A review of the predisposing, precipitating and perpetuating factors in Chronic Fatigue Syndrome in children and adolescents

Kate Lievesley, Katharine Rimes, Trudie Chalder

PII: S0272-7358(14)00049-X
Reference: CPR 1369

To appear in: Clinical Psychology Review

Received date: 12 February 2013
Revised date: 21 February 2014
Accepted date: 23 February 2014


This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
A review of the predisposing, precipitating and perpetuating factors in Chronic Fatigue Syndrome in children and adolescents

Authors: Kate Lievesley\textsuperscript{a}, Katharine Rimes\textsuperscript{c}, Trudie Chalder\textsuperscript{a,b,*}

\textsuperscript{a} Chronic Fatigue Research and Treatment Unit, South London and Maudsley NHS Trust, 1\textsuperscript{st} Floor, Mapother House, De Crespigny Park, Denmark Hill, London, United Kingdom, SE5 8AZ; 

\textsuperscript{b} Academic Department of Psychological Medicine, 3\textsuperscript{rd} Floor, Weston Education Centre, King’s College London, Cutcombe Road, London, United Kingdom, SE5 9RJ; 

\textsuperscript{c} Institute of Psychiatry, Kings College London, De Crespigny Park, Denmark Hill, London, United Kingdom, SE5 8AF; 

Corresponding author. *, Academic Department of Psychological Medicine, 3\textsuperscript{rd} Floor, Weston Education Centre, King’s College London, Cutcombe Road, London, United Kingdom, SE5 9RJ. Email: Trudie.Chalder@kcl.ac.uk; Telephone: 02032283411; Fax: 02032285074.
Abstract

Chronic Fatigue Syndrome (CFS) is a condition characterised by severe mental and physical fatigue coupled with profound disability. The purpose of this review was to investigate psychological, social and physiological factors associated with fatigue and disability in CFS in children and adolescents. The review aimed to gain an overview of the strength of evidence for the relationship between these different factors and CFS in young people. Seventy-nine studies met the inclusion criteria and were included in the review. A narrative synthesis of these studies was conducted. The strongest and most consistent finding was that rates of psychiatric co-morbidity, predominantly anxiety and depressive disorders, were higher in young people with CFS compared to healthy controls or illness control groups. Studies suggested that many children and adolescents with CFS reported that their illness began with an infection and there was some objective and prospective evidence to support this. Preliminary evidence suggested a link between CFS and a family history of CFS, high expectations from both the parent and child, personality traits such as conscientiousness and physical illness attributions. The evidence was limited by methodological problems. Few studies were prospective in nature and future research should address this. Clinical implications of the findings are discussed and a hypothesised model of the factors associated with CFS in children and adolescents is presented.

Keywords: Chronic Fatigue Syndrome (CFS); Review; Young people; Factors; Infection; Co-morbidity; Model.
Table of Contents

1. Introduction ..................................................................................................................... 4
   a) The purpose of the review ............................................................................................... 4
   b) Diagnosis ......................................................................................................................... 5
   c) Prevalence ....................................................................................................................... 6
   d) Incidence ......................................................................................................................... 7
   e) Adolescence .................................................................................................................... 8
   f) Gender ............................................................................................................................. 8
   g) Ethnicity .......................................................................................................................... 9
   h) Clinical Picture ................................................................................................................ 9
   i) Theoretical underpinnings to clinical treatment ............................................................ 11
   j) Aim of the review ......................................................................................................... 12

2. Method .......................................................................................................................... 13

3. Results ........................................................................................................................... 14
   a) Overview ....................................................................................................................... 14
   b) Predisposing / Vulnerability factors (may also act as perpetuating factors) ................. 15
      i. Genetic and familial factors ...................................................................................... 15
      ii. Psychiatric Disorder .................................................................................................. 16
      iii. Personality ................................................................................................................. 18
      iv. Self-esteem ................................................................................................................ 18
      v. High Expectations ..................................................................................................... 19
      vi. Attributions ............................................................................................................... 20
      vii. Illness perceptions and cognitions ............................................................................ 20
      viii. Parental involvement............................................................................................... 22
         a. Maternal Distress ...................................................................................................... 22
         b. Parental care and overprotection ........................................................................... 22
      ix. Immune and Endocrine Factors ............................................................................... 23
     x. Activity levels ........................................................................................................... 26
    xi. Sleep ............................................................................................................................ 27
    xii. Body Mass Index ....................................................................................................... 27
c) Precipitating or triggering factors ................................................................. 28
   i. Infection ........................................................................................................... 28

d) Studies in childhood informing adult diagnoses of CFS .................................... 29

4. Discussion .......................................................................................................... 31
   a) Main findings .................................................................................................. 31
   b) Key Limitations .............................................................................................. 36
   c) Suggested future research ............................................................................. 37
   d) Limitations of the review ............................................................................... 38
   e) A hypothesised model of CFS in children and adolescents ............................ 38
   f) Clinical Implications ....................................................................................... 41

5. Acknowledgements .............................................................................................. 43

6. References .......................................................................................................... 43

1. Introduction

   a) The purpose of the review

Chronic Fatigue Syndrome (CFS) is a condition characterised by severe mental and physical fatigue that is not alleviated by rest, coupled with significant disability. This study focuses on children and adolescents with CFS. Sometimes called Myalgic Encephalomyelitis (ME), it can be associated with a variety of physical complaints such as muscle pain, headache, sore throat and increased somnolence (Marshall et al., 1991). Petrov et al. (2011) reported that other than fatigue, headaches and sleep disturbance are the most common symptoms in young people with CFS.

The purpose of this review is to investigate factors associated with predisposing, precipitating and perpetuating fatigue and disability in children and adolescents with CFS. As a greater number of studies investigating CFS in young people emerge, a review of these findings becomes increasingly important. This review will identify strengths, limitations and methodological weaknesses in the
studies conducted to date as well as gaps in the literature. An overview of the factors involved in CFS may help in the development of interventions. Based on the findings of the review, clinicians may be able to better tailor existing interventions to suit the needs of the individual.

b) Diagnosis

For a diagnosis of CFS, fatigue must be the principal symptom, of definite onset and disabling, affecting both physical and mental functioning. According to the Oxford criteria, CFS is defined as self-reported persistent or relapsing fatigue lasting six or more consecutive months, for at least 50% of the time (Sharpe et al., 1991). Appropriate clinical tests are undertaken to rule out any medical conditions known to result in chronic fatigue.

Patients are excluded if diagnosed with current schizophrenia, substance abuse or proven organic brain disease. However, anxiety and depressive disorders are not necessarily reasons for exclusion. The Fukuda criteria (Fukuda et al., 1994) states that the criteria for severity of fatigue must be met, as well as four or more of the following symptoms being concurrently present for 6 months; 1) impaired memory or concentration 2) sore throat 3) tender cervical or sore lymph nodes 4) muscle pain 5) multi-joint pain 6) new headaches 7) un-refreshing sleep and 8) post-exertion malaise. The Fukuda case definition was devised primarily for adults with CFS. A child and adolescent focused definition has since been proposed (Jason et al., 2006). As with the adult criteria, a thorough patient history is taken along with ruling out any other possible diagnoses. The authors emphasise a need to involve the parents in this process and a key difference to the adult definition is that the authors removed the necessity for a definite onset as it may not be possible for the young person to pinpoint an exact onset for their fatigue.

In adults, the criterion duration is 6 months. For children, researchers and clinicians recognised the need for children to be diagnosed as quickly as possible at a crucial time of their development so
the diagnosis can be made after three months (e.g. Jason et al., 2006). UK clinical guidelines state that this diagnosis should be made or confirmed by a paediatrician (NICE guidelines, 2007).

c) Prevalence

Prevalence is the total number of cases of a condition in a given population at a specific time. In two community studies where CFS was confirmed by a paediatrician (Bell et al., 1991; Jordan et al., 1998), the prevalence of CFS was estimated at about 2% in 6-17 year olds. Bell et al. (1991) assumed all non-responders (353 out of 914) were asymptomatic so the prevalence was an extrapolated prevalence (2.3%). The study was carried out prior to the Fukuda et al., (1994) criteria, but they retrospectively checked that the patients had > 6 months fatigue and 6 of 8 symptoms for CFS as outlined in Holmes et al. (1988). However, other studies have found lower prevalence rates. In a large, epidemiological population study in the UK (England, Scotland and Wales), the prevalence of CFS in children and adolescents (5-15 year olds) was 0.19%, comparable to the rate found in less common childhood disorders such as severe tic disorders or eating disorders (Chalder et al., 2003). Similarly another well-conducted community based study in the US (Jordan et al., 2006) found a prevalence rate of 0.18% in 13 to 17 year olds. However, in another population based study in the US (Jones et al., 2004) no CFS case was identified (N=8586). This was a random digit dialling survey in Kansas, where parents identified fatigued children and adolescents in their home. Using questionnaires sent to GPs in a nationwide study in Holland, Nijhof et al. (2011) reported that 111 per 100000 young people (10-18 years old) had CFS. General practitioners (GPs) were questioned about practice size and the number of CFS diagnoses. It is possible that the number reported was under-represented as GPs may have overlooked some patients and other young people may have been receiving treatment in tertiary care only. Using a three month minimum symptom duration, Farmer et al. (2004) observed that the lifetime prevalence for CFS in young people was 1.90%, based on 96 young people (8-17 years) from
population based registers in South Wales and Manchester. All of these studies used the Fukuda et al. (1994) criteria for diagnoses.

d) Incidence

Incidence is a measure of the risk of developing some new condition within a specified period of time; i.e. the number of “new cases” in a population within a given time period. A UK epidemiological study (Rimes et al., 2007), found an incidence of CFS of approximately 5 per 1000 over a 4-6 month period - using the Fukuda et al., (1994) criteria - which is higher than that of asthma, type 1 diabetes or anxiety disorders for this age-group (5-15 year olds). These findings broadly compare to the incidence figures reported in the adult population (Lawrie et al., 1997). However, Nijhof et al. (2011) in the same study discussed above reported an incidence rate of 12 per 100000 per year. This was calculated from newly reported cases by paediatricians in 2008. Paediatricians were sent a questionnaire every time a new diagnosis was made. They captured patient’s demographic details as well as information about duration and severity of fatigue. Crawley et al. (2011) conducted a school based project investigating CFS in young people aged 11-16 years using the broader 3 month duration for young people as recommended by NICE guidelines (National Institute for health and Clinical Excellence, 2007). They gathered data on newly diagnosed CFS cases. A school attendance service in conjunction with a specialist CFS service identified young people missing greater than 20% of school and those with fatigue were referred to a specialist unit. Twenty-eight of the 2855 (1%) young people from the 3 state secondary schools the service was offered in were found to have CFS. The considerable variation in methodology and age-range in these studies is likely to account for some of the differences in incidence estimates.
e) Adolescence

This stage of development is very diverse but is widely considered to begin from about the age of 11. The prevalence evidence suggests that CFS-like illness is unusual before puberty. Jordan et al. (2000) reported a prevalence of 2.91% in adolescents and only 1% in pre-pubescent children. Key changes in adolescence are the hormonal and biological changes along with sexual maturation and the development of one’s own personal identity. Adolescence is described as a period in which independence is achieved. It is a time when constancy in certain characteristics such as personality and behaviour develop. The adolescent process of individuation and separation from parents can be impeded by the increased dependency which is often associated with CFS.

f) Gender

CFS is more common in females than males in children and adolescents (Farmer et al., 2004) as well as adults (Gallagher et al., 2004). The ratio is approximately 3:1 for children and young people in prevalence studies (e.g. Farmer et al., 2004). Buchwald et al. (2000) reported that female sex was a risk factor for non-recovery from infection mononucleosis at 6 months in adults. It is possible that sex hormones play a part in this disparity. Hormones, such as testosterone and oestrogen are known to profoundly impact on the central nervous system, which is responsible for perceiving and transmitting the feeling of pain (e.g. Bialek et al., 2004). Testosterone has been shown to help prevent muscle fatigue through helping to repair muscles after activity (Axell et al., 2006). It is possible given that women have less testosterone that they are prone to more muscle fatigue. However there is no evidence about hormonal differences contributing to the gender difference in CFS prevalence rates.

For some adults with CFS there is evidence of mild hypocortisolism, and this is more common in women with CFS than men (Papadopoulos & Cleare, 2012). Reasons for this hypocortisolism are unclear but one suggestion from adult CFS literature is that it is a consequence of childhood trauma.
Childhood abuse and stressors are discussed later in the review. A meta-analysis study reported a global prevalence of childhood sexual abuse as 19.7% for females and 7.9% for males (Pereda et al., 2009). It is widely accepted that those individuals who have reported childhood abuse are more likely to also suffer with depression and anxiety issues as well as more physical symptoms (e.g. Arnow, 2004). Again, these conditions are more common in females than males and have overlapping symptoms with CFS.

g) Ethnicity

Data on ethnicity in CFS in adolescents are limited. Dinos et al. (2009) reported through a narrative synthesis and a meta-analysis of population based studies (e.g. Jason et al., 1999) in the USA, a higher prevalence of CFS in some ethnic minority groups than white people in adults. However, ethnic groupings can be arbitrary in studies so it can be difficult to gain accurate prevalence rates. Studies in secondary or tertiary care report relatively low percentages of non-white patients in adults with CFS (Jason et al., 2003; Luthra & Wessely, 2004). These findings raise questions about selection bias in care settings and why those from diverse ethnic groups may not get a CFS diagnosis or be referred to specialist services. Results from population based studies give a less biased picture of the relationship between CFS and ethnicity.

h) Clinical Picture

Heterogeneity

There is some evidence that CFS in young people is a heterogeneous condition. May, Emond & Crawley (2009) undertook a factor analysis of items endorsed on a symptom checklist by young people with CFS and reported three different phenotypes. They labelled these “musculoskeletal” (e.g. muscle pain, joint pain), “migraine” (which included headache, abdominal pain and
hypersensitivity to noise, light and touch) and “sore throat” (characterised by sore throats and swollen lymph nodes). The authors reported that worse fatigue, pain and physical function were cross-sectionally associated with musculoskeletal and migraine phenotypes. In this type of study the phenotypes identified will depend on the list of symptoms chosen by the researcher. Studies in the adult literature (Nisenbaum et al., 2004; Wilson et al., 2001) do support the notion that the presentation of CFS is heterogeneous.

Neuropsychological Symptoms

There has been little research carried out on the different symptoms of CFS in children and adolescents. However, problems with memory and attention in young people with CFS have been examined. One study found that one third of child and adolescent patients with CFS reported a decrease in concentration. Patients described feeling like they were in a ‘fog’ (Krilov et al. 1998). Problems with attention - specifically attending to external cues, such as conversations or instructions - were reported by parents, teachers and the young people alike in an uncontrolled, cross-sectional study, using a population of young people with CFS who reported problems with memory or concentration (Haig-Ferguson et al., 2009). In comparison to normative means, Haig-Ferguson et al. reported significantly lower scores for the young people with CFS on sustained attention, switching attention, divided attention, immediate recall and delayed recall when using a neuropsychological assessment. This is in line with subjective reports. However, van Middendorp et al. (2001) found normal adjustment on attention problems in young people with CFS, using self-report measures.

A cross-sectional study (van de Putte et al., 2008) used a flanker task (Eriksen Flanker Task; Eriksen & Eriksen, 1974) to specifically investigate whether young people with CFS were easily distracted. A flanker task is a test of response inhibition. It requires a participant to suppress inappropriate responses in a given context. In this study, the participants had to respond to a target which was flanked by non-target stimuli which acted as distractors. Such tasks are widely used to
measure attention and distractability. The CFS group performed significantly worse on the Erikson flanker task than the healthy control group, with slower reaction time and less accurate performance. This finding of greater distractibility is supported by findings in the adult literature (De Luca et al., 1997). A further cross-sectional study using the modified Trail Making Task reported that the young people (13-15 years old) with CFS showed significantly slower alternative attention than the healthy control group (Kawatani et al., 2011). These problems may account for some of the educational difficulties reported in CFS (Sankey et al., 2006).

Disability

Symptoms of fatigue are often exacerbated by activity, with the young person being left with days of feeling unwell afterwards. The disability associated with CFS can vary considerably; at the more severe end, children and young people are unable to go to school (Sankey et al., 2006). Crawley and Sterne (2009) investigated school attendance and physical function in 211 children and adolescents (5-19 year olds) with CFS. They found that 62% attended school 40% or less. The factor most strongly associated with lower school attendance was lower physical functioning. Increased fatigue, pain and low mood were associated with worse physical function. Based on the case notes of 50 young people attending one of two London Tertiary paediatric / psychiatric centres over the previous 5 years Rangel et al. (2000b) reported that 57% were bedbound when functional handicap was at its worst, with a serious reduction in physical activity.

i) Theoretical underpinnings to clinical treatment

Cognitive behavioural therapy is the only psychological treatment that has been empirically investigated using randomised controlled trials in CFS (e.g. Stulemeijer et al., 2005; Chalder et al., 2010). It is the recommended treatment option in the UK (NICE guidelines, 2007). Stulemeijer et al. (2005) found that patients given a course of cognitive behavioural therapy over a 5 month
period reported a significantly greater decrease in fatigue severity, functional impairment and their attendance at school improved significantly, as compared to a waiting-list control group. These benefits of CBT were consistent with the findings by Chalder et al. (2010).

Theories informing such therapeutic options for young people with CFS have been broadly based on models and research evidence in adults. Wessely et al. (1989) suggested that although fatigue may often have been initially triggered by an infection, other factors may then act to maintain the condition. They propose that the individual starts to reduce their activity levels in an understandable attempt to feel less fatigued, but in fact their exercise tolerance worsens and hence fatigue increases when they try to do more. Beliefs such as “There must be something seriously wrong with me” and “If I continue with this activity I will end up feeling worse”, contribute to activity reduction and avoidance. They suggest that the individual ends up in a vicious cycle of activity reduction, exercise intolerance, fearful cognitions, fatigue and disability. This has led to cognitive behavioural interventions addressing such factors. Surawy et al. (1995) built on this initial model, developing a more cognitive-based theory which captures these important maintaining factors as well as other cognitive factors including high personal standards and self-expectations. For young people, Chalder, Tong & Deary (2002) suggested that treatment be delivered within the context of the family as they can be influential in the development and maintenance of the condition. However, this is far from clear, as so far family-based approaches have not been compared to one-to-one treatment in this condition.

**j) Aim of the review**

This review aims to document the studies in children and adolescents which have investigated biological, psychological and social factors shown in empirical studies to be potential factors in either the aetiology or maintenance of CFS. This will include a review of factors proposed in previous theoretical approaches to CFS in adults including immune functioning, infection, activity /
rest and cognitive factors. At the end of the review we will propose a multifactorial model of hypothesised factors in children and adolescents with CFS, drawing on the evidence from this review and the models of CFS already established.

2. Method
Electronic databases (Medline, Embase, Psycinfo) were searched for published studies between 1980 and August 2013 on Chronic Fatigue Syndrome in children and adolescents. Key search words¹ were; Chronic Fatigue Syndrome AND genetic, personality, self-esteem, cortisol, stress, activity, exercise, infection, physiol*, arousal, belief, depression or anxiety, psychol*, autonomic or cardiovascular. Additional search terms included adolescent or child* or young person or young people or juvenile. Studies were included if they addressed factor(s) associated with CFS in children and adolescents. Intervention studies were not included in this review. Some studies (n = 7) came from trawling through reference lists of identified papers. The search strategy identified 79 studies to be included. Information about study design, sample characteristics, measures used and main findings was extracted from the articles and tabulated (see table 1). Due to such a broad research question, as well as heterogeneity of studies, a narrative approach to this review has been taken. Factors were grouped into categories and then a mini-review of each category was conducted. Both similarities and differences across the studies were explored for issues such as methodology and sample size. This led to an overview of the nature and strength of evidence as well as directions for future research.
3. Results

a) Overview

Most of the 79 studies identified were cross-sectional (N=66). Two studies were prospective. Forty-one studies were case-control studies. Most often, self-report measures were used to measure the factors. Most sample sizes ranged between 5 and 100 (N = 58). However, some were population-based studies using a much larger sample. Most studies used an age range between 11 and 25 years – only 6 studies used a sample over 25 years of age. These are the studies looking at factors in childhood influencing a diagnosis in adulthood. Four papers included participants under 11 years of age. This paper addresses CFS in young people generally, but the majority of studies concentrate on the stage of adolescent development (11-18 years) and that is subsequently the main focus of this review. All studies included both males and females in their sample other than one study (ter Wolbeek et al., 2007). Ethnicity is not widely reported in studies investigating CFS in young people.

Thirty-eight of the studies investigated psychiatric adjustment within CFS samples as one of their outcomes, with the main disorders of interest being anxiety and depression. In these studies, analyses were primarily regression or correlation analyses.

The results are considered under 2 key headings (table 1 shows the studies separated by factors):

- Predisposing / vulnerability factors (may also act as perpetuating factors)
- Precipitating factors

It should be noted that some factors could potentially act in more than one category. For example, a particular personality characteristic might put an adolescent at risk for developing CFS and also act to maintain it once it has developed. Due to the cross-sectional nature of studies, these are reported under one heading.
b) Predisposing / Vulnerability factors (may also act as perpetuating factors)

i. Genetic and familial factors

Five cross-sectional studies (Bell et al., 1991 & 1994; Crawley & Sterne, 2009; Patel et al., 2003; Smith et al., 2010) have reported a link between a family history of CFS and developing CFS in young people. Bell et al. (1991) found that having a family member with symptoms of CFS was a strong predictor of CFS in students in a district in New York, with a risk ratio of 35.9. Further, 50% of young people with CFS referred to a Paediatrics department had a family history of CFS (Bell et al., 1994). Patel et al. (2003) found 13.9% (of 36) at a GP special interest clinic had a positive family history of CFS in a first degree relative. Crawley and Sterne (2009) report 20% of 211 young people with CFS recruited from a regional specialist survey had a first degree relative who had CFS. In comparison with offspring of healthy mothers (n=30), Smith et al. (2010) found that those exposed to mothers with CFS (n=20) met criteria for CFS more frequently (12% vs. 2%). There was only low to medium power to detect a significant difference. The authors recruited mothers with CFS from an academic referral clinic devoted to chronic fatigue and pain and all offspring had been living with their mother continuously (at least since the age of 12).

There is one study using twins to investigate genetic heritability of chronic fatigue in young people (Farmer et al., 1999). Investigating disabling fatigue in school aged twins, the genetic contribution was high, with a mono-zygotic correlation of 0.75 and di-zygotic correlation of 0.47, for fatigue lasting at least a month (Farmer et al., 1999).

Sommerfeldt et al. (2011) studied 53 patients with CFS (12-18 years) and found significant differences in genotype frequencies between the CFS group and reference samples. Specifically, they found differences on the COMT SNP Rs 4680 and the β2 adrenergic receptor SNP Rs 1042714. These receptors are associated with enzyme activity. Attenuation of enzyme activity leads to an increased concentration of catecholamines, possibly intensifying the effect of sympathetic nervous activity. This ties in with the Wyller et al. (2007, 2007b, 2008) findings
discussed later (endocrine factors). These studies found abnormalities in immune functioning and inflammatory processes in young people with CFS in comparison to controls.

ii. Psychiatric Disorder

Authors have investigated the overlap and distinction between psychiatric disorders and CFS. Concurrent psychiatric disorders (mostly depressive disorders) are reported in between a quarter to a third of young people with CFS (Smith et al., 1991 – community sample; Vereker, 1992 – specialist treatment centre sample; Walford et al., 1993 – attending an immunology clinic for CFS). Case-control studies have specifically examined the number of patients with CFS presenting with psychiatric disorders compared to healthy norms (van Middendorp et al., 2001) or healthy controls (Fry & Martin, 1996; Garralda et al., 1999; Godfrey et al., 2009; Heim et al., 2009; Smith et al., 2003; Ter Wolbeek et al., 2007; van de Putte et al., 2008; Walford et al., 1993) or illness controls using different control groups; cystic fibrosis (Walford et al., 1993), emotional disorders (Garralda & Rangel, 2005), cancer group of adolescent girls (Pelcovitz et al., 1995), inflammatory bowel disease (Richards, Turk & White, 2005), migraine (Smith et al., 2003), juvenile rheumatoid arthritis (Brace et al., 2000) and juvenile idiopathic arthritis (Rangel et al., 2003). These studies mainly focused on reports of anxiety and/or depression and will be summarised below.

In the cross-sectional studies comparing CFS patients with healthy controls/norms, scores for depression and anxiety were significantly elevated in the CFS groups. Ter Wolbeek et al. (2007) reported that CFS patients had increased depression, anxiety and somatic symptoms as compared to non-fatigued controls. Rangel et al. (2000b) reported 12% of the 25 young people with CFS reached the severity cut off for a major depressive disorder, as measured by a semi-structured interview. Unipolar depressive disorder is a common mental health problem in adolescents worldwide, with an estimated 1 year prevalence of 4-5% in mid-late adolescence (Costello, Egger & Angold, 2005). Recently, Bould et al. (2013) reported that 29% of 542 young people (12-18 years) with CFS were also depressed. This was according to a score of > 9 on the depression
subscale of the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983). Those young people with CFS who were also depressed had higher levels of disability, pain, fatigue and anxiety as well as worse school attendance than those free of co-morbid depression.

In a larger sample of young people with CFS (n=164), Crawley, Hunt and Stallard (2009) reported a significant association between the Spence Children’s Anxiety Scale total score (SCAS; Spence, 1998) and levels of fatigue (Chalder Fatigue Questionnaire; Chalder et al., 1993). Most common were separation anxiety and social phobia which were strongly associated with gender; a significantly higher proportion of girls scored above the anxiety scale cut-off than normative controls. Fisher & Crawley (2012) extended this study with eleven of the participants. These were amongst those who scored above the 90th percentile cut-off on the SCAS separation anxiety and/or social phobia subscales. They conducted interviews with the young people (12-18 years) either at home (n=10) or at the clinic (n=11) and found the young people with CFS had ‘increased emotionality’ and were more worried about schoolwork (compared to before), and were anxious about returning to school.

In comparison to young people with other illnesses, depression scores were significantly higher in many of the CFS groups (Pelcovitz et al., 1995; Rangel et al., 2003; Smith et al., 2003; Walford et al., 1993). Anxiety disorders were significantly more common in the CFS group than the juvenile idiopathic arthritis group (Rangel et al., 2003). Richards et al. (2005) reported 50% of the CFS group reached the threshold for emotional disorders which was higher than the inflammatory bowel disease control group (30%), but this did not reach statistical significance. Garralda & Rangel (2005) reported that although the CFS group had less psychiatric co-morbidity than the Emotional Disorders group, where psychological problems was the primary diagnosis, emotional disorders had been present in most of the CFS group (18 out of 27) in the previous year. On the whole, measured through different diagnostic techniques, these studies suggest that a sizeable proportion of patients with CFS have a psychiatric comorbidity, usually anxiety or depression. Yet, some clear
differences have been shown between childhood and adolescent CFS and depressive disorder. Specifically an acute onset of symptoms is more likely to be reported in patients with CFS compared to those with depression (in a sample of 16, 16 vs. 2 patients with depression). Young people with depression miss fewer days of school and young people with depression are much more likely to exhibit aggression and antisocial acts (Carter et al., 1995).

iii. Personality

Four cross-sectional studies have investigated different personality characteristics in young people with CFS. In comparison to a control group of young people with juvenile idiopathic arthritis (Rangel et al., 2000a, 2003), a CFS group had higher levels of personality difficulty and disorder. Using the Personality Assessment Schedule (Tyrer & Alexander, 1979) which is a parent-reported interview, the CFS group scored more highly for conscientiousness (Rangel et al., 2000a, 2003), vulnerability (i.e. specifically disturbed when things go wrong; Rangel et al., 2000a, 2003), worthlessness and lability (Rangel et al., 2000a), sensitivity, eccentricity, anxiousness and rigidity (Rangel et al., 2003). Self-report measures revealed that CFS patients had more problems with internalising symptoms (such as fearful or inhibited behaviour) than cancer patients (Pelcovitz et al., 1995) and CFS patients were more likely to be withdrawn or have somatic complaints in comparison to healthy norms (van Middendorp et al., 2001). The sample sizes of these studies are all quite small, between 30 and 58.

A more recent prospective study (Kato et al., 2006; see “studies in childhood informing adult diagnoses of CFS”) investigated the link between personality measured in childhood and a diagnosis of CFS in adulthood.

iv. Self-esteem

Unfavourable scores on self-esteem - especially in social competence – have been reported in CFS patients, in comparison with healthy (Garralda et al., 1999; Kennedy et al. 2010a) and normative
controls (van Geelan et al., 2010). When compared to a group with emotional disorders (Garralda & Rangel, 2005), the CFS group were comparable on self-esteem; the only exception was behavioural conduct in the CFS group (p=0.009). This sub-scale includes items such as “usually do what is expected of them” or “behave very well”. Normal adjustment in terms of psycho-social self-esteem compared to normative controls (van Middendorp et al., 2001) has been reported in one study of CFS. These were all cross-sectional studies. A recent meta-analysis of 621 studies investigating low self-esteem in people with chronic illness and healthy controls revealed that young people with chronic illnesses had lower self-esteem than healthy controls. Further, lowest self-esteem was observed in the young people with CFS and those with chronic headaches (Pinquart, 2012).

v. High Expectations

Differences in expectations and perceptions have been reported in young people with CFS compared to healthy young people in three different realms; fatigue levels (Garralda & Rangel, 2001) activity levels (Fry & Martin, 1996) and high expectations in relation to IQ (Godfrey et al., 2009). Each of these studies were cross-sectional in design, taking into account both child and parent expectations.

Either young people with CFS and / or their parents significantly underestimated the young persons’ current activity levels and had higher expectations of their post-CFS activity levels than was realistic for that age (Fry & Martin, 1996). The subjective rating (as measured by visual analogue scales) of activity was significantly lower in the CFS group than the healthy control group, but the actual activity level measured over three days with an activity monitor was comparable across groups. Corresponding with these findings, in another study (Garralda & Rangel, 2001), young people with CFS had unrealistic views of normative fatigue levels as measured by an 11-point visual analogue scale (0 = no fatigue). Expected normative fatigue levels were significantly lower (p = .001) in the young people with CFS (median = 1.2) than in a healthy
control group (median = 4). Another study found that parental expectations of IQ were significantly higher for young people with CFS than for healthy controls (Godfrey et al., 2009). The patients’ own self-estimates were not so high and overall, there was no significant difference between the groups on actual measured IQ.

vi. Attributions

Several studies have investigated child or parental attributions about the cause of the CFS. Garralda & Rangel (2001) reported that 90% of young people with CFS and 72% of parents attributed the cause of their illness to biological factors in their cross-sectional study. Similarly Kennedy et al. (2010a) found 88% of young people reported their CFS had an infectious onset. In another study of 85 young people with CFS using a cross-sectional design, thirty-six possible causes of CFS were noted, with 33% saying the cause was a virus (Gray & Rutter, 2007). Smaller qualitative studies also found that physical causes were most widely (Richards et al., 2006) or exclusively reported (Hareide et al., 2011; Jelbert et al., 2010). Rangel et al., (1999) described young people with CFS as wary of psychological explanations for symptoms. Hareide et al., (2011) reported that two-thirds of the nine adolescents interviewed rejected a psychological cause. However there is evidence that a small minority of young people with CFS do make psychological attributions. Gray and Rutter (2007) found that 13% of their sample attributed the CFS to stress or worry and Richards et al. (2006) found that family and education-related stresses were reported as causes by some young people interviewed.

vii. Illness perceptions and cognitions

Beliefs and perceptions may have important consequences for peoples’ behaviour. Gray and Rutter (2007) found, using the Illness Perceptions Questionnaire (Weinman et al., 1996; IPQ-R; Moss-Morris et al., 2002) that illness representations formed characteristic patterns that were cross-sectionally associated with both physical functioning and quality of life (through self-reported daily functioning). Those young people with CFS who reported fewer symptoms and also those who
reported their illness was caused by risk factors (hereditary, diet, poor medical care in the past, own behaviour, aging, smoking and alcohol) also remained more active, with a perception of better functioning. Contrary to what has generally been reported in studies of adults, the young people in this study perceived the symptoms and pattern of their illness to be more cyclical than chronic. Both more symptoms and a greater focus on symptoms were associated with poorer quality of life. Van de Putte et al. (2005) explored the locus of health control in 32 young people with CFS and their parents in comparison with 167 healthy young people and their parents. Using the Multidimensional Health Locus of Control questionnaire (Wallston, Wallston & De Vellis, 1978), this cross-sectional study found significantly less internal health control in young people with CFS than in healthy controls, as well as higher external loci of control in young people with CFS and their parents. Another cross-sectional study (Garralda & Rangel, 2004) compared impairment and illness attitudes of 28 young people with CFS, 30 young people with juvenile idiopathic arthritis and 27 with emotional disorders. Using interviews, young people with CFS reported significantly more illness impairment, especially school attendance than those with juvenile idiopathic arthritis and emotional disorders. The young people with CFS reported generalised illness worry and particular styles of coping (such as emotion regulation and resignation) with illness and disability. Further, Brace et al. (2000) reported that young people with CFS (n = 10) scored significantly higher than the juvenile rheumatoid arthritis group (n = 14) on the measure of parental reinforcement of illness behaviour.

Specific interest has focused on beliefs about rest and activity in patients with CFS (Richards, Turk & White, 2005). In this cross-sectional study, a group of CFS patients (10-19 years) tended to prefer rest rather than exercise as a coping strategy in comparison to the group of young people with inflammatory bowel disease. A preference for rest over exercise was associated with a greater level of functional impairment and higher levels of reported fatigue.
viii. Parental involvement

a. Maternal Distress

It has been suggested that CFS in young people is influenced by functioning within the family. More specifically, Rangel et al. (2000b) suggested a link between maternal distress and poor outcome in young people with CFS. Five cross-sectional studies (Chalder et al., 2003; Missen et al., 2012; Rangel et al., 2000b; Rangel et al., 2005; Van de Putte et al., 2006) have investigated the association between maternal distress and fatigue.

In a community sample, distress in the mother was associated with parental report of CFS in the child (Chalder et al., 2003). The mothers’ psychological distress was assessed by the General Health Questionnaire (GHQ; Goldberg & Hillier, 1979; Goldberg & Williams, 1988). This finding is supported by two small, cross-sectional studies (Rangel et al., 2000b; Rangel et al., 2005). In the Rangel et al. (2000b) study, more maternal psychiatric symptoms on the GHQ and more mothers with chronic health problems were reported in a poor outcome group of young people with CFS compared to the better outcome group (p=0.08). There was not a control group in this study. In 2005, the same authors reported greater current mental distress in the parents of the CFS group than a juvenile rheumatoid arthritis parent group as indicated by higher scores on the GHQ (Rangel et al., 2005). A more recent cross-sectional study (Missen et al., 2012), found that 72% (of 40) of mothers of young people with CFS scored above the cut-off on the GHQ compared with 20% of healthy control mothers.

Van De Putte et al. (2006) cross-sectionally found depression to be the main risk factor for the presence of CFS in the child, where distress in the mother corresponded with a 5.6 times higher chance for CFS in the child. We cannot know whether the maternal distress is a consequence of the CFS in the child or vice versa due to the nature of the study.

b. Parental care and overprotection
Parental care is characterised by emotional warmth and intimacy and overprotection characterised by intrusion and control, according to the Parental Bonding Instrument (Parker et al., 1979). These constructs have been studied cross-sectionally, with CFS patients being compared with healthy controls (Garralda et al., 1999), ill controls with juvenile rheumatoid arthritis (Rangel et al., 2005) and ill controls with Emotional Disorders (Garralda & Rangel, 2005). Garralda et al. (1999) found that young people with a history of CFS did not perceive different levels of parental care and overprotection compared to the healthy control group on the parental bonding instrument. Subsequent studies revealed contradictory findings.

Based on scores of overprotection, self-sacrificing and pre-occupation with the child, families of young people with CFS compared to families of juvenile rheumatoid arthritis (Rangel et al., 2005) or emotional disorders (Garralda & Rangel, 2005) were characterised by significantly greater emotional over-involvement and reports of greater family burden. This over-involvement has not necessarily been associated with greater accuracy of parental perceptions about the child’s illness experience: in a study of 14 young people with CFS, Vervoort et al. (2007) found that mothers and fathers were less accurate for ‘CFS thoughts and feelings’ than for beliefs related to ‘other life events’. The accuracy was determined by comparing the actual content of the child’s interview with the parent’s inferred content. There was not a control group in this study.

ix. Immune and Endocrine Factors

It is unclear whether and to what extent there are alterations in the immune functioning of young people with CFS. Ter Wolbeek et al. (2007) conducted a study to investigate the immune function in young people with CFS through blood sampling. They had 3 groups: CFS, fatigued and non-fatigued participants. The non-fatigued and fatigued groups were selected from a broader fatigue study in secondary schools (ter Wolbeek et al., 2007), whereby all girls were written to for this current study. The fatigued group did not meet criteria for CFS. Eleven CFS patients were recruited from a specialist CFS unit. The eleven female CFS patients (mean age 15) showed similarities in
self-reported complaints (including assessment of fatigue, anxiety and depression as well as school attendance) with the fatigued participants but not the non-fatigued participants. However, the CFS patients showed a distinct immune profile when compared to the severely fatigued and the non-fatigued participants, with increased levels of anti-inflammatory cytokines and reduced levels of pro-inflammatory cytokines. Cytokines help to regulate the immune system and these fatigued patients showed a ‘skewing’ of the cytokine balance towards an anti-inflammatory profile in comparison to the non-fatigued participants. Studies in adults have been published, but with contradictory findings (e.g. Lyall et al., 2003; Cho et al., 2006).

A cross-sectional study with 25 young people with CFS and 23 healthy controls (Kennedy et al., 2010b) was conducted to investigate biochemical and vascular aspects of CFS. They reported increased oxidative stress, with reduced levels of vitamins C and E as well as increased white blood cell death in the young people with CFS. This group reported similar findings in an adult population with CFS (Kennedy et al., 2005). Recent studies (e.g. Spence & Stewart, 2004; Kennedy et al., 2005) have shown that oxidative stress (OS) may be involved in the pathogenesis of CFS. Oxidative stress has been defined as a disturbance to the equilibrium status of pro-oxidant and antioxidant systems in favour of pro-oxidation. Oxidative stress can cause disruptions in normal mechanisms of cellular signalling.

Researchers have started to investigate the Hypothalamic Pituitary Adrenal axis function in young people, a major part of the neuro-endocrine system that controls reactions to stress. Hypocortisolism is commonly described in adults with CFS (Cleare, 2003). A case-control study (Segal et al., 2005) reported that young people with CFS (N=23) had significantly lower mean cortisol levels than age matched controls (N=17) in response to a low dose synacthen test (LDST). Kavelaars et al. (2000) found no differences in baseline or corticotrophin releasing hormone induced cortisol between 15 CFS patients and healthy controls, but baseline adrenaline levels were significantly higher in CFS patients. Wyller et al. (2010) found that serum cortisol concentrations
in 67 young people (12-18 year olds) with CFS were no different to cortisol levels in 55 healthy controls. They measured the serum concentrations from blood samples between 8 and 9am in all participants.

The autonomic nervous system has been investigated in several ways in young people with CFS. A number of studies have used the Head-Up Tilt (Benditt et al., 1996) task to produce orthostatic stress, in order to investigate cardiovascular regulation. Using the tilt procedure, significantly fewer episodes of orthostatic intolerance in the control group than the CFS group have been reported (Stewart et al., 1999; Galland et al., 2008). Orthostatic intolerance is defined as the development of symptoms during upright standing relieved by recumbence or sitting back down again. It occurs because standing upright is a fundamental stressor. People who suffer from orthostatic intolerance lack the effective circulatory and neurologic mechanisms to compensate for the blood pressure changes.

Lowest Heart Rate Variability (HRV) in the CFS group compared to controls (Stewart et al., 1998; 2000) both at rest and during tilt has consistently been reported using the head up tilt, with Wyller et al. (2007b) also noting that the CFS group had a greater increase in the LF/HF ratio (low frequency / high frequency ratio) during tilt than the controls. LF/HF ratio is a measure of sympathovagal balance. Low frequency reflects a mixture of sympathetic and parasympathetic activity and high frequency is a marker of parasympathetic activity (i.e. quicker changes in heart rate). More recent studies (Kennedy et al., 2010b; Sommerfeldt et al., 2011) again used the head up tilt task to investigate autonomic cardiovascular responses. They reported that during the task, the young people with CFS experienced increased heart rate, systolic blood pressure and LF/HF ratio compared to the healthy comparison group. Using a different orthostatic challenge test, a hand-grip task, (Wyller et al., 2008; Wyller et al., 2011) researchers found significantly higher heart rate and lowest heart rate variability responses in the young people with CFS compared to healthy controls leading to enhanced sympathetic predominance of heart rate control. A recent study (Hurum et al.,
2011) compared ambulatory recordings of heart rate and blood pressure in 44 young people with CFS with healthy controls. The authors reported that both during the day and at night, heart rate was significantly higher in the CFS group, as well as higher blood pressure in the CFS group during the night adding support to the above evidence of sympathetic predominance of cardiovascular control in young people with CFS.

In contrast to the above studies, Katz et al. (2012) found no evidence that orthostatic intolerance was implicated in CFS. Using a cohort of young people with CFS (N=36) and recovered controls following infection mononucleosis (N=43), they tested orthostatic tolerance using a standing orthostatic tolerance test. There were 25% of young people with CFS and 21% of recovered controls with an abnormal standing orthostatic tolerance test result – not a significant difference between groups.

Investigating changes in cardiovascular control in response to the head up tilt over time, Sulheim et al. (2012) reported that compared to baseline, young people with CFS (N=47) had significantly lower heart rate, blood pressure, total peripheral resistance index (TPRI) and LF/HF ratio 3-17 months later. TPRI is associated with blood pressure as it is the amount of resistance to blood flow present in the vascular system of the body. The patients also showed significantly less pronounced increases in heart rate, mean blood pressure, diastolic blood pressure and total peripheral resistance index during tilt compared to the first visit. However, there was not a significant correlation between improvements in responses to the head up tilt and changes in self-reported fatigue or functioning. Between baseline and time 2, all patients had been given symptom management advice and 27 reported having tried graded exercise therapy, cognitive behaviour therapy or drug treatment (propranolol or fludrocortisone).

x. Activity levels

Rangel et al. (2000b) asked CFS patients through interview and questionnaires about their ability to carry out activities at home and found significant differences between young people who had
recovered and those who still met diagnostic criteria for CFS. The authors concluded that “a serious reduction in physical activity itself seems likely to have been a perpetuating factor for physical and mental malaise”. However the direction of causality cannot be ascertained in this cross-sectional study as all patients had received treatment.

There is some evidence from pilot treatment studies that engaging in exercise may be beneficial for young people with CFS. An uncontrolled study found that young people with CFS generally reported a significant improvement from baseline scores when completing either resistance training or aerobic training (Gordon et al., 2010). Likewise, Gordon & Lubitz (2009) reported that levels of fatigue improved by 13% after exercise training was introduced in a 4-week in-patient programme for young people with CFS. Cognitive behavioural treatment trials which also focus on increasing activity will be described later.

xi. Sleep

One prospective case-control study found significantly greater amounts of time spent sleeping in young people with CFS compared to matched (age and Tanner stage) non fatigued controls after Epstein Barr Virus (Katz et al., 2009; Huang et al., 2010). When maintaining similar levels of exercise as the mononucleosis-recovered controls (6 months after diagnosis), young people with CFS reported significantly higher levels of fatigue and spent significantly more time sleeping during the day 6 and 12 months following infection.

xii. Body Mass Index

A recent study in the US (Petrov et al., 2011) conducted a retrospective cohort study of 53 participants aged 9-18 years. Greater body mass index (as measured at diagnosis) was significantly associated with prolonged duration of CFS. The assessment of body mass index at diagnosis revealed an increased prevalence of overweight patients with the duration of CFS lasting for more than 24 months. Increased body mass index may be a consequence of restricted physical activity in young people with CFS.
c) Precipitating or triggering factors

i. Infection

Infectious Mononucleosis, also known as Epstein-Barr-Virus or glandular fever may be a risk factor for CFS in young people. In cross-sectional (Feder et al., 1994; Kennedy et al., 2010a; Krilov et al., 1998; Sankey et al., 2006; Smith et al., 1991; Patel et al., 2003) and retrospective-cohort (Petrov et al., 2011) designs, several studies found that a high percentage of patients with CFS report that their fatigue began with an acute illness. Between 60% (Krilov et al., 1998) and 93% (Sankey et al., 2006) of the patients indicated that the fatigue had begun with an acute infective illness and there was evidence of past or present Epstein-Barr virus in some (5% – 36%) of the patients (Krilov et al., 1998; Marshall et al., 1991; Sankey et al., 2006). A case-control study (Galland et al., 2008) showed 10 out of 26 patients were confirmed positive for Epstein-Barr virus via antibody detection. Only 2 of the healthy control group (N=26) reported any subjective history of glandular fever-type illness. Petrov et al. (2011) identified Epstein-Barr virus in 66% of 53 CFS patients (aged 9-18 years), but there was no control group in this study. In a population based study, Nijhof et al. (2011) reported that in 22% of cases the illness started with an acute infection and in fact, in 52% of these young people, there was evidence of current or recent Epstein-Barr virus.

There is also prospective evidence of post-infectious CFS in young people. Katz et al. (2009) screened 301 young people (12-18 years) for non-recovery 6 months after infection mononucleosis, at which point 13% met the criteria for CFS. At 12 and 24 months, 7% and 4% respectively met the criteria for CFS. These rates are approximately 20 times higher than the 0.18% found in the general adolescent population (Jordan et al., 2006).
d) Studies in childhood informing adult diagnoses of CFS

Several studies have investigated childhood experiences in relation to a diagnosis of CFS in later life. A prospective study (Kato et al., 2006) considered emotional instability and stress in CFS-like illness, where individuals reported at least 4 of the 8 symptoms set out by Fukuda et al. (1994). Higher emotional instability and self-reported stress in the pre-morbid period were associated with higher risk for CFS-like illness, 25 years later.

There have been three longitudinal studies investigating the relationships between activity levels in childhood and the onset of CFS in adults. In the first, lower levels of exercise in childhood were associated with a greater risk of CFS in later life. Identified by self-report at age 30, the reported age at onset of CFS ranged from 14 to 29 years (Viner & Hotopf, 2004). This study also found that high levels of exercise in childhood, as defined by “playing sport often in their spare time”, had a significantly lower risk of CFS. Conversely, a second study, which defined high levels of exercise as “engaging in sporting activities weekly”, in childhood through to adulthood (13 years to 43 years) found high levels of exercise were associated with an increased future risk of self-reported CFS in adulthood (Harvey et al., 2008). This was a prospective study following participants in the first 53 years of their life, investigating predictors of a CFS diagnosis between the ages of 41 and 53. A third study did not replicate either of these studies finding no prospective association with either little exercise or lots of exercise in childhood and self-reported CFS in adulthood (Goodwin et al., 2011).

Early adverse experiences such as childhood illness or trauma have been investigated in adults with CFS. In three retrospective population-based studies of adult CFS patients and non-fatigued control participants, the CFS patients reported significantly higher levels of childhood trauma compared with the controls (Heim et al., 2006; Heim et al., 2009; Kempke et al., 2013). These studies used the Fukuda diagnostic criteria. The Heim et al. studies used a self-report Childhood Trauma Questionnaire (Bernstein & Fink, 1998), with moderate to severe cut-off scores. The Heim et al.
(2009) study reported above also showed that adults with CFS who reported childhood trauma had flattened cortisol awakening response profiles compared with well control participants. In this retrospective study, adults with CFS who did not report emotional maltreatment during childhood exhibited normal cortisol profiles. The authors suggest that childhood trauma might cause long-term impairment in terms of the ability to successfully adapt to stress, for example via disturbances to the hypothalamic pituitary adrenal axis, thereby conveying a risk to developing CFS. Kempke et al. (2013) found that over half of the 90 adult CFS patients reported at least one form of childhood trauma on the Childhood Trauma Questionnaire, the most common being emotional trauma (46.7%). Total trauma and emotional abuse scores, and a higher number of trauma types were associated with higher levels of daily fatigue and pain over a 14-day period when controlling for demographic characteristics and depressed mood.

Fisher & Chalder (2003) also used a retrospective case-control design to compare early illness experience (up to the age of 16) between 30 adults with CFS, diagnosed at a tertiary referral clinic and 30 patients attending a fracture clinic. No differences were found between the two groups on any self-reported childhood illness category but they found increased levels of childhood maternal over-protectiveness in those with CFS compared with the ill controls.

In a prospective study, Harvey et al. (2008) reported those with CFS at age 53 years were no more likely to have experienced childhood illness than the healthy participants. In another longitudinal study, Viner and Hotopf (2004) reported no association between maternal psychological distress in childhood/adolescence (measured by the Rutter Malaise Inventory; Rutter, Tizard & Whittmore, 1970) and risk of CFS in adulthood as reported by questionnaire.
4. Discussion

a) Main findings

Ethnicity is not widely reported in studies investigating CFS in young people. Jones et al. (2004) in a study in the US reported that 72.2% of the population was white. However, when ethnicity was measured in adult studies, a small number of community based studies (e.g. Alisky et al., 1991; Steele et al., 1998) reported higher rates of fatigue among certain ethnic groups. For example, Jason et al. (1999) reported that African American and Latino populations had significantly higher fatigue scores than populations of Caucasian people.

Most studies in the UK report a female excess of two thirds to a third (Farmer et al., 2004; Dowsett & Colby, 1997; Patel et al., 2003) as do the US studies (Dobbins et al., 1997; Bell et al., 1991) and the Australian study (Lloyd et al., 1990). Crawley & Sterne (2008) reported that 69.2% of their sample was female which is consistent with the specialist cohorts (Bell et al., 2001; Rangel et al., 2000; Krilov et al., 1998; Feder et al., 1994). Of the studies reviewed, the strongest evidence regarding the aetiology of CFS in young people is that the Epstein-Barr virus is associated with an increased risk of CFS. A prospective study found that CFS developing after infection was 20 times more likely than in the general population (Katz et al., 2009). However, most individuals who experience Epstein-Barr virus do not go on to develop CFS, so an understanding of other contributory factors is required.

This review identified strong evidence of increased rates of psychiatric co-morbidity in young people with CFS compared to healthy or ill control groups. Depressive disorders and anxiety disorders are the most commonly reported co-morbid problems. From such cross-sectional studies it is not possible to ascertain the direction of causality. In adults there is evidence from prospective studies that psychiatric disorders increase the risk of subsequent CFS. (e.g. Wessely et al., 1996) and a prospective study of young people found that anxiety, depression and conduct disorders at time 1 were associated with increased fatigue and chronic fatigue 4-6 months later (Rimes et al.,
2007) so we suggest that this may be both a predisposing and perpetuating factor for CFS in young people. However more research is needed into this issue. Ter Wolbeek et al. (2011) reported that vulnerability to develop fatigue and associated symptoms in young adulthood can to a certain extent be identified already, years before the manifestation of complaints. They found that in young people who experienced a notable increase in fatigue, fatigue development was preceded by emotional problems and CFS-related complaints during adolescence. The nature of the association is unknown and it is possible that genes, early life experiences and learned psychological responses act individually or together (e.g. via differences in hypothalamic pituitary adrenal axis responding) as risk factors for both psychiatric disorders and CFS.

There are some measurement issues which warrant discussion. Some studies (n = 13) used self-report questionnaires to identify symptoms of anxiety or depression (e.g. Van Middendorp et al., 2001; Fry & Martin, 1996). These self-report scales measured psychological distress and symptoms of anxiety or depression. Fewer studies (n = 6) used semi-structured interviews to make clinical diagnoses of anxiety and / or depressive disorders (Rangel et al., 2000b; Smith et al., 1991; Garralda et al., 1999; Heim et al., 2009; Rangel et al., 2003; Garralda & Rangel, 2005). Both self-report measures and clinical interviews reported higher rates of anxiety and depression symptoms in the CFS group than the illness controls. However, caution must be taken when interpreting results of studies using self-rating scales as they are not necessarily evidence of a diagnosis of clinical anxiety / depression. Interviews have some advantage over self-report measures as they capture all information needed for a diagnosis (Cohen et al., 1993).

It is clearly important to have developmentally sensitive assessment tools. This can prove challenging in this age group (Beesdo et al., 2009) and one should be aware of developmental issues as a possible limitation to both semi-structured interviews as well as self-report scales. With adolescents however, this is less of a problem and clinicians can more confidently make diagnostic decisions based on the self-report by the young person rather than relying on parental report (Schniering et al., 2000).
The emergence of certain psychopathologies during adolescence could be related to typical adolescent maturation changes which occur in concert with psychosocial factors (e.g. school or social stresses). This time period appears to be the central period of risk for the development of mild symptoms of anxiety through to full anxiety disorders (Kessler et al., 2005), depression (Cyranowski et al., 2000) and chronic fatigue and CFS (Chalder et al., 2003; Rimes et al., 2007). Given that anxiety disorders and depression have been found to be associated with chronic fatigue and they occur at a similar stage of development it seems likely that these disorders have some common risk factors. These may include stress (Cohen et al., 1987), parenting style and certain vulnerable personality characteristics.

Some evidence was found for certain personality traits, including excessive conscientiousness, rigidity, fearful behaviour and sensitivity being reported more frequently in young people with CFS (Rangel et al., 2000a, 2003; Pelcovitz et al., 1993; van Middendorp et al., 2001). As personality traits are generally assumed to be persistent individual characteristics, we suggest that these may be predisposing factors. Indeed it is not difficult to speculate that being excessively conscientious or rigid may make it more likely for the individual to become stressed and hence more fatigued in the context of extra challenges such as physical illness or life events. However, due to the cross-sectional nature of these studies, the possibility of personality change occurring as a result of CFS cannot be ruled out. However, there is a lot of research to support the notion that personality shows great continuity from the age of 3 throughout the adolescent years and into adulthood (Caspi, 1998). For example, if a young child was shy and inhibited, they are more likely to be anxious and inhibited when they reach adolescence (Kagan et al., 1994). Recent research using different methodologies suggests that personality can be reliably assessed in adolescence (e.g. Westen et al., 2003).

There is consistent, cross-sectional evidence of high expectations in young people with CFS in comparison to control groups. Inaccurate expectations and unrealistic perceptions were reported
with regards to fatigue, activity and IQ levels, in young people with CFS and their parents. High standards appear to be problematic in a general sense across aspects of life (Garralda & Rangel, 2001; Godfrey et al., 2009).

Evidence for an association between maternal distress and CFS in young people has been shown in cross-sectional research. Again the causal direction cannot be ascertained and clearly it is very stressful for parents to have a child with a chronic health problem. Children with psychosocial problems are more likely to have mothers who are depressed (Downey & Coyne, 1990), and mothers with depression are more likely to report psychosocial problems in their children (Boyle & Pickles, 1997a, b). Rimes et al. (2007) prospectively found that maternal distress at time 1 was associated with the persistence of fatigue as well as new onset Chronic Fatigue at time 2 (4 to 6 months later). Although not CFS specifically, it suggests maternal distress may be contributing to CFS-like symptoms.

A family history of CFS seems to be associated with an increased risk of CFS in young people (e.g. Bell et al., 1991), but the nature of genetic vulnerability and how this might interact with environmental factors is not known. Sommerfeldt et al. (2011) reported differences in adrenergic receptors of young people with CFS which are associated with enzyme activity, which may affect sympathetic nervous activity.

Research into the pathophysiology of CFS is in its infancy. Subtle differences in cortisol response profiles and hypothalamic pituitary adrenal axis function in young people with CFS patients in comparison to healthy controls has been reported in one cross-sectional study (Segal et al., 2005). However, hypothalamic pituitary adrenal axis disturbance has been well-documented in adults with this condition (e.g. Cleare, 2003). In adults with CFS a study found that only patients with a history of childhood trauma showed a reduced cortisol response but this association has not been investigated in young people (Heim et al., 2009). There is some cross-sectional evidence of differences in autonomic arousal in young people with CFS, with young people with CFS having
lower heart rate variability than controls during a head up tilt task and significantly higher heart rate than healthy controls (e.g. Wyller et al., 2007b; 2008). There is preliminary evidence that these differences in cardiovascular response normalise over time but there was no indication that these improvements correlated with self-reported improvements in symptoms or functioning (Sulheim et al., 2012). From the cross-sectional evidence, it is unknown whether these physiological differences contribute to the initial development of the condition but they may well be contributing to the on-going symptom experience. There are many possible causes of these physiological differences including stress or changes in activity or other health behaviours associated with the condition. The hypothesis that differences in physiological responding in conditions of stress is a pre-existing risk factor for CFS needs further investigation, especially in prospective studies.

Cross-sectional research has consistently reported that young people with CFS (and their families) attribute the cause of their CFS to a physical / biological cause, often rejecting a psychological explanation. This is not necessarily surprising given that in many cases the fatigue began in the context of a virus. However, families may be overlooking other factors that made the young person vulnerable for fatigue becoming a more chronic problem. It has been suggested in adult models of CFS that the tendency to make somatic attributions is due to beliefs about negative emotions being unacceptable and a sign of weakness (Surawy et al., 1995). In adults there is evidence that such beliefs are indeed reported to a greater extent in people with CFS than healthy individuals (Rimes & Chalder, 2010) but this has not been investigated in young people or their parents.

Cross-sectional studies investigating levels of over-protection (control and higher levels of parental care) in young people with CFS have thus far produced mixed findings. It could be argued that over-protection is a natural response to a chronically ill child, or may be in response to characteristics already shown in the child. However, it is also possible that parental responses may be acting inadvertently to perpetuate the fatigue and / or disability in young people with CFS. For example, in their understandable efforts to aid recovery, parents may be inadvertently encouraging too much rest which could cause de-conditioning and make young people cautious or fearful about
engaging in activity. Indeed a retrospective study reported that increased levels of maternal 
overprotection in childhood were found in participants with a diagnosis of CFS in adulthood. This 
was in comparison to a fracture clinic group of patients – suggesting that overprotection is not 
purely a response to an ill child. It may be that communication from an adult to a child about being 
cautious in response to a range of situations may be relevant to the formation of fearful belief 
systems in the child. In some this may contribute to the development of CFS. It is also possible that 
maternal over-protection is illness-focused and that cognitions develop which are centred around 
fear of increasing symptoms which then leads to the avoidance of activity, which has been found to 
be an important maintaining factor in adult CFS (Vercoulen et al., 1994).

Little is known about the role of physical activity in the development of CFS in a child and 
adolescent population. The only studies investigating this area have been prospective studies which 
have found contradictory results regarding childhood activity levels acting as a risk factor for adult-
onset CFS later in life. Both too little (Viner & Hotopf, 2004) and too much (Harvey et al., 2008) 
exercise have been identified as risk factors. A small, cross-sectional study (Rangel et al., 2000b) 
noted that a reduction in activity may perpetuate the disorder. Objective measurements of physical 
activity would improve our understanding, as self-reports of activity levels are not necessarily 
reliable. It is possible that prolonged inactivity leads to physical de-conditioning such that 
symptoms emerge at progressively lower levels of physical activity. On the other hand, many 
patients report being very active before they developed CFS symptoms (Harvey et al., 2008).

b) Key Limitations

The key limitation is that most of the studies are cross-sectional in design, which makes specifying 
the direction of causality impossible. Longitudinal evidence is needed. Furthermore we cannot yet
answer questions regarding the relative contributions of these factors to the development and perpetuation of CFS in young people.

Some studies did not use a control group which means it is not clear whether the results are specific to CFS or may be true for other chronic illnesses or indeed the general population. Additionally, there is reliance in many of these studies on self-report measures. This subjectivity means limited conclusions can be drawn. Also, different measures across studies can make it difficult to compare results. Many of the studies used patients drawn from specialist settings. However, it may be that those seen in the specialist clinic are representative of a clinical population. Many of the studies used small samples, which may mean the findings cannot be generalised to larger populations.

A final limitation is that not all studies have used the same diagnostic criteria to identify participants for study inclusion. However, although there should be some caution in comparisons across studies the diagnostic criteria are not very different from one another and most studies used the Fukuda criteria.

c) Suggested future research

All findings reported in the review would benefit from further evaluation. Well-designed studies addressing the methodological weaknesses raised above will enhance our understanding of the various factors. Large, prospective studies are needed. Experimental designs could help us better understand the cognitive, behavioural and emotional coping behaviours in young people with CFS. Beliefs about illness could be investigated experimentally. For example, as exercise gradually increases, beliefs concerning the link between increased activity and a worsening of physical symptoms could be evaluated. Research into the autonomic nervous system shows promising preliminary results and this could be a focus for future research, for example using experimental stress-induction paradigms.
d) Limitations of the review

A number of limitations of this review must be considered. Firstly, all of the studies discussed here are published studies. It was beyond the scope of the review to locate any unpublished research or to search the ‘grey literature’. With this in mind, there may be a potential for publication bias. The search strategy used here is not exhaustive, so it is possible a study has not been identified, although unlikely given all reference lists were searched as well.

Due to the heterogeneity of the studies, an overall statistical synthesis of findings was not possible. However the review highlights areas for useful future study and the findings have helped to contribute to the development of a model of CFS in children and adolescents as suggested below.

Due to the emphasis the studies have placed upon chronic fatigue as the key symptom of CFS, there has been less emphasis here regarding other symptoms of CFS that may contribute to this associated disability experienced in CFS. For instance, in addition to the chronic fatigue are self-reported post-exertional malaise (e.g. Jordan et al., 2000) and also neurocognitive dysfunction (e.g. Rowe et al., 2002).

e) A hypothesised model of CFS in children and adolescents

A model incorporating the above-reviewed research findings reviewed and drawing on existing adult and child and adolescent models of CFS (e.g. Wessely et al., 1989, Chalder et al., 2002, Surawy et al., 1995) will now be described (also see Figure 1). Since the research presented in this review has primarily focused on vulnerability to developing CFS in young people, this is the main focus of the following model but perpetuating factors are also included.

Vulnerability factors

A stress-diathesis model of chronic fatigue syndrome in young people is proposed. It is suggested that that young people who go on to develop CFS are likely to have had a pre-existing vulnerability
to stress which interacts with precipitating factors in the aetiology of this condition. There is likely
to be variation in the form of this stress vulnerability. For example, this may take the form of
personality characteristics, differences in physiological arousal responses, vulnerability to
psychological distress, or beliefs about symptoms and illness. Genetic factors are likely to have
contributed to this stress vulnerability, although the extent nature of this contribution is unclear.
Parental factors such as parental distress or overprotection may also contribute to stress
vulnerability in their child, as will environmental factors such as abuse or other adverse
experiences.

Personality factors such as high self-expectations or conscientiousness are likely to be associated
with less flexibility in changing behaviour in the context of stress or illness (e.g. Surawy et al.,
1995). This can mean that the young person keeps on trying to maintain high standards despite
illness or other life demands, resulting in greater fatigue and stress. Stress vulnerability in terms of
differences in autonomic arousal could mean that the young person experiences more physical
symptoms than other individuals when under challenging circumstances. If the young person or
their parents makes physical illness attributions for these symptoms, this may result in inadvertent
unhelpful responses such as prolonged rest or school absence or reduction in everyday activities
rather than directly addressing the source of stress. It is suggested that for some young people, the
pre-existing stress vulnerability has already resulted in clinically severe levels of distress, usually
in the forms of depression or anxiety, which in turn put them at increased risk of developing CFS.

Precipitating factors and initial responses

A trigger for the development of CFS is often reported retrospectively to be an infection, other
illness or stress. The only prospective evidence is for the role of the Epstein-Barr virus as an
infective trigger (Katz et al., 2009). However, most young people who experience such a virus do
not go on to develop CFS so further factors must also be involved. Cross-sectional evidence
summarised in this review is consistent with the suggestion that at least some patients with CFS
may be vulnerable to stress and / or more sensitive to stress than healthy young people. Following a
stress trigger such as a challenging life event, the young person will have experienced a stress
response associated with a number of physical and mental symptoms, including fatigue,
concentration problems and sleep disturbance. However, the individual may fail to recognise the
cause of the symptoms and / or attribute the cause of the symptom to something physical. Several
studies have reported physical attributions for illness in young people with CFS and their parents
(e.g. Kennedy et al., 2010a). It is not difficult to understand why a physical illness attribution may
be made if the challenging life event, such as changing schools or exams, are things that other
children are able to experience without such severe or prolonged physical symptoms, because they
are less vulnerable to the effects of stress than the young person who goes on to develop CFS.
Similarly, if the fatigue was initially triggered by a virus, it makes sense that the family would view
prolonged fatigue as a continued result of this causal factor, rather than taking into account that
factors contributing to persistent fatigue may be different to those triggering fatigue initially.

Perpetuating factors

If there is an on-going stressful situation, the direct impact on fatigue levels will continue.
However, once fatigue has developed, it is proposed that additional factors act to perpetuate the
fatigue which may be different to those that initially triggered it. For example, the above-described
factors associated with stress vulnerability in the young person may result in more negative and
fearful beliefs about the symptoms themselves, such as meaning that they are seriously ill or that a
small increase in fatigue could herald a major relapse. Such beliefs have been reported in adults
with CFS but need investigation in young people. In an understandable response to such beliefs, the
young person may use coping responses that can help control fatigue in the short-term but in the
long-term will inadvertently add to symptom severity and impairment in daily living activities
(Chalder et al., 2002). One such proposed maintaining factor is excessive rest, which can result in
reductions in physical conditioning and difficulties tolerating normal activities. There is evidence
from a cross-sectional study that young people with CFS tend to favour rest over exercise as a coping strategy (Richard, Turk & White, 2005) but prospective evidence is still needed.

As the young person continues to experience fatigue and disability, they may reduce their daily activities further in an attempt to control the symptoms, including missing school or social activities. This puts them at risk of becoming more isolated from their peers and increasingly behind with their school work. This can contribute to the development of further distress, sometimes anxiety or depression, which in turn causes more fatigue and other physical symptoms. The young person may also increasingly focus on their symptoms in an attempt to try to understand or gain control over the fatigue. However, a greater focus on symptoms has been found to be associated with poorer quality of life in a cross-sectional study (Gray & Rutter, 2007).

The family may also respond in ways that inadvertently act to maintain fatigue. Parental distress may result in higher levels of on-going stress for the child, or parental responses such as over-protection may have the unintended effect of impeding the child in returning to normal daily activities. Advice from others outside of the family may also be inadvertently unhelpful, such as teachers or health professionals recommending rest or avoidant responses. These areas need further research.

f) Clinical Implications

The findings from this review have highlighted the complex nature of this condition. The exact aetiology of CFS in young people remains unclear, but existing evidence suggests that there are a number of variables involved in the development of symptoms and disability. It seems highly likely that both the symptoms of fatigue and the associated disability are a result of a complex interplay of cognitions, behaviour, physiology, emotional and social factors which have evolved over time. Each of these factors needs to be considered during treatment. As familial factors may
be important in the development and perpetuation of CFS we suggest that the family should be involved in both the assessment and treatment. Both over-protection and maternal distress should be considered here. Given the overlap with psychiatric disorders management plans should address such problems. Treatment should be tailored to specific personality types, and should address certain individual characteristics such as high expectations and/or low self-esteem. Fisher & Crawley (2012) suggest that those with high levels of anxiety require individualised treatments tailored to their different types of anxiety as part of their treatment. The nature of the reported biological differences remains unknown, but it may be useful to monitor the subtle cortisol differences and lower heart rate variability in young people with CFS during treatment to see how they change over time and whether the changes correlate with change in behaviour. There is preliminary evidence to suggest that cortisol levels normalise after cognitive behavioural therapy in adults (Roberts et al., 2009) and in young people (Rimes et al., in submission). Treatment should also be tailored to take account of, stress and trauma where indicated.

Cognitive behaviour therapy attempts to address a range of factors that may be contributing to the condition including unhelpful beliefs and behaviours, and often this involves parents as well as the young person. Three randomised controlled trials provide evidence for treatment of CFS in young people. Stulemeijer et al. (2005) found that patients given a course of cognitive behavioural therapy over a 5 month period reported a significantly greater decrease in fatigue severity, functional impairment and their attendance at school improved significantly, as compared to a waiting-list control group. These findings were supported by Chalder et al. (2010) who found that initially after a course of family-focused CBT, school attendance and fatigue improved more in the CFS group than in the group of young people receiving psycho-education. However, this increase slowed and the psycho-education was as effective as the cognitive behavioural therapy group by 6 month follow-up. Both studies showed that improvements after cognitive behavioural therapy are maintained 5 months after treatment (Chalder et al., 2010; Stulemeijer et al., 2005) and still 2 years
after discharge from treatment (Lloyd et al 2012a). Recently, a randomised controlled trial, found that an internet-based cognitive behavioural treatment was significantly more effective than usual care across outcome measures: fatigue, school attendance, and physical functioning (Nijhof et al. 2012).

A non-randomised cohort study investigating the role of telephone guided self-help for 63 young people with CFS reported a significant decrease in fatigue and a significant increase in school attendance between pre-treatment and 6 month follow-up, using principles of cognitive behavioural therapy (Lloyd et al., 2012b). Early evidence from a pilot study suggests that a gradual increase in exercise may be associated with a decrease in levels of fatigue (Gordon et al., 2010).

**Figure 1: A conceptual model of CFS in children and adolescents**

***(see attached sheet)***

5. **Acknowledgements**

The authors acknowledge the financial support from the Department of Health via the National Institute for Health Research (NIHR) Specialist Biomedical Research Centre for Mental Health award to South London and Maudsley NHS Foundation Trust (SLaM) and the Institute of Psychiatry at King’s College London.

6. **References**


Table 1: Studies investigating the factors associated with Chronic Fatigue Syndrome in children and adolescents

<table>
<thead>
<tr>
<th>Factor</th>
<th>Methodology</th>
<th>Total</th>
<th>Case-Control?</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cross-sectional</td>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>1) Predisposing and perpetuating factors</td>
<td>Prospective</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetics</td>
<td>7</td>
<td>7</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Psychiatric Disorder</td>
<td>20</td>
<td>20</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Personality</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>High expectations</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Attributions</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Illness Perceptions and Cognitions</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Parental Involvement – Maternal distress</td>
<td>0</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Parental care and over-protection</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Endocrine Factors</td>
<td>14</td>
<td>16</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Activity Levels</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Sleep</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2) Precipitating Infection</td>
<td>10</td>
<td>11</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>
Model 1: A hypothesised model of Chronic Fatigue Syndrome in children and adolescents based on research evidence

**Stress Vulnerability**
- Pre-existing beliefs about symptoms and illness (i.e. physical illness attributions)
- Anxiety and depression
- Personality e.g. conscientiousness and high expectations
- Physiological arousal (individual tendencies)

**Precipitating factors e.g. virus, extra school demands, life events**

**CFS and distress**
- Attritions of symptoms to virus or physical illness
- Negative beliefs about symptoms
- Symptom focusing
- Coping strategies e.g. excessive rest and reduction in activity

**Parental distress**

**Genetic factors**

**Parental Overprotection**

**Environmental contributions to stress vulnerability e.g. early stress or trauma (evidence in adults)**

Footnote 1:
This is not a causal model; the review highlights how factors may interact.

Footnote 2:
The only evidence which is prospective relates to a viral onset.
Model 1: A hypothesised model of Chronic Fatigue Syndrome in children and adolescents

Stress Vulnerability

- Pre-existing beliefs about symptoms and illness (i.e. physical illness attributions)
- Personality, e.g. conscientiousness
- Anxiety and depression
- Physiological arousal
- Genetic factors

Parental distress
- Parental overprotection

Precipitating factors e.g. virus, extra school demands

CFS and distress
- Attribution of symptoms to virus or physical illness
- Symptom focusing
- Coping strategies e.g. excessive rest and reduction in activity

FIGURE 1
- The strongest evidence for the aetiology of CFS in adolescents is that the EBV is associated with an increased risk of CFS

- Rates of psychiatric co-morbidity, predominantly anxiety and depressive disorders were higher in adolescents with CFS

- Treatment should be tailored to specific personality types, and should address certain individual characteristics