage their condition and adhere to treatment schedules. The effect on the family as a whole is also positive, with benefits including positive attitudinal shifts for parents, and an improved family climate (Pavuluri et al., 2004).

1.8 Disagreement and Limitations in Previous Research

Several previous RCTs have investigated treatment for paediatric CFS/ME. In 2013, Knight et al. conducted a systematic review of these trials, comparing interventions including: exercise-based; pharmacological; psychological; and multidisciplinary. The authors concluded that CBT was the most beneficial intervention in reducing symptoms of CFS/ME, and the most acceptable to patients. The authors therefore recommended that any intervention for paediatric CFS/ME adopt a CBT framework. Further support for the treatment comes from studies with adult populations, with recommendations largely based on positive results of a systematic review by Price et al. (2008), and a large scale trial by White et al. (2011). Since this time, numerous studies of CFS/ME treatments in adult populations have supported these results, documenting improvement in fatigue severity after CBT (Stubhaug et al., 2018). However, recent research has re-analysed the results of the studies by Price et al. (2008) and White et al. (2011), and found serious methodological errors in their design, reporting that these studies show no positive effect of CBT on symptom reduction for CFS/ME, and that it may even be detrimental to patients (Marks et al., 2016; Vink, 2019). CBT as a treatment for CFS/ME therefore remains controversial, and further clarification regarding the success or otherwise of this treatment is required.

There is also disagreement in the current literature regarding the effectiveness of remotely-delivered CBT. The importance of a therapeutic bond between therapist and patient

is well established as a factor in the successfulness of CBT treatment (Horvath et al., 2011; King & Bambling, 2001; Martin et al., 2000). In the context of remote CBT, concerns have been raised that a lack of visual cues and time delay (in the context of online therapy) may hinder the therapist's ability to convey warmth and empathy, resulting in a weaker therapeutic bond (King et al., 2006; Reynolds et al., 2006; Rochlen et al., 2004). However, other studies have demonstrated that a comparable therapeutic alliance is able to be developed through remotely-delivered therapy (Preschl et al., 2011), and that outcomes are equally as successful as in traditional, face-to-face CBT (Janse et al., 2018; Lenhard et al., 2014; Lovell et al., 2006).

As yet, there have been no systematic reviews or meta-analyses that have specifically investigated the effect of CBT on fatigue severity outcomes in a paediatric population, nor compared the effectiveness of different CBT delivery methods.

1.9 The Current Systematic Review and Meta-Analysis

Due to the devastating impacts that CFS/ME can have on the lives of paediatric patients, it is crucial that a treatment is found to reduce fatigue severity and enable sufferers to reach their pre-morbid level of functioning. This is an important outcome at the individual and familial level, but also at a public health level to reduce healthcare utilisation and costs, and at a societal level to maximise future workforce participation. Although an effective therapy that targets the biological basis of CFS/ME remains to be found, CBT is currently the recommended treatment for young people with this condition. CBT has been shown to reduce fatigue severity in this population, but standard face-to-face CBT may not be feasible in all contexts or acceptable to all consumers. It is important that the delivery method of CBT considers the physical constraints of sufferers, as well as the financial and logistical aspects of treatment. It is also essential to consider the family environment, and the developmental, social, and educational concerns that are unique to a paediatric population.

This new systematic review and meta-analysis aims to: 1. Determine the effect of CBT on fatigue severity in adolescent sufferers of CFS/ME; and 2. Compare fatigue severity outcomes between different CBT delivery methods. This information could potentially be used to optimise effective and accessible treatments for young people diagnosed with CFS/ME.

Chapter 2

Methods

2.1 Literature Search

A systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Liberati et al., 2009) in May 2020. Three electronic databases were searched: Embase (a biomedical research database with coverage from 1947 to present); PsychInfo (a psychological and social sciences research database with coverage from 1806 to present); and PubMed (a biomedical and life sciences research database with coverage from the late 1700s to present). A list of constructs to be included as search terms were compiled with the help of a Liaison Librarian at the University of Adelaide.

Synonyms for each search term were compiled from the Emtree thesaurus in the Embase database. Search terminology was varied slightly between databases in order to adapt for differing truncation, wildcard, and adjacency operations. Variations in spelling of search terminology was also accounted for depending on the preferences of each database (See Appendix A for logic grids). Truncation was only used for single words or for the last word of phrases in the PubMed search, due to a limitation in the PubMed truncation enforcement (Vieira et al., 2019). Complete logic grids for search terms with Boolean operators are shown in Appendix A.

2.2 Eligibility Criteria

To be included in the present study, articles were required to fulfil the following criteria:

1. The study design was a randomised controlled trial (RCT), or a cohort study. Articles were available in full text format, and available in English. No publication date restriction was applied.

2. Participants were children or adolescents (i.e. aged 18 years or under), and those classified as having CFS/ME met criteria as defined by the United States Centres for Disease Control and Prevention (Fukuda et al., 1994), the Canadian Consensus Criteria (CCC) (Carruthers et al., 2003), the NICE Clinical Guidelines (National Institute for Health and Care Excellence, 2007), the Oxford criteria (Sharpe et al., 1991), or the International Association of Chronic Fatigue Syndrome (IACFS) criteria (Jason, 2006). Studies involving both adult and paediatric patients were included only if data for a subgroup <18 years of age were provided separately.
3. The intervention administered was CBT or based on CBT principles according to the author of the respective study and did not involve pharmacotherapy.
4. Fatigue severity was measured as an outcome using a reliable and valid self-report scale.

Articles were excluded if they met any of the following criteria:

1. Full text was not available.
2. Full text was not available in English.
3. Data for paediatric patients were not provided separately.
4. Participants were reported as having significant history of trauma or severe psychiatric comorbidity.
5. Fatigue severity was not assessed using a self-report scale.
6. The delivery method of CBT was not specified.
7. The study design was not amenable to meta-analysis (i.e. qualitative research, systematic reviews, or case reports).

2.3 Study Selection

The screening protocol is depicted in Figure 2. The initial search yielded a total of 4021 results. Duplicate articles were then removed, resulting in a total of 3885 records.

Citation screening of titles and abstracts was conducted with these records, which resulted in 60 full texts being retained. Full text articles were then obtained, and these were screened against the eligibility criteria. A further 45 articles were removed through this process. Most articles removed through full text screening were studies involving adult participants, but the age range was not specified in the title or abstract.

The remaining articles were then screened to check for independence of samples. Five studies were identified in which results were from the same sample of participants: Heins et al. (2010); Wiborg et al. (2010); Knoop, Prins, et al. (2007); Knoop, Bleijengerg, et al. (2007); and Stulemeijer et al. (2005). In this case, only the study by Stulemeijer et al. (2005) was retained, as the additional studies did not add any unique data.

Two studies were long-term follow ups of previous trials (also included), with the same cohort of participants. One of these (Knoop et al., 2008) provided separate data for an additional sample of participants who had received CBT since the first trial, including their baseline and post-treatment scores. The other study (Nijhof et al., 2013) provided only post-treatment and long-term follow up data for the original sample, and was therefore excluded. The removal of this article reduced the total number of articles retained to 10.

To minimise bias in study selection, eligibility assessment of the 60 full text articles was performed independently by a second reviewer (an honours psychology student), with excellent inter-rater reliability demonstrated (100%, $\kappa = 1$).

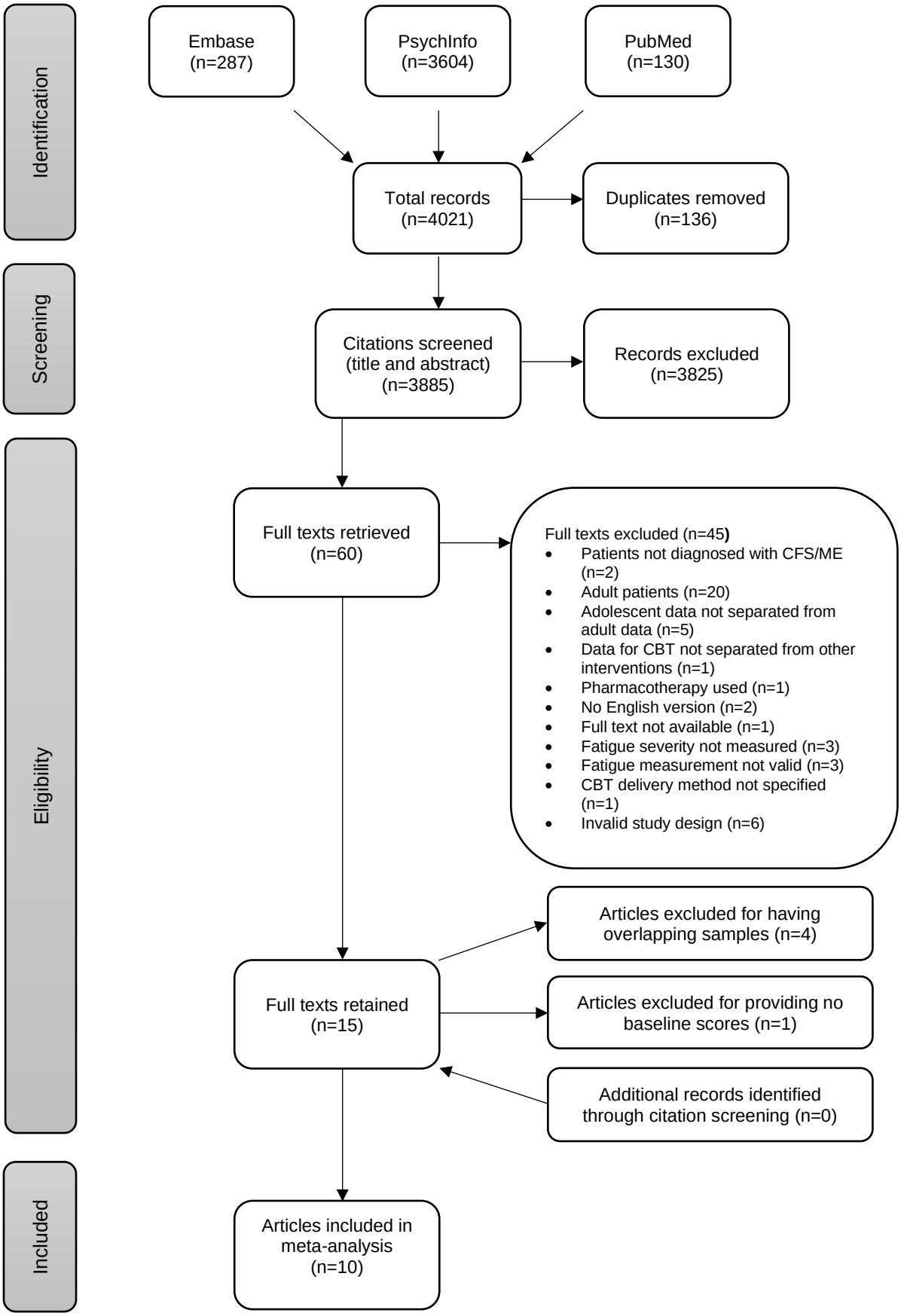

Figure 2

Screening Protocol

2.4 Data Collection

In accordance with the PRISMA statement (Liberati et al., 2009), a data extraction sheet was created to obtain required information from the retained studies (see Appendix B). The information collected included study characteristics (i.e. year, country); participant characteristics (i.e. age range, CFS/ME diagnostic criteria); outcome measure (i.e. fatigue measure and time period for outcome assessment); intervention details (i.e. CBT delivery method); and effect size data (means and standard deviations). One study (Chalder et al., 2002) provided only median and interquartile range information, so estimated mean scores and standard deviations were calculated in accordance with a formula developed by Wan et al. (2014).

2.5 Risk of Bias in Individual Studies

The likelihood that treatment effects reported in meta-analyses reflect a true treatment effect is dependent on the validity of the included studies (Liberati et al., 2009). To determine the extent to which errors and biases were minimised in the included studies, quality was assessed using the QualSyst tool (Kmet et al., 2004). This was chosen above the Cochrane risk of bias tool (as is recommended by the PRISMA statement (Liberati et al., 2009)), as the QualSyst tool is designed to be used with various types of study designs, rather than only RCTs.

Each study was assessed on 14 criteria (shown in Appendix D) and given a score of two (completely meeting criteria), one (partially meeting criteria), or zero (not meeting criteria). After accounting for criteria that were not applicable to certain studies, a total score and a summary score were calculated. This process was repeated by a second independent reviewer, with results demonstrating substantial agreement and good interrater reliability (91.43%, $\kappa = 0.83$). Where disagreement occurred, discussion between the two reviewers was undertaken and studies re-evaluated to reach consensus.

2.6 Meta-Analysis

Data were entered into Comprehensive Meta-Analysis software (CMA, Version 3.0, Biostat, Englewood, NJ). The primary outcome measure was the difference in fatigue severity scores between pre- and post-CBT treatment. The included studies provided post-treatment scores for differing time points, so a time point was selected as per the guidelines provided by Borenstein et al. (2009). Fatigue scores from six months post-treatment were used where possible, as most studies provided scores for this time point. Where this was not possible, the closest time point to six months post-treatment was used (see Appendix C).

As the outcome variable was continuous in nature and was derived from different scales of measurement for different studies, the meta-analyses were performed by computing the standardised mean difference between pre- and post-treatment scores. Pre-post treatment correlation coefficients were needed to calculate effect sizes. As the included studies did not provide this data, Rosenthal's (1995) conservative estimate of $r = 0.7$ was used. The direction of the measurement scale did not differ between studies (all were positive), so no further adjustment was required to account for this. Hedges' *g* and 95% confidence intervals (CIs) were used to measure effect size, and were calculated using means, standard deviations (SDs) and sample sizes for each study. Hedges' *g* expresses the average intervention effect in units of the pooled standard deviation of difference scores (Higgins, 2008). This measure was chosen instead of Cohen's *d*, as one of the included studies had a small sample size, and Cohen's *d* can overestimate the standardised mean difference in small samples (Knouse et al., 2017). As per Cohen's (1992) effect size guidelines, an effect of 0.20 was considered small, and effect 0.50 was considered medium, and an effect of 0.80 was considered large.

A random effects model was chosen for the analyses, as the CBT delivery methods between studies were vastly different, meaning the studies were assumed to be heterogeneous in nature. The random effects meta-analysis was computed using the DerSimonian and Laird

method (Dersimonian & Laird, 1986), in which the standard errors of the effect size of each study are adjusted to incorporate a measure of assumed heterogeneity (Higgins, 2008).

2.7 Evaluation of Heterogeneity

Assessing heterogeneity is necessary to determine the consistency of effects across studies, and therefore the generalisability of the findings of a meta-analysis (Higgins et al., 2003). Heterogeneity is demonstrated when the observed intervention effects are more different from each other than would be expected due to chance alone. Although the included studies were assumed to be heterogeneous due to the differing methods of CBT used in each, they were sufficiently homogenous in terms of participants, interventions, and outcomes for meta-analysis to be undertaken (Higgins, 2008).

Heterogeneity between studies was first examined visually by inspecting the forest plot for overlapping confidence intervals. Secondly, a chi-squared test (Cochrane's Q) assuming the null hypothesis (that all studies are measuring an equal effect) and its corresponding p value were then used to quantify heterogeneity. Lastly, the impact of any heterogeneity was then examined using the I^2. This statistic determines the total variation in estimated effect size that is due to heterogeneity rather than chance (Higgins, 2008). Interpretation of I^2 was based on guidelines provided by Higgins (2008) while also taking into consideration the significance value from the chi-squared test.

2.8 Subgroup Analysis

When heterogeneity is evident across the studies used in meta-analysis, it is not always appropriate to draw conclusions from the pooled treatment effect estimate (Richardson et al., 2019). Therefore, subgroup analysis was undertaken to determine whether the treatment effect varies as a function of CBT delivery method. The studies were grouped according to the method of CBT delivery used in each. These methods were: *standard* (therapy sessions were face-to-face and one-on-one between clinician and patient); *family-*

focused (one or more family members were present for some of the treatment sessions); and *remote* (therapy was delivered via telephone, email, or online modules). The summary effects for each subgroup within the meta-analysis were calculated based on a random-effects model assuming a common among-study variance. Significant results were then compared using Cochran's *Q* test in the SPSS software (IBM SPSS Statistics for Windows, 2017. Version 25.0 Armonk, NY: IBM Corp.).

2.9 Risk of Bias Across Studies

Issues such as publication bias and selective reporting in individual studies can be problematic when drawing conclusions from the results of meta-analyses (Liberati et al., 2009). To address this, CMA was used to plot the standardised difference in means for each included study against the inverse of its standard error to generate a funnel plot of precision. The funnel plot was first examined visually to check for any deviation from the funnel-shaped distribution which is assumed in the absence of any bias (i.e. the larger studies will be shown towards the top of the graph and close to the mean effect size, and the smaller studies will be close to the bottom of the graph and dispersed across a wider range of values) (Borenstein et al., 2009).

After visual inspection of the funnel plot, the Egger test was used to quantify any bias captured by the plot. In this test, the standardised effect for each study is regressed on the inverse of its standard error (i.e. precision). In the absence of bias, it is assumed that small studies will be associated with small standard effects, and large studies will be associated with large standard effects. This test examines whether the association between estimated treatment effect and study size is greater than what would be expected to occur by chance (Egger et al., 1997).

Chapter 3

Results

3.1 Study Characteristics

Ten studies comprising a total of 363 children and adolescents diagnosed with CFS/ME were included in the meta-analysis. Six studies were RCTs, and four were cohort studies. The median sample size was 33.5 (range = 6 – 68). The study with the largest sample size was the Dutch cohort from Nijhof et al. (2012) (n = 68), which comprised 18.73% of the pooled sample. Studies from the UK made up the greatest percentage of the pooled sample (52.9%; $N_{studies}$ = 6; n = 192), with studies from the Netherlands (33.33%; $N_{studies}$ = 3; n = 121) and Egypt (13.77%; $N_{studies}$ = 1; n = 50) comprising the remainder.

The CDC was the most commonly used criteria for diagnosis of CFS/ME and was used in 40% of studies. The Oxford criteria was used in 30%, and a combination of the Oxford and CDC criteria were used in the remaining 30%. Studies from the Netherlands used the Chalder Fatigue Questionnaire (Chalder et al., 1993) as a fatigue severity measure, with most studies using Likert scoring (with the exception of the study by Chalder et al. (2002), in which bimodal scoring was used). Studies from the UK used the Checklist Individual Strength fatigue severity subscale (Worm-Smeitink et al., 2017), and the study from Egypt utilised the Fatigue Assessment Scale (Michielsen et al., 2003). All fatigue scales used in the included studies are reliable and valid, measure an identical construct, and have high internal consistency (Chalder et al., 1993; Michielsen et al., 2003; Worm-Smeitink et al., 2017).

Four studies deviated from the selected outcome assessment period of 6 months after the conclusion of treatment: Stulemeijer et al. (2005) and Knoop et al. (2008) assessed outcome at 5 months post-treatment commencement; Chalder et al. (2002) assessed outcome at 6 months post-treatment commencement; and Al-Haggar et al. (2006) assessed outcome at 18 months post-treatment commencement.

Table 1

Included Study Details

Study Name (First Author and Year)	Country	Study Design	*N*	Age *(Years) (Mean ± SD)*	Gender *(% F)*	CFS/ME Criteria	Fatigue Measure	Outcome assessed	CBT method
Al-Haggar 2006	Egypt	RCT	50	13.1 ± 3.2	60%	CDC	FAS	18 months post-treatment commencement	Standard
Burgess 2019	UK	Cohort study	6	11-18[†]	33%	Oxford	CFQ	6 months post-treatment	Family-focused
Chalder 2009	UK	RCT	32	15 ± 0.61[*]	66%	Oxford/CDC	CFQ	6 months post-treatment	Family-focused
Chalder 2002	UK	Cohort study	18	15.25 ± 0.90[*]	85%	Oxford	CFQ	6 months post-treatment	Family-focused
Knoop 2008	Netherlands	RCT	18	10-17.2[†]		CDC	CIS	5 months post-treatment commencement	Standard
Lloyd 2012a	UK	RCT	24	15 ± 1.47		Oxford/CDC	CFQ	6 months post-treatment	Family-focused

Lloyd 2012b	UK	Cohort study	63	15.12 ± 0.75*	63%	Oxford	CFQ	6 months post-treatment	Remote
Nijhof 2012	Netherlands	RCT	68	15.9 ± 1.3	79%	CDC	CIS	6 months post-treatment commencement	Remote
Rimes 2014	UK	Cohort study	49	14.9 ± 1.7	63%	Oxford/CDC	CFQ	6 months post-treatment	Remote
Stulemeijer 2005	Netherlands	RCT	35	15.6 ± 1.3	89%	CDC	CIS	5 months post-treatment commencement	Standard

Notes. Participants in the study by Knoop et al. (2008) were a smaller cohort within a larger study. CDC = United States Centres for Disease Control and Prevention; RCT = randomised controlled trial; FAS = Fatigue Assessment Scale; CFQ = Chalder Fatigue Questionnaire; CIS = Checklist Individual Strength.
*Means and standard deviations were not reported, and these data were calculated based on medians and IQRs (Wan et al., 2014).
†Age range provided only.

3.2 Participant Demographics

Based on the eight studies that provided sufficient age information for participants, the pooled sample had a mean age of 14.98 (SD = 0.83, *n* = 339; see Table 1). Based on the eight studies that provided gender information, the sample consisted of more females than males, with females comprising 70.81% and males comprising 29.19% (*n* = 281; see Table 2).

Table 2

Sample Demographics and CBT Methods ($N_{studies}$ = 10; $N_{participants}$ = 363)

	$N_{studies}$	$N_{participants}$	%	Mean	SD
Participant demographics					
Age (years)	8	339		14.98	0.83
Gender	8				
Female		227	70.81		
Male		94	29.19		
		321	100%		
CBT method					
Standard	3	103	28.37%		
Family-focused	4	80	22.04%		
Remote	3	180	49.59%		
	10	363	100%		

3.3 Risk of Bias in Individual Studies

Reporting quality was high, and risk of bias was low in all included studies, with a mean summary score of 93% (SD = 0.06%; see Appendix D). All studies met the conservative criteria (75%) for inclusion in meta-analyses as provided by Kmet et al. (2004). Studies by Chalder et al. (2002), Lloyd, Chalder, Sallis, et al. (2012), and Nijhof et al. (2012) fulfilled 100% of applicable criteria. Studies by Al-Haggar et al. (2006) and Stulemeijer et al. (2005) fulfilled 96% of applicable criteria; Knoop et al. (2008), Lloyd, Chalder, and Rimes

(2012), and Rimes et al. (2014) fulfilled 90% of applicable criteria; and Chalder et al. (2009) and Burgess et al. (2019) respectively fulfilled 88% and 82% of applicable criteria.

The proportion of studies meeting the QualSyst tool criteria (Kmet et al., 2004) can be seen in Figure 3. All included studies were of an appropriate design, utilised an appropriate method for selecting participants, reported their assessment methods, reported variance, and made conclusions that were supported by their results (Criteria 2, 3, 8, 11 and 14: 100% met; see Figure 3). Criteria 6 and 7 (blinding of participants and investigators) were not applicable for any of the included studies. Most studies controlled for confounding variables (90%), and sufficiently reported the participant characteristics and the results (80%). Over half the studies sufficiently described the question under investigation and used appropriate methods for analysis (60%). Random allocation of participants was not applicable for 60% of studies, but was appropriately described in the studies for which it was. Sample size was appropriate in all but one study (Burgess et al., 2019), in which there were only six participants, and no estimated effect size was reported.

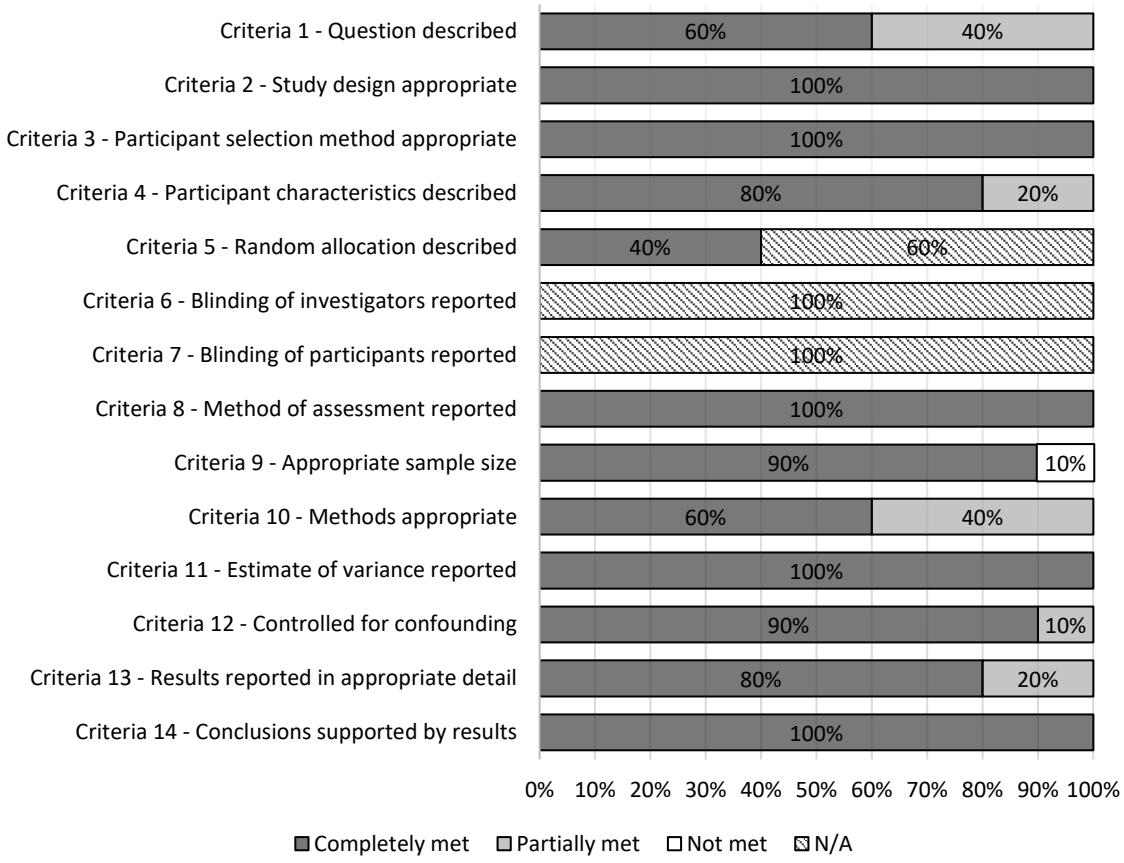

Figure 3

Proportion of Individual Studies Meeting the QualSyst Tool Criteria (Kmet et al., 2004)

3.4 Meta-analysis

3.4.1 Effect Size

A very large estimated treatment effect was found across the ten pooled studies for fatigue severity scores between pre- and post-CBT (Hedges' $g = 1.87$, $p < 0.001$). Visual inspection of the forest plot shows several CIs do not overlap, indicating statistical heterogeneity is likely present (Figure 4). A large chi-squared statistic relative to its degrees of freedom indicate significant heterogeneity of treatment effects ($Q(9, N = 363) = 257.29$, $p < 0.001$)). The I^2 statistic of 96.5% demonstrates that nearly all the variability across studies is due to heterogeneity rather than chance.

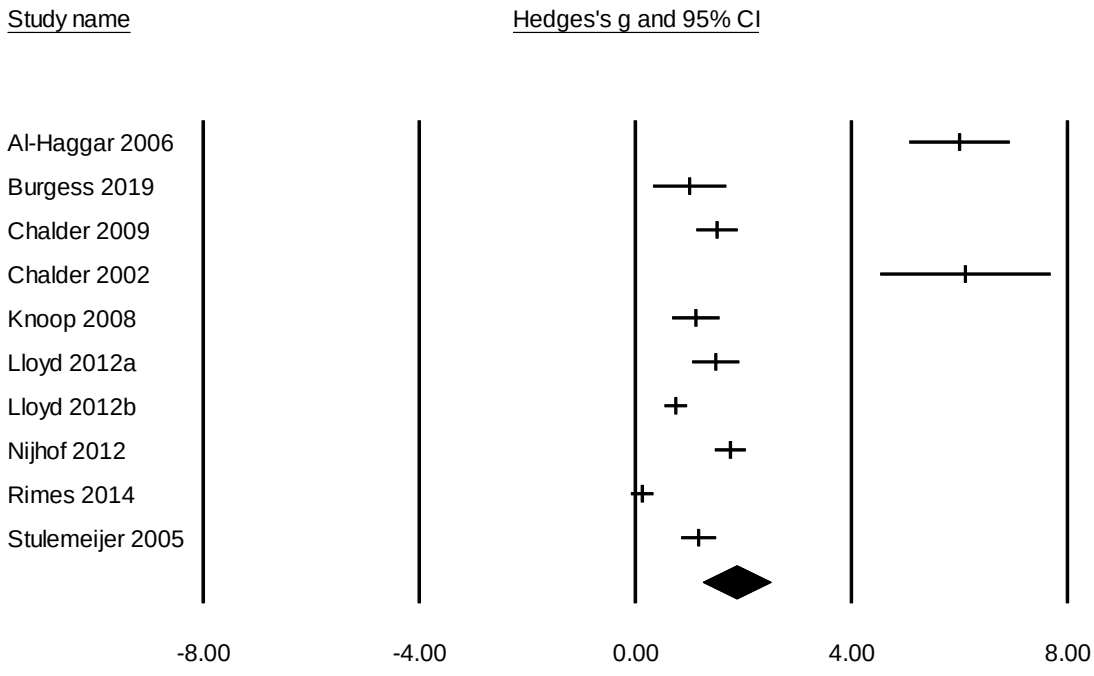

Figure 4

Forest Plot Showing Hedges' g with 95% CIs for Individual Studies, and Overall Summary Effect (Diamond)

Table 3

Difference Between Fatigue Severity Scores Pre- and Post-CBT Treatment

Study name	*Statistics for each study*						
	Hedges' *g*	Standard error	Variance	Lower limit	Upper limit	Z-value	*p*-value
Al-Haggar 2006	6.00	0.48	0.23	5.07	6.94	12.58	<0.001
Burgess 2019	1.00	0.35	0.12	0.32	1.69	2.89	<0.001
Chalder 2009	1.51	0.20	0.04	1.12	1.9	7.63	<0.001
Chalder 2002	6.11	0.81	0.65	4.53	7.7	7.56	<0.001
Knoop 2008	1.12	0.23	0.05	0.68	1.57	4.95	<0.001
Lloyd 2012a	1.49	0.23	0.05	1.05	1.93	6.59	<0.001
Lloyd 2012b	0.75	0.11	0.01	0.53	0.96	6.85	<0.001
Nijhof 2012	1.76	0.15	0.02	1.47	2.05	11.79	<0.001
Rimes 2014	0.13	0.11	0.01	-0.09	0.34	1.17	<0.24
Stulemeijer 2005	1.17	0.17	0.03	0.84	1.5	6.99	<0.001
Total	**1.87**	**0.32**	**0.1**	**1.25**	**2.5**	**5.86**	**<0.001**

3.4.2 Subgroup Analyses

A random effects subgroup analysis was conducted to investigate the method of CBT delivery as a potential cause of heterogeneity, and to compare effect size across these methods. The largest treatment effect was found for standard CBT (Hedges' $g = 2.70$, $p = 0.01$), followed by family-focused CBT (Hedges' $g = 2.17$, $p = <0.001$) and remote CBT (Hedges' $g = 0.87$, $p = 0.05$). Significant effects were found for standard and family-focused CBT, and a borderline significant effect found for remote CBT. Comparison of these effects using Cochrane's *Q* test indicated the difference between subgroups was not statistically significant ($\chi^2(2) = 2$, $p = 0.37$).

Substantial heterogeneity was still evident across subgroups, and was greatest for standard CBT ($Q(2, N = 103) = 95.56$, $p = <0.001$; $I^2 = 97.91\%$), followed by remote ($Q(2, N = 180) = 77.83$, $p = <0.001$; $I^2 = 97.43$) and family-focused ($Q(3, N = 80) = 34.42$, $p = <0.001$; $I^2 = 91.28$).

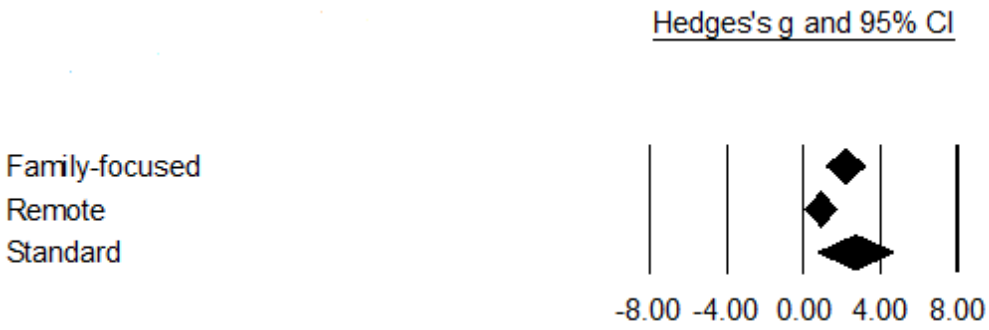

Figure 5

Forest Plot Showing Hedges' g and 95% CIs for Subgroups Within Meta-Analysis

3.4.3 Risk of Bias Across Studies

On visual inspection, the funnel plot of precision (Figure 6) showed a higher concentration of studies on one side of the mean. This indicates the likely presence of bias in some of the included studies, and suggests smaller studies were more likely to be published because they had larger than average effects. Egger's test quantified this information, indicating the possibility of bias across studies cannot be excluded (intercept = 8.81; p = 0.01; CI = 3.05-14.57).

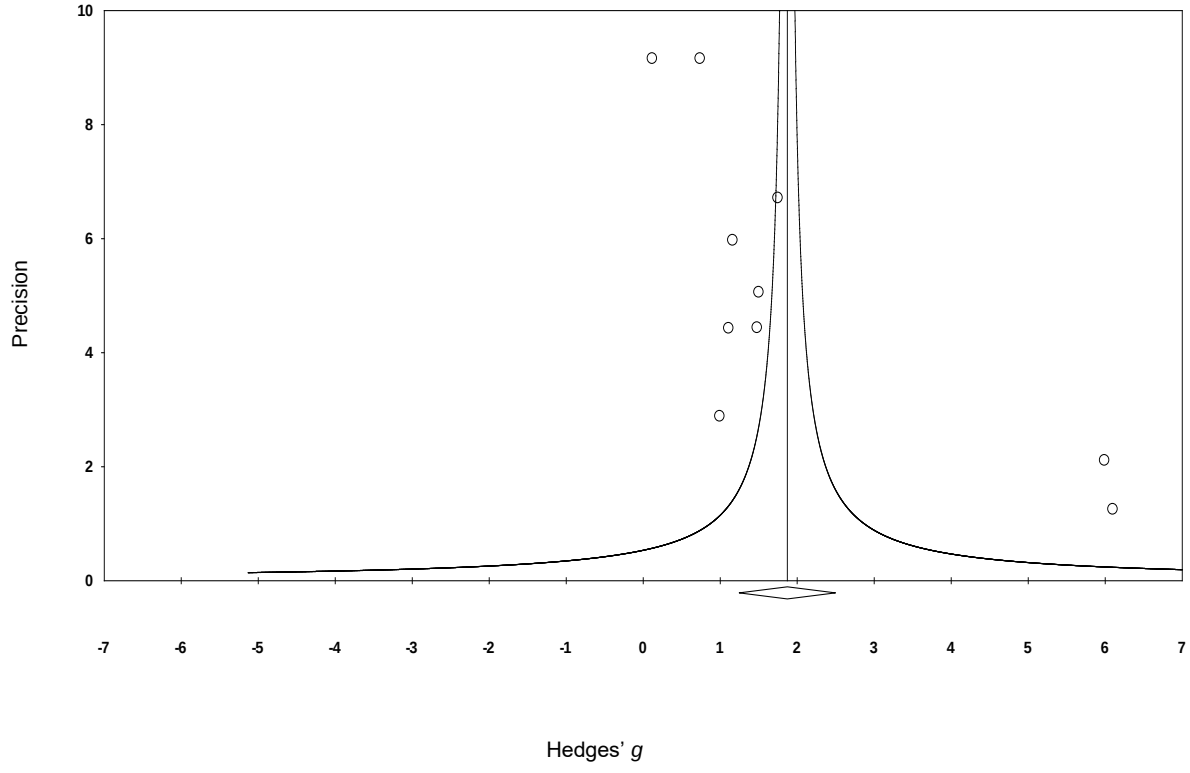

Figure 6

Funnel Plot of Precision by Hedges' g for Fatigue Severity Pre- and Post-CBT

Chapter 4

Discussion

4.1 Key Findings

This review and meta-analysis primarily aimed to determine the effect of CBT on fatigue severity in young people diagnosed with CFS/ME. A secondary aim was to compare pre- and post-CBT fatigue severity scores between different CBT delivery formats, including standard, remote, and family-focused. After a systematic review of the literature and screening of abstracts and full-text articles, ten studies consisting of RCTs and cohort studies were selected for meta-analysis. This analysis identified a very large treatment effect for CBT on fatigue severity in the pooled sample of 363 children and adolescents diagnosed with CFS/ME. Subgroup analysis revealed the largest treatment effect was for standard CBT, followed by family-focused, then remote. However, the difference in effect size between the three formats was not significant.

4.2 CBT for Reducing Fatigue Severity

For both adult and paediatric patients diagnosed with CFS/ME, current recommendations generally favour CBT above other common treatments (National Institute for Health and Care Excellence, 2007; Vink, 2019). A systematic review by Knight et al. (2013) found strong evidence for CBT in successfully treating symptoms of CFS/ME in paediatric patients when compared with other interventions, including GET and medication. However, there are also critics of CBT interventions, who claim that to treat CFS/ME with a psychological-based therapy is to disregard the physical nature of the condition. These critics suggest that CBT is not only ineffective, but that recommending it as a treatment frustrates patients and their families, and perpetuates the long-discredited theory that CFS/ME is psychogenic in nature (Byrne, 2020; Dickson et al., 2007). The present systematic review and meta-analysis found promising results consistent with those of Knight et al. (2013).

Subjective levels of fatigue in the pooled sample were found to be significantly lower after CBT, therefore extending support for the current recommendation of CBT as a first-line treatment for children and adolescents diagnosed with CFS/ME (National Institute for Health and Care Excellence, 2007; Vink, 2019). This finding is also supportive of the cognitive behavioural model of CFS/ME, which suggests that the physical symptoms of the illness are perpetuated by negative cognitions relating to them (Janse et al., 2017; Loades & Chalder, 2017). By actively addressing and challenging unconstructive illness-related beliefs and assumptions, CBT effectively reduced fatigue severity in the pooled sample of children and adolescents diagnosed with CFS/ME. Although this is an encouraging result which extends our understanding of effective treatments for CFS/ME, an important limitation should be noted before drawing conclusions from this finding. Due to restrictions imposed by the inclusion and exclusion criteria, this systematic review and meta-analysis did not use results from untreated control groups for comparison of fatigue severity scores. Rather, fatigue severity was measured in the same participants over an average time period of approximately seven months. While data relating to the natural course of paediatric CFS/ME when left untreated is uncertain (Joyce et al., 1997), we cannot rule out the possibility that some observed reduction in fatigue severity post-CBT may have happened regardless of treatment.

Heterogeneity across the included studies was considerable, indicating significant variability in the intervention effects found. One reason for this was likely the clinical diversity in the studies due to the different types of CBT delivery methods used. Therefore, CBT delivery format as a potential source of heterogeneity was explored further in the subsequent subgroup analysis. While it was beyond the scope of the present study to explore any further explanations for the observed heterogeneity beyond this subgroup analysis, the use of a random effects approach means that the meta-analytic model is adjusted to account

for assumed variation. Therefore, the presence of heterogeneity should not discount the significant treatment effects found (Higgins et al., 2003).

4.3 CBT Delivery Method

4.3.1 Remote

Reluctance on behalf of clinicians and policymakers to recommend remotely-delivered CBT has traditionally centred around concerns that a therapeutic bond between therapist and patient may not develop to the same extent as in face-to face therapy, thus reducing the effectiveness of treatment (King et al., 2006; Preschl et al., 2011). However, previous research comparing standard and remotely-delivered interventions has shown the two formats to be equally efficacious for a diverse array of conditions (including tinnitus, social anxiety, and obsessive compulsive disorder) (Lenhard et al., 2014; Lovell et al., 2006; Spence et al., 2011; Wagner et al., 2014). Results of the present study were consistent with this previous research. Although the significance was borderline and the effect size was smaller than for other CBT delivery methods, no significant difference in effect was identified between remotely-delivered CBT and other formats. These results are unsurprising for several reasons: Firstly, previous research by Preschl et al. (2011) and Reynolds et al. (2006) has compared online and face-to-face CBT for adults diagnosed with conditions including depression and anxiety, and found that a therapeutic bond is able to develop to a comparable extent through both formats. This means that concerns around the lack of the development of a therapeutic alliance in remotely-delivered CBT are unfounded. Secondly, it has been suggested that the cognitive behavioural approach translates well to remote delivery. This is because CBT interventions are characteristically systematic, with treatments often detailed in a manual or protocol. Therapy is structured in such a way that the therapist functions as a coach, providing information to the patient, and teaching them reproducible

skills that are then practised between sessions (Musiat & Tarrier, 2014). It could therefore be assumed that CBT could be operationalised for remote delivery in a similar way to other online or computerised educational courses.

4.3.2 Family-focused

Despite the noted benefits of a family-focused approach in the context of CBT for children and adolescents (including the facilitation of treatment self-management and improved relationships with family members) (Smith et al., 2020), the present study found no significant difference in fatigue severity outcomes between individuals with CFS/ME who received family-focused CBT and those who received standard or remote therapy. This finding is consistent with previous studies by Reynolds et al. (2013) and Bodden et al. (2008), which showed no significant difference in outcomes between young people who received standard CBT and those who received therapy in a family-focused context. It should also be noted that some studies have demonstrated that family involvement in CBT can actually increase some of the noted barriers to therapy, such as financial cost to the consumer and difficulties coordinating the availabilities of family members for appointments (Bodden et al., 2008). However, while previous literature and the present study have found no greater benefit of family-focused CBT for the affected individual, in the context of chronic childhood illness, it is vital to take into account the impact on other family members. As it has been documented that paediatric CFS/ME can have a significant negative effect on the mental health of parents and siblings of the affected individual (Missen et al., 2012; Velleman et al., 2016), it is important to consider that family-focused CBT can lead to improved mental health outcomes for the family as whole (Pavuluri et al., 2004). The studies included in this systematic review and meta-analysis in which family-focused CBT was used (Burgess et al., 2019; Chalder et al., 2009; Chalder et al., 2002; Lloyd, Chalder, & Rimes, 2012) only

examined outcomes of intervention in the young person diagnosed with CFS/ME. It is therefore suggested that future research examines mental health outcomes for all family members before and after family-focused CBT intervention.

4.4 Strengths and Implications of the Present Study

The foremost strength of this systematic review and meta-analysis lies in the close adherence to the PRISMA criteria. The design of the PRISMA checklist and flowchart means that when followed, the methods used to identify, screen, and describe included studies are easily reproducible. Following the PRISMA criteria also means that reporting quality is of a high standard, with results reported fully and transparently, therefore increasing the potential veracity of these results (Liberati et al., 2009). A second important strength of the present study are the measures taken to decrease potential bias. The full-text article screening and risk of bias stages in the systematic review process were undertaken independently by two separate reviewers. Any discrepancies in the decisions made were then resolved through collaboration and discussion until consensus was reached. This process reduces the possibility of rejecting any relevant articles, as well as the possibility of including any articles that are of a poor quality. Lastly, the present study provides a unique contribution to available literature in the field of paediatric CFS/ME treatment. There have previously been no systematic reviews or meta-analyses that have specifically investigated the effect of CBT on fatigue severity in the context of paediatric CFS/ME, nor compared the effectiveness of different CBT formats. The contribution to the literature by the present study will be valuable in optimising not only the treatment used for young people with CFS/ME, but also the method of delivery that will be most suitable.

Key findings of this study have several important implications for the future treatment of young people diagnosed with CFS/ME. Firstly, the significant reduction in fatigue severity post-CBT in the pooled sample suggests CBT is an effective treatment, and should remain a

first-line recommendation. Results indicating there is no significant difference between standard and remotely-delivered CBT is also an important finding, with practical implications for young people for whom face-to-face therapy in a clinic may not be appropriate. Patients may be hindered by logistical aspects such as geographical location or lack of transport, or by physical aspects determined by the severity of their fatigue and other CFS/ME symptoms (Burgess & Chalder, 2011; Mohr et al., 2006). Some patients may also choose to avoid face-to-face CBT appointments due to psychological barriers, such as the perceived stigma of attending a mental health clinic or seeing a psychologist (Cuijpers et al., 2008). For individuals who are not able, or would prefer not to attend standard CBT sessions due to these constraints, the option to work through online modules, or speak to a therapist via phone or email from their home may be a welcome opportunity. Further hinderances, such as long waiting lists and lack of therapist availability (Mohr et al., 2006), may also be reduced by remotely delivered CBT. CBT delivered via phone or email may require significantly fewer therapist hours (Lovell et al., 2006; Spence et al., 2011), potentially allowing therapists to take on more patients, and thereby reducing waiting periods.

4.5 Limitations of the Present Study

In addition to those already noted, the present study has several limitations that are likely to affect the accuracy of the calculated treatment effect. Firstly, the search strategy and choice of databases meant that grey literature and studies published in languages other than English were not included. Therefore, it is possible that studies otherwise meeting inclusion criteria were omitted. Secondly, in order to calculate Hedges' g from the data provided by each included study, pre- and post-CBT correlation coefficients were needed, but were not provided by the study authors. Therefore, Rosenthal's (1995) suggested estimate of $r = 0.7$ was used, meaning a strong, positive correlation between pre- and post-CBT fatigue severity scores was assumed. The use of an approximation influences how confidently and accurately

we can say the overall effect size represents a true population effect. However, the approximation used was conservative, meaning it likely underestimated rather than overestimated the true effect. Thirdly, the funnel plot and Egger's test indicate that bias was likely evident in some of the included studies. The funnel plot showed an asymmetry in the scatter of the smaller studies, with more showing a positive than a negative result. This suggests that the estimated effect size calculated may be an overestimation of the true effect (Higgins, 2008). Egger's test quantified this asymmetry with an intercept that deviated from zero, thereby suggesting the occurrence of selective reporting and publication bias (i.e. perhaps smaller studies that showed negative results were left unpublished) again leading to a possible overestimation of treatment effect (Egger et al., 1997).

A further limitation to note is that heterogeneity remained evident even after the studies were grouped by CBT delivery method and subgroup analysis was undertaken. This suggests that methodological diversity was likely present across the included studies. Two suggestions as to the cause of this may be variations in the fatigue measurement scales used, and the differing duration of treatment. Although the FAS, the CFQ, and the CIS all measure the construct of fatigue (Chalder et al., 1993; Michielsen et al., 2003; Worm-Smeitink et al., 2017), the complex, subjective, and multifaceted nature of fatigue means there is likely to be differences between them. For example, the CFQ measures fatigue through two dimensions (physical fatigue and mental fatigue) (Chalder et al., 1993), whereas the CIS measures four (fatigue severity, concentration problems, reduced motivation, and reduced activity levels) (Worm-Smeitink et al., 2017), as does the FAS (subjective experience of fatigue, reduction of concentration, reduction of motivation, reduced level of physical activity) (Michielsen et al., 2003). Low concurrent validity has also been identified between the CIS and the CFQ (Worm-Smeitink et al., 2017), adding to the possibility that these differences in measurement scales contributed to the high levels of heterogeneity within the included studies. The number

of CBT sessions and duration of treatment also varied considerably between studies. These variables ranged from six CBT sessions over three months in the study by Lloyd et al. (2012), to 40 CBT sessions over 18 months in the study by Al-Haggar et al. (2006). It is therefore likely that the differing intensities of interventions contributed to the heterogeneity between studies that was evident even after CBT delivery method was controlled for. The use of a random-effects model throughout limits the impact this heterogeneity has on the overall estimated effect size, indicating that this heterogeneity need not detract from the potential usefulness of the results found.

One final limitation to be considered is the reliance of the included studies on the use of self-report fatigue measurement scales. The use of self-report measures means that any reduction in fatigue severity will be subjective rather than objective in nature. While some may argue that a subjective reduction in fatigue is still a promising outcome, it means that we cannot conclusively determine whether CBT was responsible for the improvement. Several researchers have suggested that self-report responses as an outcome measure of CBT in unblinded trials may simply be the participants writing what they believe the researchers want to hear, and that a subjective reduction in fatigue should be supported by an objective increase in activity (Edwards, 2017; Lilienfeld et al., 2014). Ghatineh and Vink (2017) also noted this potential problem, and suggest an actometer (a device designed to record activity and rest) could be used in future research as an objective outcome measure.

4.6 Suggestions for Future Research

It is evident from reviewing the current literature, and from the limited number of studies available for inclusion in the present study, that current recommendations for the treatment of paediatric CFS/ME are based primarily on results of trials with adult patients. With the exception of the systematic review by Knight et al (2013), there is a clear lack of research into treatments and interventions that are effective for young people diagnosed with

this condition. Therefore, due to the unique familial, educational, and social needs that make paediatric patients distinct from adults with CFS/ME, there is a need for further research into specialised treatments for this population. It is suggested that this research compare fatigue severity post-treatment to fatigue severity in an untreated, waiting list control group, or a group treated with other methods, including GET and medication. This would allow a more accurate treatment or intervention effect to be determined than if fatigue severity is measured pre- and post-treatment in the same cohort.

Due to the relatively small number of studies included in this systematic review and meta-analysis, CBT was only compared between three delivery formats. Further research into more diverse methods of CBT with children and young people could lead to more informative comparisons. For example, group-based therapy, or school-based CBT for those well enough to attend school, may be preferable to some patients and families if these methods are found to be as efficacious as other formats. Additionally, further research into CBT delivery methods may mean that future systematic reviews and meta-analyses are able to have a broader scope, and potentially further divide subgroups (e.g. remote delivery may be separated into telephone and computer-delivered therapy). Lastly, this further research may provide more definitive effect size information for remotely delivered CBT, as the significance of the effect in the present study was borderline.

4.7 Conclusion

The current systematic review and meta-analysis aimed to determine the effect of CBT on fatigue severity in children and adolescents diagnosed with CFS/ME. It also aimed to compare the effectiveness of different CBT delivery methods, including standard, remote, and family-focused. This study found a very large treatment effect for CBT in reducing the severity of fatigue in the population under investigation. These results support previous research (Knight et al., 2019), and show promising evidence for CBT in the future treatment

of fatigue associated with CFS/ME in children and adolescents. The reduction in fatigue severity post-CBT was evident regardless of whether therapy was delivered in a standard, remote, or family-focused format. Large treatment effects were found for each of these delivery methods, with no significant difference in effectiveness identified. While conclusions drawn from these results are limited due to some weaknesses and inconsistencies within the included studies, some valuable recommendations are able to be made based on the findings. Firstly, it is suggested that CBT remains a first-line treatment for fatigue in children and adolescents diagnosed with CFS/ME. Standard CBT is effective in reducing fatigue in this population, and is a beneficial treatment tool when there are no logistical, physical, psychological or financial barriers preventing the young person from attending sessions. Furthermore, as remote and family-focused CBT delivery formats have also been shown to be effective, these options should certainly be considered, and their use based on the needs and preferences of the young person and their family. As controversy remains surrounding the use of CBT in the treatment of CFS/ME, it is recommended that future research in the field aims to establish an accurate treatment effect estimate. As the lack of control groups were a major limitation evident in the present study, it is suggested that RCTs are undertaken in which patient outcomes after CBT are compared to outcomes of those on a waiting list or in an untreated control group. It is also suggested that objective fatigue measurements, such as actometer readings, are used in addition to subjective fatigue measurement scales. This would reduce potential biases that come from reliance on purely self-report measures to assess outcomes. Finally, until there is a consensus within the medical community as to the nature of CFS/ME, patients are likely to be victims of the stigma and uncertainty that surrounds this condition. It is therefore crucial that research into the biological basis of CFS/ME continues, with the objective that finding a cause will allow

patients to receive fast, conclusive diagnoses, and effective, unanimously accepted treatments.

References

Note. References included in meta-analysis are denoted by *

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Appendices

Appendix A: Logic Grids with Boolean Operators

Embase

Cognitive behavioural therapy	AND	CFS/ME	AND	Adolescents
"Cognitive behavioral therapy"/exp OR "Cognitive behav* therap*":ti,ab OR "Cognitive behav* treatment*":ti,ab OR "Cognitive therap*":ti,ab OR "Cognitive treatment*":ti,ab OR CBT:ti,ab		"Chronic fatigue syndrome"/exp OR "Chronic fatigue syndrome":ti,ab OR "Fatigue syndrome":ti,ab OR "Myalgic encephalomyelitis":ti,ab OR Fatigue/exp OR Fatigue:ti,ab OR "Epidemic neuromyasthenia":ti,ab OR "Iceland* disease":ti,ab OR "Systemic exertion intolerance disease":ti,ab OR CFS:ti,ab OR ME:ti,ab		Adolescent/exp OR Adolescen*:ti,ab OR Child/exp OR Child*:ti,ab OR Juvenile/exp OR Juvenile*:ti,ab OR Teen*:ti,ab OR Youth*:ti,ab OR "Young adult*":ti,ab OR "Young person":ti,ab OR "Young people":ti,ab OR Pediatric*:ti,ab OR Paediatric*:ti,ab

PsychINFO

Cognitive behavioural therapy	AND	CFS/ME	AND	Adolescents
Cognitive behavior therapy.sh OR Cognitive behav$ therap$.tw OR Cognitive behav$ treatment$.tw OR Cognitive therapy.sh OR Cognitive therap$.tw OR Cognitive treatment$.tw OR CBT.tw		Chronic fatigue syndrome.sh OR Chronic fatigue syndrome.tw OR Fatigue syndrome.tw OR Myalgic encephalomyelitis.tw OR Fatigue.sh OR Fatigue.tw OR Epidemic neuromyasthenia.tw OR Iceland$ disease.tw OR Systemic exertion intolerance disease.tw OR CBT.tw OR ME.tw		Adolescen$.tw OR Child$.tw OR Juvenile$.tw OR Teen$.tw OR Youth$ OR Young adult$.tw OR Young person.tw OR Young people.tw OR Pediatric$.tw OR Paediatric$.tw

PubMed

Cognitive behavioural therapy	AND	Chronic fatigue syndrome	AND	Adolescents
Cognitive behavioral therapy[mh] OR Cognitive behavioral therap*[tiab] OR Cognitive behavior therap*[tiab] OR Cognitive behavioural therap*[tiab] OR Cognitive behaviour therap*[tiab] OR Cognitive behavioral treatment*[tiab] OR Cognitive behavioural treatment*[tiab] OR Cognitive behavior treatment*[tiab] OR Cognitive behaviour treatment*[tiab] OR Cognitive therap*[tiab] OR Cognitive treatment*[tiab] OR CBT[tiab]		Fatigue syndrome, chronic[mh] OR Chronic fatigue syndrome[tiab] OR Fatigue syndrome[tiab] OR Chronic fatigue[tiab] OR Myalgic encephalomyelitis[tiab] OR Fatigue[mh] OR Fatigue[tiab] OR Epidemic neuromyasthenia[tiab] OR Iceland* disease[tiab] OR Systemic exertion intolerance disease[tiab] OR CFS[tiab] OR ME[tiab]		Adolescent[mh] OR Adolescen*[tiab] OR Child[mh] OR Child*[tiab] OR Juvenile*[tiab] OR Teen*[tiab] OR Youth*[tiab] OR Young adult[mh] OR Young adult*[tiab] OR Young person[tiab] OR Young people[tiab] OR Pediatric*[tiab] OR Pediatrics*[tiab]

Appendix B: Data Extraction Coding Sheet

Citation (lead author and year)	
Country	
Study design	• Randomised controlled trial • Cohort study
Intervention group sample size	
Intervention group demographics	• Age range • Gender
CFS/ME diagnostic criteria	• Oxford • US CDC • CCC • NICE Clinical Guidelines • IACFS

Fatigue measure	• Chalder Fatigue Questionnaire
	  ○ Likert scoring
	  ○ Bimodal scoring
	• Checklist Individual Strength
	• Fatigue Assessment Scale

CBT delivery method	• Standard • Family-focussed • Remote
Outcome assessment time points	• Baseline • Post-treatment • 6-12 months • 12 months and over

Effect size data	• Mean
	  ○ Baseline
	  ○ Post-treatment
	• Standard deviation
	  ○ Baseline
	  ○ Post-treatment

Appendix C: Risk of Bias in Included Studies

	Al-Haggar 2006	Burgess 2019	Chalder 2009	Chalder 2002	Knoop 2008	Lloyd 2012a	Lloyd 2012b	Nijhof 2012	Rimes 2014	Stulemeijer 2005
1. Question sufficiently described?	1	2	1	2	2	1	2	2	1	2
2. Study design evident and appropriate?	2	2	2	2	2	2	2	2	2	2
3. Method of subject/comparison group selection or source of information/input variables described and appropriate?	2	2	2	2	2	2	2	2	2	2
4. Subject (and comparison group if applicable) characteristics sufficiently described?	2	2	2	2	1	1	2	2	2	2
5. If interventional and random allocation was possible, was it described?	2	N/A	2	N/A	N/A	N/A	N/A	2	N/A	2
6. If interventional and blinding of investigators was possible, was it reported?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
7. If interventional and blinding of subjects was possible, was it reported?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
8. Outcomes and (if applicable) exposure measures well defined and robust to measurement/misclassification bias? Means of assessment reported?	2	2	2	2	2	2	2	2	2	2

9. Sample size appropriate?	2	0	2	2	2	2	2	2	2	2
10. Analytic methods described/justified and appropriate?	2	1	1	2	1	2	2	2	2	1
11. Some estimate of variance is reported for the main results?	2	2	2	2	2	2	2	2	2	2
12. Controlled for confounding?	2	1	2	2	2	2	2	2	2	2
13. Results reported in sufficient detail?	2	2	1	2	2	2	2	2	1	2
14. Conclusions supported by the results?	2	2	2	2	2	2	2	2	2	2
Total score	23	18	21	22	20	20	22	24	20	23
Total possible score	24	22	24	22	22	22	22	24	22	24
Summary score	0.96	0.82	0.88	1	0.9	0.9	1	1	0.9	0.96