Sanne Nijhof

Chronic Fatigue Syndrome in Adolescents

Treatment, clinical features and epidemiology

CHRONIC FATIGUE SYNDROME IN ADOLESCENTS
TREATMENT, CLINICAL FEATURES AND EPIDEMIOLOGY

Thesis, Utrecht University, The Netherlands

ISBN nummer	978-94-6108-527-6
Printed by	Gildeprint Drukkerijen B.V., Enschede
Cover	Peter Walschots, Ooltgensplaat, naar het schilderij *Meisje in witte kimono* van George Hendrik Breitner, 1894
Layout	Annelies Wisse, Amsterdam, www.annelieswisse.nl

CORRESPONDENCE
S.L. Nijhof, KE 04.133.1, University Medical Center Utrecht, PO Box 85090, 3508 AB, Utrecht, The Netherlands.
Telephone: +31 887 555 555, Fax: +31 887 555 349, Email: s.l.nijhof@umcutrecht.nl

Chronic Fatigue Syndrome in Adolescents

Treatment, clinical features and epidemiology

Chronisch Vermoeidheidssyndroom bij Adolescenten

Behandeling, klinische kenmerken en epidemiologie

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties in het openbaar
te verdedigen op vrijdag 6 december 2013 des middags te 2.30 uur

door

SANNE LAURA NIJHOF

geboren op 21 juni 1982 te Hoorn

PROMOTOREN
Prof.dr. J.L.L. Kimpen
Prof.dr. G.Bleijenberg

CO-PROMOTOREN
Dr. E.M. van de Putte
Dr. C.S.P.M. Uiterwaal

The research described in this thesis was financially supported by
ZonMw the Dutch Organisation for Health Research and Development
(ID ZonMw 60-60800-98-013)

Design and technical development of the FITNET portal was financially supported by
Innovatiefonds Zorgverzekeraars and Stichting Voorzorg Utrecht

Printing of this thesis was kindly financially supported by
Eye Wish opticiens Wisse, Raadhuisstraat Roosendaal; Stichting Artsen voor Kinderen;
UMC Utrecht

Aan mijn ouders

Contents

1
General introduction

Sanne L Nijhof

This chapter is adapted from: Werker CL, Nijhof SL, van de Putte EM. Clinical Practice: Chronic fatigue syndrome. *Eur J Pediatr. 2013 Oct;172(10):1293-8*

INTRODUCTION TO THIS THESIS

Fatigue is a common complaint among adolescents and particularly among girls.[1–3] A recent large population study in the Netherlands revealed a prevalence rate of 16.4% of severe fatigue lasting more than one month in adolescent girls.[1] Fatigue in adolescence seems to be a growing social issue, which is often attributed to hormonal changes during puberty, psychological struggles and new educational and social demands. The onset and persistence of fatigue are associated with an increasing number of other somatic complaints (such as dizziness or pain) and comorbid symptoms of anxiety and depression.[4,5] There seem to be ordinary explanations for these regular fatigue symptoms in healthy adolescents, and they do not interfere substantially with daily life activities.[1]

In contrast, adolescent chronic fatigue syndrome (CFS) is a disabling disorder, characterized by persistent or relapsing severe fatigue for at least 6 months, which is not the result of ongoing exertion and cannot be alleviated by rest.[6] In adolescents, CFS often has an extensive disease course that may lead to considerable school absence and long-term consequences for their educational and social development.[7–10]

One of the most successful possibilities for the treatment of adolescents with CFS is cognitive behavioural therapy (CBT), but it requires specialized therapeutic skills that are not often available in the local region of the adolescent.[11]

This lack of skilled cognitive behavioural therapists to treat adolescents with CFS made us decide to develop a comprehensive, more accessible, and interactive web-based portal combining CBT by a skilled therapist with a regular internet contact. It was called FITNET (Fatigue In Teenagers on interNET), especially developed for adolescents diagnosed with CFS and their parents. The development of FITNET was a close collaboration between the Wilhelmina Children's Hospital (University Medical Centre Utrecht, UMCU) and the Expert Centre for Chronic Fatigue (Radboud University Nijmegen Medical Centre, ECCF).

This thesis describes the results of the accompanying longitudinal FITNET research program. It focusses on the FITNET-trial, where the effectiveness of web-based therapy for adolescent CFS was compared with usual care. Factors related to recovery and long-term effects were assessed as well, in an attempt to give more insight into which factors predict treatment outcomes. Secondly, the epidemiology of adolescent CFS, as diagnosed by general practitioners and paediatricians was assessed. Thirdly, additional research was conducted on understanding clinical features of adolescent CFS, with an emphasis on the reversibility of (biological) deviations after recovery.

CHRONIC FATIGUE SYNDROME IN ADOLESCENTS

A historical overview of fatigue and CFS

It was not until the middle of the 19th century that fatigue was recognized as a medical problem with the introduction of the term 'neurasthenia', a diagnostic entity with fatigue as the principal symptom.[12] Some decades later the term 'myalgic encephalomyelitis' (ME) was first mentioned in a leading article in 1956, in which similar symptoms were described in response to several outbreaks of fatigue and neuromuscular weakness among the nursing and medical staff of a specific hospital in London.[13] The conceptualization of chronic fatigue syndrome (CFS) began in the mid-1980s, a term more neutral in respect of its causes.[14] The first publication of CFS in children was in 1989 in the BMJ 'Myalgic encephalomyelitis by proxy', describing a diagnosis pushed forward by parents, while the separately interviewed child reported no symptoms at all.[15,16]

Epidemiology

Symptomatic fatigue in 5-18 year olds is common, but chronic fatigue and chronic fatigue syndrome are relatively rare.[1,17] Adolescent girls are more susceptible to fatigue and comorbidity than boys.[1,18] The prevalence of adolescent CFS has been estimated to range from 0.19% to 1.29%, with a female-to-male ratio ranging from 2:1 to 5:1.[19–22] Most of these estimates were primarily established by questionnaires and telephone interviews reflecting self-reported symptoms, which might overestimate true CFS incidence. Accurate diagnosis of CFS is a complex task that requires exclusion of other illnesses that could cause similar complaints but require different treatment. Therefore, clinical estimates of CFS prevalence and incidence can be of value in addition to these population surveys.

Clinical presentation and criteria

Several diagnostic criteria for CFS in adults were developed, such as the Oxford Criteria[23], the Canadian Consensus Criteria[24] and the Centre for Disease Control and Prevention Criteria (CDC-1994).[6] The CDC-1994 criteria are commonly used in paediatric studies.[6,11,25] According to these criteria CFS is characterized by severe and disabling new-onset fatigue lasting for at least six months, accompanied by four or more of the following symptoms: impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, new onset headaches, unrefreshing sleep and post-exertion malaise. Somatic and psychiatric illnesses should

be excluded.[6]

Specific criteria for children are less common, with the exception of the UK Royal College of Paediatrics and Child Health guidelines, according to which a minimum period of 3 months of severe disabling fatigue suffices for the diagnosis of CFS/ME.[26]

The importance of early diagnosis, and effective and prompt advice on managing CFS is vital because early intervention can improve patient outcomes. However, starting an intervention too early in children and adolescents when they do not yet comply with CFS-criteria, can have an adverse effect. It reduces motivation and increases incidence of persistent fatigue with significant school absence.[27] Moreover, half of the adolescents with severe disabling fatigue during a period shorter than 6 months will recover spontaneously within 6 months, without intervention.[28]

Aetiology

The aetiology of adolescent CFS remains largely unknown, though many potential mechanisms have been proposed. No single triggering factor, deviant laboratory test, or infectious vector could be assigned as the primary causative agent of CFS.[29,30] Neuroendocrine studies, however, have consistently found a mild hypocortisolism with enhanced negative feedback and increased sensitivity of the glucocorticoid receptor, as well as an impaired response to activation of the hypothalamic-pituitary-adrenal (HPA) axis in adults.[31]

Besides its role in metabolic functions and energy regulation, the HPA axis is, in addition to the central nervous system, traditionally viewed as the "stress regulatory system". The HPA axis consists of a chain of stimulatory hormones and feedback loops and is under the control of the higher cerebral centres that determine its overall activity. It ultimately stimulates the secretion of cortisol by the adrenal gland. When, in situations of chronic stress, the HPA axis is often or persistently addressed, prolonged production of cortisol can cause tissue damage in both the brain and the periphery with negative influences on psychological processes and on behavior.[32] Also, alterations in negative feedback function have been associated with stress.[33] It is hypothesized that when stress persists over a long period of time, the initially HPA axis hyperactivity is followed by hypoactivity, as indicated by hypocortisolism ('attenuation hypothesis').[34]

Recently, reversion of this hypocortisolism after successful treatment has been shown in a study of adult patients with CFS by measuring salivary cortisol upon awakening.[35] This finding has not yet been replicated in adolescents. The change to the HPA axis, though, is not specific for CFS and it is yet not known whether dysfunction of the stress responsive systems plays a causal role in the aetiology. Prospective studies in adults discuss that hypocortisolism is a consequence, rather than a cause of CFS.[31] A

potential etiological link between the HPA axis and CFS emerges from the potential of HPA axis hypoactivity to increase pain perception and to cause fatigue.[34,36]

Furthermore, impaired neuropsychological test performance and structural cortical changes have been found in adults with CFS.[37,38] Whereas deviations in neurocognitive functioning has been extensively studied in both adult and adolescents CFS, the role of intelligence in the pathogenesis or persistence of CFS has been relatively ignored.

Several studies have reported a high prevalence of psychopathology in patients with CFS, predominantly depression, somatization disorder, anxiety and hypochondria.[39,40] Other studies have focused on personality disorders or personality traits,[41] reporting among others higher levels of neuroticism and alexithymia for adolescents with CFS.[42,43]

Up till now there is insufficient support for either a purely somatic or psychic cause. It is more likely that we need to apply a multifactorial model to understand CFS. The bio-psycho-social model was proposed by Engel in 1977, in which both biological and psychological factors are relevant.[44]

The bio-psycho-social model

The bio-psycho-sociological approach is currently the most comprehensive description of CFS and offers a framework for treatment of the disease. Previous research has shown that it is useful to distinguish between predisposing, precipitating and perpetuating factors at both a biological and psychosocial level.[45,46] Research into predisposing factors has identified a number of items that make a person more vulnerable to the development of CFS; being female, physical inactive or extreme levels of exercise, a high academic achievement level, and early adverse experiences such as physical or emotional neglect or abuse.[47–50] There is also some evidence that a genetic predisposition exists for CFS.[47,51] Various somatic and psychological stressors, such as surgery, Epstein-Barr virus infection, or the loss of a loved one, can precipitate or trigger CFS.[49,52] Psychological processes seem to be major factors in perpetuating, or maintaining CFS symptoms.[46,47] An overview of these factors in adolescents is shown in detail in table 1.

Diagnostic work-up

Taking a full clinical history is the most crucial diagnostic tool for CFS, primarily to complete the differential diagnosis and secondarily to recognize key features in the histories of the child and parents.[53] Comprehensive physical examination is vital, if only to help exclude other conditions. A positive diagnosis can usually be made from the clinical history and examination alone. There is no definitive test for CFS since

	Biological	Psychological	Social
Predisposing	Genetic vulnerability	Parent's excessive attention to physical complaints of their children	Family members with physical or mental diseases
	Physical vulnerability	Early adverse experiences	Somatization of the parents
	Physical diseases	Neglect or bonding problems	
	Early physical and/or sexual trauma	High academic achievement	
	Genetic vulnerability to stress	Anxiety, depression	
	Gender	Personality disorders	
		Somatization	
Precipitating	Physical overload	Stress	Life events inside or outside the family
	Physical stress (infections, operations, trauma)	Psychological trauma	
Perpetuating	Disturbed sleep-wake cycle	Concentration problems	Isolation
	Disordered food intake	Avoidant attitude	Excessive medical consumption
	Physical inactivity	Anxiety, depression	Somatization of the parents
	Pain	Reinforcement of unhelpful coping thoughts	
	Overactive or underactive lifestyle	Externalizing attributions	
		Focusing on bodily symptoms	

TABLE 1. Possible factors involved in Chronic Fatigue Syndrome in adolescents

there are no confirmatory physical signs or characteristic abnormalities on laboratory testing. Therefore routine screening tests in the diagnosis of CFS are performed only to rule out any alternative diagnoses and not to diagnose CFS.[54] The basic tests to assist in differential diagnosis are listed in table 2.

Differential diagnosis

Accurately diagnosing CFS requires exclusion of other illnesses (both physical and psychiatric) that could cause similar complaints, but require different treatment. Red flags are signs and symptoms that refer to other (treatable) conditions; they should not be attributed to CFS without careful consideration of alternative diagnoses or comorbidities.

The following features warrant further investigation:[54]

- Localizing/focal neurological signs
- Signs and symptoms of inflammatory arthritis or connective tissue disease
- Signs and symptoms of cardiorespiratory disease
- Significant weight loss
- Sleep apnoea
- Clinically significant lymphadenopathy

Additional red flags in the history and physical examination of children are:

- Deviant height growth
- Deviant pubertal development (in children)

The following psychiatric differential diagnoses should be ruled out (in children and adolescents):

- Eating disorders
- Bipolar disorders
- Depression
- Anxiety disorders (post-traumatic stress disorder)

Dialogue with adolescent and parent

Full Blood count
Urea and electrolytes
Liver function
Thyroid function
Random blood glucose
Erythrocyte sedimentation rate
C-reactive protein
Serum creatinine
Blood-screening for gluten sensitivity
Serum calcium
Creatine kinase
Urinalysis for protein, blood and glucose
Assessment of serum ferritine levels

TABLE 2 Basic tests to assist in differential diagnosis in children (NICE 2007)[54]

Shared decision-making between the patients, their parents and healthcare professionals should take place during all phases of care. The dialogue starts with a full history of the main complaints and the related disabilities, completed with an assessment of the cognitions on the perceived causes of fatigue. It is important to acknowledge the impact of the condition and the symptoms and to provide information on the possible causes, nature and course of CFS. Furthermore it is important to take into account the person's age, the severity of CFS, individual preferences and experiences, and the outcome of previous treatment.

It is essential to speak to the adolescent

alone, to reveal factors that have been important in the development of chronic fatigue, for example intoxications or negative life-events (sexual assault, child abuse, neglect).

Management

General management strategy after diagnosis

Evidence for the effect of treatment on children and adolescents with CFS is present for cognitive behavioural therapy (CBT)[11,55] and to a lesser extent physiotherapist-guided graded exercise therapy (GET).[56] There is no known pharmacological treatment for CFS. Treatment with intravenous gamma globulin has been proposed, but the benefit is equivocal.[57] Two randomized controlled trials in adults have shown that low-dose cortisol replacement therapy can produce short-term reductions in fatigue and other features of CFS.[58,59] It should be noted however, that although pharmacologically raising levels of cortisol can temporarily alleviate symptoms, it is currently not recommended as a treatment in CFS. Reasons for caution are the potentially dangerous side-effects, a rapid loss of efficacy upon discontinuation, and the observation that only a minority of patients benefit.[60]

Graded exercise therapy

GET aims at gradually increasing physical activity, under the guidance of a physiotherapist or rehabilitation specialist. Currently, no RCTs have been published regarding GET for CFS in adolescents. Recently, efficacy has been studied in adult CFS and treatment effects are comparable with CBT.[61] In adolescents, improvement in quality of life and school attendance has been described in an open study.[56] Long-term effects and sustainability have currently not been well studied.

Cognitive behavioural therapy

Conservative CBT is an intensive face-to-face behavioural intervention with a treatment duration of 5-6 months, aiming at patients' cognition of perpetuating factors. The main treatment focuses are fatigue-related cognitions, restoration of the circadian rhythm, and a gradual increase in activity. It is (often implicitly) assumed that other symptoms, such as pain or concentration problems, will also decrease if patients become less fatigued.

CBT for adolescents with CFS has only been compared with patients being on a waiting list[11] or receiving psychoeducation,[55] and resulted in a clinically significant improvement of 60–70% directly after treatment, with sustainable effect.[62] Results of both studies also showed the importance of family-focused CBT to treatment success in adolescents. The biggest practical challenge of CBT is its restricted availability

because it requires specialized therapeutic skills,[11] to which there is unequal access for adolescents with CFS.

Prognosis

Adolescents diagnosed with unexplained chronic fatigue, not so severe as to comply with CFS criteria, generally have a good prognosis.[28] Untreated CFS in adolescents seems to have a better prognosis compared to CFS in adults,[19,22] but the high disabilities during illness affecting all aspects of life during a crucial stage of development, require prompt recognition and treatment. Also, not all patients suffering from CFS recover with the current treatment modalities. Reports on long-term prospects after treatment are variable. Study results with a follow-up of 2 years vary between 50% to 70% significant improvement for adolescents who were respectively treated with the usual care or face-to-face CBT.[62,63]

The factors that influence treatment outcomes in adolescent CFS are largely unknown. Several patient- and parent-factors have been suggested, such as: age at inclusion, pain, mental health, self-esteem and general health perception,[61] and the psychological distress of the mother.[63] Earlier studies have identified the role of family, especially the fatigue severity of the mother, as a factor related to treatment success.[11,18,55] Improving prognosis also depends on identifying which patients will benefit from treatment in order to change content, duration, or choice of treatment.

AIMS AND OUTLINE OF THIS THESIS

In this thesis studies were conducted on three topics, resulting in the following objectives:

1. To gain insight into the epidemiology and morbidity of adolescent CFS, where CFS diagnosis was primarily confirmed by either a GP or a paediatrician.
2. To determine the effectiveness of internet-based cognitive behavioural treatment (FITNET) for adolescents with CFS and to establish predictors of treatment outcome.
3. To providing insight into the complex interaction between (biological) features of adolescent CFS, in particular with regard to potential reversibility.

Chapter 2 focuses on the epidemiology of clinically diagnosed adolescent CFS in the Netherlands. Up-to-date data provide a better understanding of the impact of CFS on the Dutch health-care system. These data are derived from a national prospective registration database and cross-sectional surveys among paediatricians and general practitioners.

Chapter 3 describes the design of the FITNET trial and the FITNET program in detail. This aided in the transparency of the research underlying this thesis.

Chapter 4 is the main chapter of this thesis. The results of the FITNET trial are presented. The FITNET trial was a randomized controlled trial where patients were assigned to either FITNET or usual care. After 6 months of treatment, the effectiveness of FITNET was compared between the two groups. Thereafter, patients were allowed to cross over if needed.

Chapter 5 focuses on the long-term outcome of CFS in adolescents after FITNET treatment and after usual care (on average 2.7 years after the commencement of treatment). Additionally, factors related to recovery at long-term follow-up were explored.

Chapter 6 sets out accompanying research regarding pain perception and pain threshold in CFS adolescents and their relationship to recovery from CFS.

Chapter 7 of this thesis tries to determine the effects of adolescent CFS on intellectual and school performance.

Chapter 8 explores the role of the HPA axis on recovery from adolescent CFS, using the salivary cortisol awakening response. Additionally, our longitudinal FITNET trial enabled us to provide insight into potential confounders of the association between HPA axis dysfunction and CFS in adolescents.

Chapter 9 provides a general discussion which addresses our main findings. Suggestions for future research are given, followed by a Dutch summary of the outcomes of this thesis.

REFERENCES

1. ter Wolbeek M., van Doornen LJ, Kavelaars A, Heijnen CJ. Severe fatigue in adolescents: a common phenomenon? Pediatrics 2006; 117(6): e1078-86.

2. Rhee H, Miles MS, Halpern CT, Holditch-Davis D. Prevalence of recurrent physical symptoms in U.S. adolescents. Pediatr Nurs 2005; 31(4): 314,9, 350.

3. Fowler T, Duthie P, Thapar A, Farmer A. The definition of disabling fatigue in children and adolescents. BMC Fam Pract 2005; 6: 33.

4. van de Putte EM, Engelbert RH, Kuis W, Kimpen JL, Uiterwaal CS. How fatigue is related to other somatic symptoms. Arch Dis Child 2006; .

5. ter Wolbeek M, van Doornen LJ, Kavelaars A, Heijnen CJ. Predictors of persistent and new-onset fatigue in adolescent girls. Pediatrics 2008; 121(3): e449-57.

6. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994; 121(12): 953-9.

7. Crawley E, Sterne JA. Association between school absence and physical function in paediatric chronic fatigue syndrome/myalgic encephalopathy. Arch Dis Child 2009; 94(10): 752-6.

8. Marshall GS. Report of a workshop on the epidemiology, natural history, and pathogenesis of chronic fatigue syndrome in adolescents. J Pediatr 1999; 134(4): 395-405.

9. Dowsett EG, Colby J. Long-Term Sickness Absence Due to ME/CFS in UK Schools -- An Epidemiological Study with Medical and Educational Implications. J Chronic Fatigue Syndrome 1997; 3(2): 29-42.

10. Rangel L, Garralda ME, Levin M, Roberts H. The course of severe chronic fatigue syndrome in childhood. J R Soc Med 2000; 93(3): 129-34.

11. Stulemeijer M, de Jong LW, Fiselier TJ, Hoogveld SW, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. BMJ 2005; 330(7481): 14.

12. Beard G. Neurasthenia, or nervous exhaustion. Bost Med Surg J 1869; 3: 217-21.

13. Anon. A new clinical entity? Lancet 1956; i: 789-90.

14. Straus SE, Tosato G, Armstrong G, *et al.* Persisting illness and fatigue in adults with evidence of Epstein-Barr virus infection. Ann Intern Med 1985; 102(1): 7-16.

15. Harris F, Taitz LS. Damaging diagnosis of myalgic encephalitis in children. BMJ 1989; 299(6702): 790.

16. Myalgic encephalomyelitis by proxy. BMJ 1989; 299(6706): 1030-1.

17. Chalder T, Goodman R, Wessely S, Hotopf M, Meltzer H. Epidemiology of chronic fatigue syndrome and self reported myalgic encephalomyelitis in 5-15 year olds: cross sectional study. BMJ 2003; 327(7416): 654-5.

18. van de Putte EM, van Doornen LJ, Engelbert RH, Kuis W, Kimpen JL, Uiterwaal CS. Mirrored symptoms in mother and child with chronic fatigue syndrome. Pediatrics 2006; 117(6): 2074-9.

19. Bell DS, Jordan K, Robinson M. Thirteen-year follow-up of children and adolescents with chronic fatigue syndrome. Pediatrics 2001; 107(5): 994-8.

20. Farmer A, Fowler T, Scourfield J, Thapar A. Prevalence of chronic disabling fatigue in children and adolescents. Br J Psychiatry 2004; 184: 477-81.

21. Jones JF, Nisenbaum R, Solomon L, Reyes M, Reeves WC. Chronic fatigue syndrome and other fatiguing illnesses in adolescents: a population-based study. J Adolesc Health 2004; 35(1): 34-40.

22. Rimes KA, Goodman R, Hotopf M, Wessely S, Meltzer H, Chalder T. Incidence, prognosis, and risk factors for fatigue and chronic fatigue syndrome in adolescents: a prospective community study. Pediatrics 2007; 119(3): e603-9.

23. Sharpe MC, Archard LC, Banatvala JE, *et al.* A report--chronic fatigue syndrome: guidelines for research. J R Soc Med 1991; 84(2): 118-21.

24. Carruthers BM, van de Sande MI, De Meirleir KL, *et al.* Myalgic encephalomyelitis: International Consensus Criteria. J Intern Med 2011; 270(4): 327-38.

25. Nijhof SL, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte

EM. Fatigue In Teenagers on the interNET--the FITNET Trial. A randomized clinical trial of web-based cognitive behavioural therapy for adolescents with chronic fatigue syndrome: study protocol. [ISRCTN59878666. BMC Neurol 2011; 11: 23,2377-11-23.

26. Royal College of Paediatrics and Child Health. Evidence based guideline for the management of CFS/ME (chronic fatigue syndrome/ myalgic encephalopathy) in children and young people. 2004.

27. Bakker RJ, van de Putte EM, Kuis W, Sinnema G. Effects of an educational video film in fatigued children and adolescents: a randomised controlled trial. Arch Dis Child 2011; 96(5): 457-60.

28. Bakker RJ, van de Putte EM, Kuis W, Sinnema G. Risk factors for persistent fatigue with significant school absence in children and adolescents. Pediatrics 2009; 124(1): e89-95.

29. Devanur LD, Kerr JR. Chronic fatigue syndrome. J Clin Virol 2006; 37(3): 139-50.

30. Afari N, Buchwald D. Chronic fatigue syndrome: a review. Am J Psychiatry 2003; 160(2): 221-36.

31. Tak LM, Cleare AJ, Ormel J, Manoharan A, Kok IC, Wessely S, Rosmalen JG. Meta-analysis and meta-regression of hypothalamic-pituitary-adrenal axis activity in functional somatic disorders. Biol Psychol 2011; 87(2): 183-94.

32. Raison CL, Miller AH. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. Am J Psychiatry 2003; 160(9): 1554-65.

33. Miller DB, O'Callaghan JP. Neuroendocrine aspects of the response to stress. Metabolism 2002; 51(6 Suppl 1): 5-10.

34. Fries E, Hesse J, Hellhammer J, Hellhammer DH. A new view on hypocortisolism. Psychoneuroendocrinology 2005; 30(10): 1010-6.

35. Roberts AD, Papadopoulos AS, Wessely S, Chalder T, Cleare AJ. Salivary cortisol output before and after cognitive behavioural therapy for chronic fatigue syndrome. J Affect Disord 2009; 115(1-2): 280-6.

36. Heim C, Ehlert U, Hellhammer DH. The potential role of hypocortisolism in the patho-physiology of stress-related bodily disorders.

Psychoneuroendocrinology 2000; 25(1): 1-35.

37. Cockshell SJ, Mathias JL. Cognitive functioning in chronic fatigue syndrome: a meta-analysis. Psychol Med 2010; : 1-15.

38. de Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JW, Toni I. Gray matter volume reduction in the chronic fatigue syndrome. Neuroimage 2005; 26(3): 777-81.

39. Garralda E, Rangel L, Levin M, Roberts H, Ukoumunne O. Psychiatric adjustment in adolescents with a history of chronic fatigue syndrome. J Am Acad Child Adolesc Psychiatry 1999; 38(12): 1515-21.

40. Garralda ME, Rangel L. Annotation: Chronic Fatigue Syndrome in children and adolescents. J Child Psychol Psychiatry 2002; 43(2): 169-76.

41. van Geelen SM, Sinnema G, Hermans HJ, Kuis W. Personality and chronic fatigue syndrome: methodological and conceptual issues. Clin Psychol Rev 2007; 27(8): 885-903.

42. Taillefer SS, Kirmayer LJ, Robbins JM, Lasry JC. Correlates of illness worry in chronic fatigue syndrome. J Psychosom Res 2003; 54(4): 331-7.

43. van de Putte EM, Engelbert RH, Kuis W, Kimpen JL, Uiterwaal CS. Alexithymia in adolescents with chronic fatigue syndrome. J Psychosom Res 2007; 63(4): 377-80.

44. Engel GL. The need for a new medical model: a challenge for biomedicine. Science 1977; 196(4286): 129-36.

45. Knoop H, Prins JB, Moss-Morris R, Bleijenberg G. The central role of cognitive processes in the perpetuation of chronic fatigue syndrome 6. J Psychosom Res 2010; 68(5): 489-94.

46. Vercoulen JH, Swanink CM, Galama JM, *et al.* The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: development of a model. J Psychosom Res 1998; 45(6): 507-17.

47. Prins JB, van der Meer JW, Bleijenberg G. Chronic fatigue syndrome. Lancet 2006; 367(9507): 346-55.

48. Heim C, Nater UM, Maloney E, Boneva R, Jones JF, Reeves WC. Childhood trauma and risk for chronic fatigue syndrome: association with neuroendocrine

dysfunction. Arch Gen Psychiatry 2009; 66(1): 72-80.

49. van Middendorp H, Geenen R, Kuis W, Heijnen CJ, Sinnema G. Psychological adjustment of adolescent girls with chronic fatigue syndrome. Pediatrics 2001; 107(3): E35.

50. Viner R, Hotopf M. Childhood predictors of self reported chronic fatigue syndrome/myalgic encephalomyelitis in adults: national birth cohort study. BMJ 2004; 329(7472): 941.

51. Buchwald D, Herrell R, Ashton S, *et al.* A twin study of chronic fatigue. Psychosom Med 2001; 63(6): 936-43.

52. Hickie I, Davenport T, Wakefield D, *et al.* Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. BMJ 2006; 333(7568): 575.

53. Horton SM, Poland F, Kale S, *et al.* Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) in adults: a qualitative study of perspectives from professional practice. BMC Fam Pract 2010; 11: 89,2296-11-89.

54. NICE clinical guideline (2007) Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy). National Institute for Health and Clinical Excellence.

55. Chalder T, Deary V, Husain K, Walwyn R. Family-focused cognitive behaviour therapy versus psycho-education for chronic fatigue syndrome in 11- to 18-year-olds: a randomized controlled treatment trial. Psychol Med 2010; 40(8): 1269-79.

56. Viner R, Gregorowski A, Wine C, Bladen M, Fisher D, Miller M, El Neil S. Outpatient rehabilitative treatment of chronic fatigue syndrome (CFS/ME). Arch Dis Child 2004; 89(7): 615-9.

57. Rowe KS. Double-blind randomized controlled trial to assess the efficacy of intravenous gammaglobulin for the management of chronic fatigue syndrome in adolescents. J Psychiatr Res 1997; 31(1): 133-47.

58. McKenzie R, O'Fallon A, Dale J, *et al.* Low-dose hydrocortisone for treatment of chronic fatigue syndrome: a randomized controlled trial. JAMA 1998; 280(12): 1061-6.

59. Cleare AJ, Heap E, Malhi GS, Wessely S, O'Keane V, Miell J. Low-dose hydrocortisone in chronic fatigue syndrome: a randomised crossover

trial. Lancet 1999; 353(9151): 455-8.

60. Cleare AJ. The HPA axis and the genesis of chronic fatigue syndrome. Trends Endocrinol Metab 2004; 15(2): 55-9.

61. White PD, Goldsmith KA, Johnson AL, *et al.* Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet 2011; 377(9768): 823-36.

62. Knoop H, Stulemeijer M, de Jong LW, Fiselier TJ, Bleijenberg G. Efficacy of cognitive behavioral therapy for adolescents with chronic fatigue syndrome: long-term follow-up of a randomized, controlled trial. Pediatrics 2008; 121(3): e619-25.

63. van Geelen SM, Bakker RJ, Kuis W, van de Putte EM. Adolescent chronic fatigue syndrome: a follow-up study. Arch Pediatr Adolesc Med 2010; 164(9): 810-4.

2

Adolescent Chronic Fatigue Syndrome: Prevalence, Incidence, and Morbidity

Sanne L. Nijhof, Kimberley Maijer, Gijs Bleijenberg, Cuno S.P.M. Uiterwaal, Jan L.L. Kimpen and Elise M. van de Putte

Pediatrics 2011;127:e1169-75

ABSTRACT

Objective

To determine nationwide general practitioner (GP)-diagnosed prevalence and pediatrician–diagnosed incidence rates of adolescent chronic fatigue syndrome (CFS), and to assess CFS morbidity.

Design and setting

We collected data from a cross-sectional national sample among GPs and prospective registration of new patients with CFS in all pediatric hospital departments in the Netherlands.

Patients and methods

Study participants were adolescents aged 10 to 18 years. A representative sample of GPs completed questionnaires on the prevalence of CFS in their adolescent patients. Pediatric hospital departments prospectively reported new cases of CFS in adolescent patients. For every new reported case, a questionnaire was sent to the reporting pediatrician and the reported patient to assess CFS morbidity. Prevalence was estimated through the data from GP questionnaires and incidence was estimated on the basis of cases newly reported by pediatricians from January to December 2008.

Results

Prevalence was calculated as 111 per 100 000 adolescents and incidence as 12 per 100 000 adolescents per year. Of newly reported patients with CFS, 91% scored at or above cutoff points for severe fatigue and 93% at or above the cutoff points for physical impairment. Forty-five percent of patients with CFS reported >50% school absence during the previous 6 months.

Conclusions

Clinically diagnosed incidence and prevalence rates show that adolescent CFS is uncommon compared with chronic fatigue. The primary adverse impact of CFS is extreme disability associated with considerable school absence.

INTRODUCTION

Chronic fatigue syndrome (CFS) in adolescents often has an extensive disease course that may lead to considerable school absence and long-term consequences for educational and social development.[1–3] To assess the effects of chronic fatigue on Dutch society and adolescent health care, the determination of sound prevalence and incidence rates is mandatory. Almost all currently available estimates of incidence and prevalence were determined in adult populations. Moreover, international research has revealed a wide variation in rates, partly because of differences in patient age limits and methods (eg, settings and applied diagnostic criteria) used in various studies. In adolescents, population surveys revealed annual incidence rates of 0.5% and prevalence rates of 0.19% to 1.29%,[4–7] with female-to-male ratios that varied from 2:1 up to 3:1.[5,8,9] Most of these estimates were primarily determined on the basis of self-reported data obtained from patients by use of questionnaires and telephone interviews.

Several diagnostic criteria for CFS exist, of which the 1994 Centers for Disease Control and Prevention (CDC) criteria are commonly used in the Netherlands.[10–13] According to these criteria CFS is characterized by severe and disabling new-onset fatigue that lasts for at least 6 months and is accompanied by 4 or more of the following symptoms: impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, multiple joint pain, new headaches, unrefreshing sleep, and postexertional malaise. Somatic and psychiatric illnesses should be excluded.[10]

Accurate diagnosis of CFS is a complex task that requires exclusion of other illnesses that could cause similar complaints but require different treatment. Therefore, clinical estimates of CFS prevalence and incidence can be of value in addition to the aforementioned population surveys.

The primary aim of this study was to determine adolescent CFS prevalence and incidence rates as reported by general practitioners (GPs) and pediatricians, respectively, in the Netherlands. We also investigated the severity of symptoms and disability and the extent of school absence associated with CFS in adolescents and assessed the attitude of GPs and pediatricians toward the diagnosis and management of this disease.

METHODS

Prevalence Estimations Obtained From GPs

In March 2008 a questionnaire was mailed to a sample of 735 GPs, 10% of all GPs in the Netherlands, who were randomly selected by the Dutch Institute for Research of Health Services (NIVEL). The GPs were given the opportunity to respond by mail, e-mail, fax, or telephone. Reminders were sent every 3 months during the period from November 2008 to May 2009.

The GPs were asked to submit their practice size and the number of patients with CFS aged 10 to 18 years who were receiving care. Specifically, the GPs were asked to query their ICPC coding-system database (International Classification of Primary Care), which is used by all Dutch GPs, for "fatigue" and its derivatives. Additional questions to the GPs concerned the criteria for the diagnosis and management of these patients. If a GP indicated not to have any patients with CFS, the GP was asked for a possible reason.

Population estimates were made by extrapolation of sample data to the population level, because the entire Dutch population is obliged to be registered within the practice of a GP and the average GP practice sizes are comparable (~2000 patients). Furthermore, referral by a GP is mandatory for patients to access hospital care (ie, pediatric care) in the Netherlands, and in turn GPs are informed on the progress of diagnostics and/or treatment of patients referred to the hospital and other health care professionals and facilities (eg, psychologists and rehabilitation centers).

Incidence Estimations Obtained From Pediatricians

During the period from July 2007 to December 2008 all new cases of CFS in adolescents (aged 10 –18 years) were assessed monthly by the Dutch Pediatric Surveillance Unit (DPSU). The DPSU is a national registry for pediatric disorders that includes all 103 pediatric hospital departments in the Netherlands and consequently reaches all pediatricians working in the Netherlands. The DPSU is 1 of 12 active pediatric-surveillance registries worldwide. Each pediatric department in the Netherlands receives a monthly (electronic) card to report new cases of various pediatrics disorders. For more information on survey methods see www.inopsu.com.[14] For validation of the estimated incidence number, a postal questionnaire was sent to all pediatric departments that had not reported any adolescent patients with CFS in 2008 to verify that there were no cases of CFS in adolescent patients that had not been reported. These questionnaires also queried for information on whether management of patients suspected to have

CFS by these pediatricians differed from that of prospective reporting departments. Incidence was calculated as the total number of patients reported from January to December 2008.

For every prospectively reported patient with CFS, the pediatrician and patient were requested by the DPSU to complete a questionnaire. Pediatricians were asked whether they diagnosed CFS according to the 1994 CDC criteria. Patients received, through their pediatricians, an anonymized short survey regarding gender, age, duration of complaints before diagnosis, assessment of fatigue and concentration problems, functional impairment, type of complaints, and school absence. Fatigue was assessed with the self-report questionnaire Checklist Individual Strength-20 (CIS-20) subscales "fatigue severity" (8 items) and "concentration problems" (5 items). The CIS-20 is a reliable assessment tool with excellent internal consistency (Cronbach's α: 0.93) and discriminative validity for CFS.[15,16] The cutoff point for severe fatigue was set at ≥40 on the subscale fatigue severity.[16,17] Disabilities were measured by using the self-report Child Health Questionnaire-Child Form subscale "physical functioning" (9 items). This assessment tool is reliable and has been validated with good internal consistency (Cronbach's α: 0.56–0.90).[18,19] The cutoff point for impaired physical functioning was set at ≤85 (healthy population's mean of 96.8 minus 2 SD [2x 5.4]).[19] As a reference group, students at a Dutch secondary school (de Breul, Zeist) were invited to participate. Adolescents who were suffering from a chronic illness and adolescents currently under treatment were excluded. The participation rate was 85%. From this group of students we randomly selected individuals for a control group matched for age and gender (n=144; mean age: 15.3 ±0.6 years; 79% girls).

Ethics

The medical ethics committee of the University Medical Center Utrecht approved this study. Case data obtained by the GP registration surveys were anonymous; investigators did not have access to information that would allow them to identify or contact these patients and their families. The requirement for informed consent was thus waived. Informed consent was obtained in all cases for which data were traceable to the individual patient, ie, the in which questionnaires were sent to the patients of reporting pediatricians.

Analysis

For estimation of the prevalence and incidence rates, the total number of adolescents in the Netherlands in 2008 was determined to be 1786 933 according to figures of the Dutch Bureau of Statistics.[20]

Statistical analyses were performed by using SPSS version 15.0 (SPSS Inc, Chicago, IL). Outcome variables were presented as means with SDs and percentages.

RESULTS

Prevalence Estimates

A total of 354 GPs (48%) responded, of whom 304 (41%) returned a completed questionnaire. There were 81 adolescent patients with CFS reported by 42 GPs. Absolute CFS number was estimated to be 1976 adolescents nationwide. The point prevalence of adolescent CFS was calculated at 111 per 100 000 adolescents (0.11%). For details on prevalence calculation, see Fig. 1.

Incidence Estimates

Of 103 Dutch pediatric departments, 92 reported 200 adolescent patients with newly diagnosed CFS cases in 2008. Of these patients, a total of 16 were excluded because of age (n = 3), double report (n = 9), or a revised diagnosis by the reporting pediatrician (n = 4), leaving 184 newly reported cases. Eleven pediatric departments did not respond to the questionnaires of the DPSU. Therefore, the overall pediatric department response rate was 89%.

Analysis of the 11 hospitals that did not report new cases of adolescent CFS did not reveal trends in hospital size, location (urban versus rural), or organization level (academic versus regular). The locations of the nonreporting hospitals seemed randomly associated, so different incidence rates of patients with CFS in these hospitals

Incidence and Prevalence Rate Calculations

Number of adolescents in The Netherlands in 2008 (10-18 year old):1,786,933*

Prevalence
GP sample size: 10% of Dutch GPs were contacted
Overall GP response: 4,1% (GP sample size * GPs completing the questionnaire = 10% * 41%)
Absolute CFS in NL = Number of reported patients (81)/ Overall GP response (4,1%) = 1976
Prevalence = Absolute CFS in NL (1976)/ Adolescents in NL (1,786,933) = 111 per 100,000

Incidence
Total number of Dutch PDs: 103**
34 PDs reported prospectively, 58 PDs reported on request (89% PD response rate)
Absolute new CFS cases in NL in 2008 = Number of reported cases (184)/ Overall PD response (89%) = 207
Incidence = Absolute new CFS in NL (207)/ Adolescents in NL (1,786,933) = 12 per 100,000

GP: General Practioner - CFS: Chronic Fatigue Syndrome - NL: Neterlands - PD: Peadiatric department
* Dutch Central Bureau of Statistics, http://www.cbs.nl
** Dutch Peadiatric Society, http://www.nvk.pedianet.nl

FIGURE 1: Incidence and prevalence rate calculations

	CFS		Healthy peers		p-value
Age (mean, SD)	15.2 (1.9)		15.3 (0.6)		0.556*
Gender (% girls)	85		79		0.250**
Duration of symptoms (months, SD)	17 (18.1)				
Onset of disease (%)					
Acute	10				
Gradual	68				
Post-infectious	22				
Checklist Individual Strength CIS-20 (mean, SD)					
Subscale fatigue severity, range: 8-56	49.8 (6.4)		22.6 (10.7)		0.000*
Subscale concentration problems, range: 5-35	26.5 (6.9)		16.3 (7.1)		0.000*
Child Health Questionnaire CHQ-CF87 (mean, SD)					
Subscale physical functioning, range: 0-100	58.6 (20.4)		95.1 (7.6)		0.000*
School absence (%)	*Last 2 wks*	*Last 6 mos*	*Last 2 wks*	*Last 6 mos*	
Mean school absence (SD)	58.5 (33.0)	54.2 (29.1)	1.5 (3.9)	4.9 (6.9)	0.000*
Minimal (< 5%)	7.1	4.0	91.2	75.6	
Mild (5-15%)	4.0	5.0	5.9	18.5	
Considerable (15-50%)	34.3	46.5	2.9	5.9	
Severe (50-75%)	18.2	15.8	0.0	0.0	
Almost complete to complete (75-100%)	36.4	28.7	0.0	0.0	
Number of reported CDC symptoms (%)					
Mean, range: 0-8 (SD)	5.0 (1.6)		-		
Unrefreshing sleep	84.4		-		
Post-exertional malaise lasting more than 24 hr	79.7		-		
Memory and/or concentration problems	78.9		-		
Headaches	78.1		-		
Muscle pain	59.4		-		
Joint pain	48.4		-		
Sore throat	43.0		-		
Tender lymph nodes	31.3		-		

* independent student t-test
** χ2-test/ Fisher's Exact test

TABLE 1. Morbidity of adolescents with CFS reported by pediatric departments in 2008

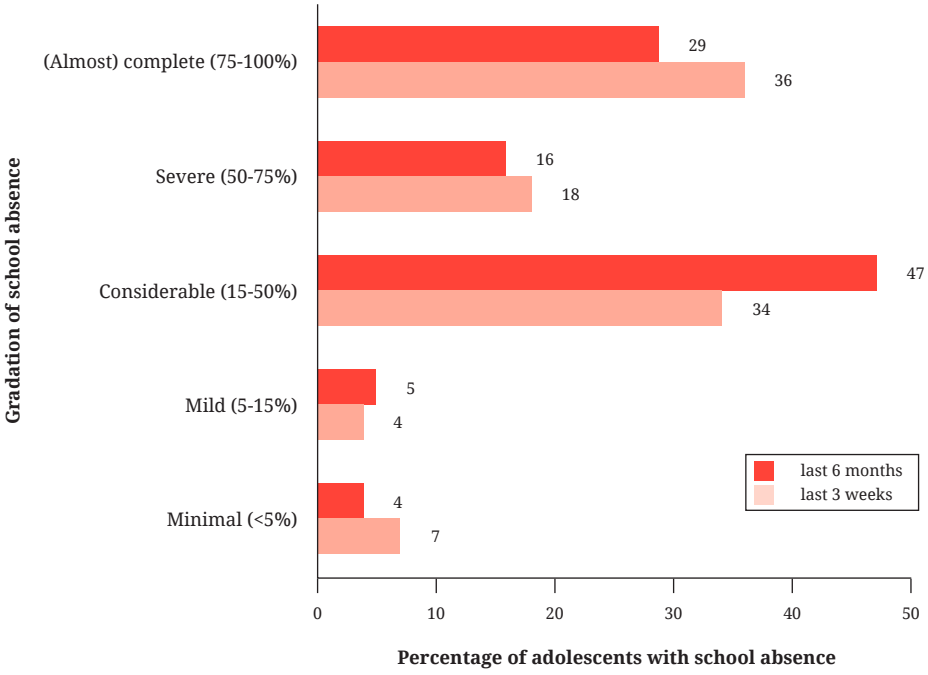


FIGURE 2 Distribution of school absence.

are not expected.

On the basis of the assumption that the same number of adolescents with CFS were referred to nonresponding departments the incidence rate was corrected for the 11% nonresponse. The CFS incidence rate was 12 per 100 000 adolescents per year (0.012%). For details on incidence calculation, see Fig. 1.

From all DPSU-derived reports, completed questionnaires were obtained for 81% of patient questionnaires and 96% of pediatrician questionnaires. In all reported cases the CFS diagnosis was in compliance with CDC criteria.

Demographics and Morbidity

Demographic characteristics were obtained from 184 CFS cases. The average age of illness onset was 15 years (SD: ±1.9 years), with a female-to-male ratio of 5:1. Median illness duration from start of complaints until diagnosis was 17 months (SD: ±18.1 months), but illness duration ranged widely (6 –110 months). In 22% of patients the illness started after an acute episode of infectious disease (of these patients 52% had a current or recent Epstein Barr virus infection); 10% of patients had an acute noninfectious onset. The remaining majority of patients (68%) had a gradual onset of

the symptom pattern over weeks to months. The morbidity of patients compared to their healthy peers is summarized in Table 1. Most patients (91%) scored at or above the cutoff point of 40 for severe fatigue (mean: 49.8) on the CIS-20 fatigue-severity subscale. Most patients (93%) also scored at or beyond the cutoff point of 85 on the Health Questionnaire-Child Form physical-functioning subscale. School absence was high: ~90% of patients with CFS reported "considerable" (defined as 15%–50% school absence) to complete school absence in the previous 2 weeks and 6 months (Fig. 2).

GPs with adolescent CFS patients	**Answers**	**GP Responses, n (%)**
Total		42 (13.8)
Who diagnosed the patient?	Myself (GP)	18 (42.9)
	Pediatrician	22 (52.4)
	Other	10 (23.8)
If you diagnosed the patient yourself* which criteria did you use?	CDC-criteria	6 (33.3)
	Other	12 (66.7)
Did you refer this patient?*	Yes, to a pediatrician	11 (61.1)
	Yes, but not to a pediatrician	4 (22.2)
	No	3 (16.7)
How do you register this chronic fatigued patient?**	Chronic fatigue syndrome	22 (52.4)
	Chronic fatigue	6 (14.3)
	Fatigue/weakness	15 (35.7)
	Malaise	2 (4.8)
	Other	2 (4.8)
GPs with no adolescent CFS patients N, (%)		
Total		262 (86.2)
For what reason do you not have any adolescent CFS patients in your practice?**	There are no adolescents in my practice that can be considered to have this diagnosis	161 (61.5)
	I only consider this diagnosis in adults	26 (9.9)
	I find this diagnosis inadequate	98 (37.4)
	I don't acknowledge this diagnosis	33 (12.6)
	Other	17 (6.5)

* Percentage of self diagnosing GPs
** Multiple answers could apply per GP

TABLE 2. GPs Attitudes Toward and Management of Adolescent CFS According to Questionnaire Responses

The mean number of concurrently present CDC symptoms was 5, with "unrefreshing sleep" the most commonly reported (84.4%) and "tender lymph nodes" the least reported (31.3%).

Attitudes to Diagnosis and Disease Management

Among contacted GPs, 7% indicated that they were too busy to cooperate or never cooperated with postal surveys. Forty-three percent of GPs reported that they themselves diagnosed adolescent CFS in their patients, and 1 of 3 of these GPs used CDC criteria. CFS in adolescents was accepted as a distinct diagnosis by 51% of all responding GPs. For detailed information on GP attitudes, see Table 2.

Ninety-six percent of the consulted pediatric departments regarded CFS as a distinct diagnosis, and 92% used CDC criteria for diagnosing CFS. Of the departments who had never diagnosed CFS in an adolescent patient, 1 stated that this diagnose is applicable only in adults and 3 that this diagnosis is inadequate. For CFS treatment, patients were referred to a psychologist, physical therapist, rehabilitation center, and/or a tertiary care center.

DISCUSSION

This study was the first, to our knowledge, in which nationwide crosssectional prevalence data as well as prospective incidence data on adolescent patients with CFS were collected and in which CFS diagnosis was primarily confirmed by either a GP or a pediatrician. We estimated the GP-diagnosed prevalence of adolescent CFS to be 111 per 100 000 adolescents (0.11%) per year and the pediatrician-diagnosed incidence of adolescent CFS to be 12 per 100 000 adolescents (0.012%) per year. Fatigue severity and physical impairment as well as school absence were found to be remarkably high in adolescents with CFS. These data strongly suggest that adolescent CFS should be regarded as a serious illness with corresponding consequences such as delay in educational and social development.

Strengths and Weaknesses

Both for prevalence rates and incidence rates we made use of the independent institutes NIVEL and DPSU, which use reliable methods to assess the impact of nationwide public health issues. To determine reliable prevalence numbers, a representative sample of GPs was selected by NIVEL to allow for extrapolation. In regard to the validity of prevalence rates, we assumed that the GPs, as a gatekeepers of health care, were well informed by health care professionals involved in the diagnostic process and treatment of CFS in adolescents, which suggests that the prevalence estimates were accurately reported. The data present in Table 2 do indeed show that almost 75% of the CFS diagnoses in adolescents were made by health care professionals other than the GP. Unfortunately, although we sent several reminders and GPS had the option to respond by mail, e-mail, or telephone, the GP response rate remained low (48%) and possibly introduced a selection bias.

The nationwide response rate on adolescent CFS incidence among pediatric departments that was prospectively derived by the DPSU was high (89%). Furthermore, the rate of adherence to CDC criteria (92%) suggested that Dutch pediatricians adequately diagnosed CFS in adolescents. Although CFS seemed to be diagnosed adequately by pediatricians in our study, underreferral to pediatricians by the GPs might have led to an underestimation of incidence. However, if a GP does not diagnose CFS in adolescents this does not necessarily mean the GP is reluctant to refer a severely fatigued and disabled adolescent to a pediatrician or other health care professional. Our study does not supply data on the referral pattern of the GP.

Determination of prevalence rates in pediatric practices would have led to an underdetermination of CFS prevalence, because after the diagnostic process pediatricians referred adolescents for treatment to specialized psychologists or to a rehabilitation center.

Comparison With Other Studies

The estimated rates of the occurrence of CFS in adolescents that we report were lower than those found in previous studies. However, most recent studies on CFS incidence and prevalence rates in adolescents are based on population surveys performed with methods that were different from those used in our study.

Rimes et al used telephone questionnaires in a random adolescent population sample to longitudinally determine the incidence and prevalence of disabling fatigue. A validated questionnaire was used to assess psychological/ psychiatric diagnoses, but no physical examinations or investigations to exclude physical causes of fatigue were performed. In 824 adolescents, 4 new cases of CFS were reported, ie, a incidence rate of 0.5%.[7]

Chalder et al determined the prevalence of adolescent CFS in a cross-sectional interview study, in which diagnosis based on CDC criteria (by interview only) was compared with self-report by patients and parental report. Prevalence rates were, respectively, 0.19%, 0.57%, and 0.038%. There was no concordance between parental report that a child had CFS and operationally defined CFS (CDC criteria).[4] These findings illustrate the effect of the use of different diagnostic methods.

Jones et al also conducted a random digit-dialing survey in which adolescents with CFS-like illness were identified. Of all identified adolescents (31 of 8586) only 35.5% volunteered to undergo clinical evaluation. None of these adolescents met the CFS case definition. The authors extracted an estimated adolescent CFS prevalence of the adult population of 50 per 100 000.[6]

Farmer et al used 2 twin registries to derive life-time prevalence estimates of chronic fatigue in adolescents. Selected families were sent questionnaires and parents were interviewed by telephone. Recorded physician diagnoses were reviewed on paper by an independent doctor, but patients did not undergo an additional medical examination. When the diagnosis was made in adherence to CDC criteria, the CFS incidence was 1.29%. When fatigue duration was only 3 months, the incidence increased to 1.90%. For fatigue without any of the 4 accompanying symptoms the incidence increased to 2.43%.[5] These findings illustrate the effect of applied criteria on CFS incidence.

Adherence to the UK NICE (National Institute for Health and Clinical Excellence) criteria leads to higher incidence rates, because the diagnosis of CFS according to NICE guidelines requires symptoms that persist for only 3 months instead of 6 months.[21]

Demographical data from the newly reported patients with CFS regarding age of onset and gender ratio are in line with earlier studies.[1,4,8,9,22] Our findings support previous evidence on the disabling character of this illness and high level of school absence.[1,8,9,22–24] Our data regarding GPs attitudes toward adolescent CFS are in line with results of previous studies of CFS attitudes in adults in the Netherlands. Among GPs, 58%– 98% accepted CFS as a recognizable clinical entity[25–27] and 48%–66% felt unconfident in diagnosing CFS.[26,27]

Implications of the Findings

Although both prevalence and incidence rates are possibly underestimated, this does not change the fact that adolescent CFS seems uncommon in comparison with the high prevalence of severe fatigue in the Netherlands. A recent study showed a prevalence rate of adolescent severe fatigue of 20.5% in girls and 6.5% in boys, of whom 80% and 61.5%, respectively, reported fatigue lasting1 month and 46.9% and 35.2% for 3 months.[17] These data support the theory that CFS is a specific clinical entity in the spectrum of chronic and severe fatigue. The burden to society mainly consists of the associated extensive school absence and its long-lasting and disabling effects.

Although CFS in adolescent patients seemed to be diagnosed adequately by pediatricians in our study, underreporting remains a point of attention in clinical studies. Results of a recent population-based study in the Netherlands showed a 1% prevalence rate of adult self-reported CFS. Strikingly, 70% of these adults consulted their GP for their complaints of fatigue, but GPs diagnosed CFS in only 6.7% of these patients.[28] We suggest that all adolescents who consult their GP for a complaint of severe and long-lasting fatigue should be referred to a pediatrician for proper disease diagnosis and initiation of treatment.

CONCLUSIONS

Adolescent CFS is an uncommon illness compared with chronic fatigue. The primary adverse impact of CFS in adolescents is its extremely disabling character and associated high rates of school absenteeism. In contrast to the high acceptance of adolescent CFS among pediatricians, CFS is probably underrecognized by other primary health care providers.

REFERENCES

1. Crawley E, Sterne J. Association between school absence and physical function in paediatric chronic fatigue syndrome/ myalgic encephalopathy. Arch Dis Child. 2009;94(10):752–756.

2. Marshall GS. Report of a workshop on the epidemiology, natural history, and pathogenesis of chronic fatigue syndrome in adolescents. J Pediatr. 1999;134(4):395– 405

3. Dowsett EG, Colby J. Long term sickness absence due to ME/CFS in UK schools: an epidemiological study with medical and educational implications. J Chron Fatigue Synd. 1997;3(2):29–42

4. Chalder T, Goodman R, Wessely S, Hotopf M, Meltzer H. Epidemiology of chronic fatigue syndrome and self reported myalgic encephalomyelitis in 5–15 year olds: cross sectional study. BMJ. 2003;327(7416): 654–655

5. Farmer A, Fowler T, Scourfield J, Thapar A. Prevalence of chronic disabling fatigue in children and adolescents. Br J Psychiatry. 2004;184:477– 481

6. Jones JF, Nisenbaum R, Solomon L, Reyes M, Reeves WC. Chronic fatigue syndrome and other fatiguing illnesses in adolescents: a population-based study. J Adolesc Health. 2004;35(1):34–40

7. Rimes KA, Goodman R, Hotopf M, Wessely S, Meltzer H, Chalder T. Incidence, prognosis, and risk factors for fatigue and chronic fatigue syndrome in adolescents: a prospective community study. Pediatrics. 2007; 119(3). Available at: www.pediatrics.org/ cgi/content/ full/119/3/e603

8. Bell DS, Jordan K, Robinson M. Thirteenyear follow-up of children and adolescents with chronic fatigue syndrome. Pediatrics. 2001;107(5):994 –998

9. van de Putte EM, Uiterwaal CS, Bots ML, Kuis W, Kimpen JL, Engelbert RH. Is chronic fatigue syndrome a connective tissue disorder? A cross-sectional study in adolescents. Pediatrics. 2005;115(4). Available at: www.pediatrics.org/cgi/content/ full/115/4/e415

10. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its

definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med. 1994;121(12):953–959

11. Holmes GP, Kaplan JE, Gantz NM, *et al.* Chronic fatigue syndrome: a working case definition. Ann Intern Med. 1988;108(3): 387–389

12. Lloyd AR, Hickie I, Boughton CR, Spencer O, Wakefield D. Prevalence of chronic fatigue syndrome in an Australian population. Med J Aust. 1990;153(9):522–528

13. Sharpe MC, Archard LC, Banatvala JE, *et al.* A report: chronic fatigue syndrome: guidelines for research. J R Soc Med. 1991;84(2): 118 –121

14. Hira Sing RA, Rodrigues PR. [The Dutch Pediatric Surveillance System; a quality focused instrument for prevention and research]. Ned Tijdschr Geneeskd. 2002; 146(50):2409 –2414

15. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res. 1994;38(5): 383–392

16. Stulemeijer M, de Jong LW, Fiselier TJ, Hoogveld SW, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. BMJ. 2005;330(7481):14

17. ter Wolbeek M, van Doornen LJ, Kavelaars A, Heijnen CJ. Severe fatigue in adolescents: a common phenomenon? Pediatrics. 2006; 117(6). Available at: www.pediatrics.org/ cgi/content/full/117/6/e1078

18. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. J Psychosom Res. 2004;56(2):157–170

19. Raat H, Landgraf JM, Bonsel GJ, Gemke RJ, Essink-Bot ML. Reliability and validity of the child health questionnaire-child form (CHQCF87) in a Dutch adolescent population. Qual Life Res. 2002;11(6):575–581

20. Statistics Netherlands, Centraal Bureau voor de Statistiek. National Dutch datacollection of 2008. Available at: http://cbs.nl. Accessed March 18, 2011

21. National Institute for Health and Clinical Excellence. Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis (or Encephalopathy): Diagnosis and Management of CFS/ME in Adults and Children. London, UK: National

Institute for Health and Clinical Excellence; 2007. Available at: www.nice.org.uk/nicemedia/pdf/CG53NICEGuideline.pdf. Accessed March 18, 2011

22. van de Putte EM, Engelbert RH, Kuis W, Sinnema G, Kimpen JL, Uiterwaal CS. Chronic fatigue syndrome and health control in adolescents and parents. Arch Dis Child. 2005; 90(10):1020 –1024
23. Patel MX, Smith DG, Chalder T, Wessely S. Chronic fatigue syndrome in children: a cross sectional survey. Arch Dis Child. 2003; 88(10):894–898
24. Rangel L, Garralda ME, Levin M, Roberts H. The course of severe chronic fatigue syndrome in childhood. J R Soc Med. 2000; 93(3):129 –134
25. Bazelmans E, Vercoulen JH, Galama JM, van WC, van der Meer JW, Bleijenberg G. [Prevalence of chronic fatigue syndrome and primary fibromyalgia syndrome in The Netherlands]. Ned Tijdschr Geneeskd. 1997; 141(31):1520 –1523
26. Bowen J, Pheby D, Charlett A, McNulty C. Chronic fatigue syndrome: a survey of GPs' attitudes and knowledge. Fam Pract. 2005; 22(4):389 –393
27. Fitzgibbon EJ, Murphy D, O'Shea K, Kelleher C. Chronic debilitating fatigue in Irish general practice: a survey of general practitioners' experience. Br J Gen Pract. 1997; 47(423):618–622
28. Van't Leven M, Zielhuis GA, van der Meer JW, Verbeek AL, Bleijenberg G. Fatigue and chronic fatigue syndrome-like complaints in the general population. Eur J Public Health. 2009

3

Fatigue In Teenagers on the interNET- the FITNET Trial

A randomized clinical trial of web-based cognitive behavioural therapy for adolescents with chronic fatigue syndrome: study protocol

Sanne L. Nijhof, Gijs Bleijenberg, Cuno S.P.M. Uiterwaal,
Jan L.L. Kimpen and Elise M. van de Putte

BMC Neurol 2011 Feb 19;11:23

ABSTRACT

Background

Chronic Fatigue Syndrome (CFS) is increasingly recognized as a cause of disability and inactivity in adolescents in the Netherlands. CFS is characterized by unexplained fatigue lasting more than 6 months. Cognitive Behavioural Therapy (CBT) has proven to be effective. However, CBT availability for adolescents with CFS is limited and requires special therapeutic skills not always readily available. An alternative to the face-to-face CBT is FITNET, a web-based therapeutic program designed specifically for adolescents diagnosed with CFS, and their parents. This new CBT approach appeals to the modern youth, who grow up with internet as their main source of information. A web-based program offers the opportunity to lower thresholds for the acceptance and realization of healthcare. This treatment can be activated at any chosen time. The communication between patient and therapist can elapse asynchronously. If effective, this web-based program would greatly increase the therapeutic accessibility.

Methods/Design

A randomized clinical trial is currently conducted. One-hundred-forty adolescents aged 12-18 years diagnosed with CFS will be recruited and randomized to one of two groups: FITNET or usual care. After 6 months, the usual care group will have access to the FITNET program. Outcomes will be assessed at baseline, post intervention, and at 6 months follow-up. Primary outcome measures are school presence, fatigue severity, and physical functioning.

Discussion

The FITNET study is the first randomized clinical trial which evaluates the effect of web-based CBT versus usual care in adolescents with CFS. The intervention is based on a theoretical existing model of CBT for patients with CFS. The results of this study will provide information about the possibility and efficacy of web-based CBT for adolescents with CFS and will reveal predictors of efficacy.

Trial registration

ISRCTN: ISRCTN59878666 and ClinicalTrials.gov: NCT00893438

INTRODUCTION

Chronic fatigue syndrome (CFS, also known as myalgic encephalomyelitis/encephalopathy or ME) is a disabling disorder, characterized by persistent or relapsing severe fatigue that is not the result of an organic disease or ongoing exertion and is not alleviated by rest. Symptoms last for at least 6 months and are accompanied by other symptoms like muscle pain and concentration problems.[1]

The cause of CFS is still unknown. CFS is explained in terms of a central neurobiological disturbance with triggering, predisposing and perpetuating factors both on a biological and psychosocial level.[2] Cognitions concerning these perpetuating factors are subject of the cognitive behavioural therapy (CBT) regimen for adolescents. CBT is the only evidence-based treatment with a recovery rate of 70% directly after treatment.[3] An uncontrolled study of the efficacy of family cognitive behaviour therapy for adolescents with CFS, revealed even better results with a recovery rate of 83%, with a maintained gain at 6 months follow-up.[4] However, the availability of this treatment in the Netherlands is limited and it requires special therapeutic skills that are not always readily available.

Furthermore, not all cases of CFS are adequately recognised, neither by the patient nor by their doctor. A large population study in the Netherlands revealed a prevalence rate of 16.4% of severe fatigue lasting more than one month in adolescent girls.[5] The proportion of undiagnosed cases of CFS among these girls is unclear. The lack of treatment possibilities within reach may enhance the reticence in diagnosing CFS.

Although untreated CFS in adolescents has a better prognosis than in adults, the risk of disruption of development and education asks for a prompt recognition of the syndrome and an effective treatment method.[3,6] The longest follow-up study, covering a 13 year follow-up period, showed that the majority of adolescents have mild to moderate persisting symptoms with a considerable period of school absence.[6]

The lack of skilled cognitive behavioural therapists to treat adolescents with CFS made us decide to develop a web-based application combing CBT by a skilled therapist with a regular internet contact. In a recently published non-inferiority randomised controlled trial (RCT) by the Expert Centre for Chronic Fatigue (ECCF) in Nijmegen, a minimal intervention based on CBT for CFS, consisting of a self help booklet (workbook) supported by email contact with a cognitive behavioural therapist, appeared to be effective.[7] This Self Help Program resembles a web-based CBT in certain aspects, such as the absence of face-to-face contact between therapist and patient. However, in the minimal intervention study the contact between therapist and patient was minimal,

whereas in the web-based CBT there will be frequent email contact between therapist and patient.

Web-based CBT for illnesses other than CFS has been found effective, but most research has been conducted with adults.[8,9] For adolescents, web-based CBT has been developed for disorders such as obesity,[10] depression,[11] anxiety,[12] headache[13] and smoking cessation.[14] The efficacy of these web-based CBT programs in general is comparable with the face-to-face treatments.[8,9,13,15]

FITNET (web-based treatment for Fatigue In Teenagers) is a Dutch web-based program developed in close collaboration between the Wilhelmina Children's Hospital (University Medical Centre Utrecht, UMCU) and the Expert Centre for Chronic Fatigue (Radboud University Nijmegen Medical Centre, ECCF). FITNET is a highly structured program for adolescents with CFS and consists of two parts: a psycho-educational part for both adolescents and parents and a CBT part based on the protocol of the ECCF.[16] The efficacy of this protocol in a face-to-face setting for adolescents has been demonstrated in a randomized controlled trial.[3]

The primary aim of this study is to determine the efficacy of FITNET for adolescents with CFS in the Netherlands. The second goal of this study is to explore predictors of outcome.

METHODS

Study design

A single-blinded randomized clinical trial (RCT) with 6 months follow-up will be conducted to evaluate the efficacy of FITNET compared to usual care for adolescents with CFS. Efficacy of FITNET compared to usual care will be determined after 6 months, the maximum duration of the treatment. Patients assigned to FITNET have to agree to not have any further medical examinations or other treatments for fatigue whilst in therapy.[17] The adolescents who have been assigned to the usual care will get the opportunity to attend the program after these 6 months. The total follow-up time is 12 months after the start of the web-based program (see Figure 1).

CFS will be diagnosed after a uniform diagnostic work-up by a paediatrician specialised in CFS (EP), according to CDC-criteria.[1] Once the diagnosis is established, study eligibility will be assessed by completing self-reported questionnaires on fatigue, physical complaints, physical functioning, depression and anxiety. Eligible patients will be asked to participate in this RCT. If the patient is willing to participate, the primary investigator (SN) will check the inclusion and exclusion criteria (table 1). When a patient meets all criteria, oral and written consent will be obtained from both patient and at least one parent, according to the declaration of Helsinki. The patients with a possible psychiatric comorbidity and their parents will be examined by an experienced child psychologist before randomisation. Patients with a primary psychiatric diagnosis, as assessed by this psychologist, will be excluded from the trial. If the adolescent or the parent(s) decide not to participate in the study, the reason will be asked and specified, although they are not obligated to reveal such reasons. During the intervention we expect some adolescents to drop-out. The reason to stop will be asked and specified.

Study population

It is intended to include 140 adolescents aged 12-18 years old, referred to the University Medical Centre Utrecht (UMCU) and diagnosed with CFS using the CDC-criteria.[1] The patients will be recruited from second-line medical care by means of the National Surveillance Centre for Children (NSCK), which is part of the International Network of Pediatric Surveillance Units, INoPSU.[18] The NSCK survey guarantees a high percentage of reporting (83-92%) of the diagnosis under consideration. Recruitment from primary care will be realised by announcement of this study to all General Practitioners in the Netherlands (with help of the NIVEL, the Dutch Collaborating Centre of the WHO). In

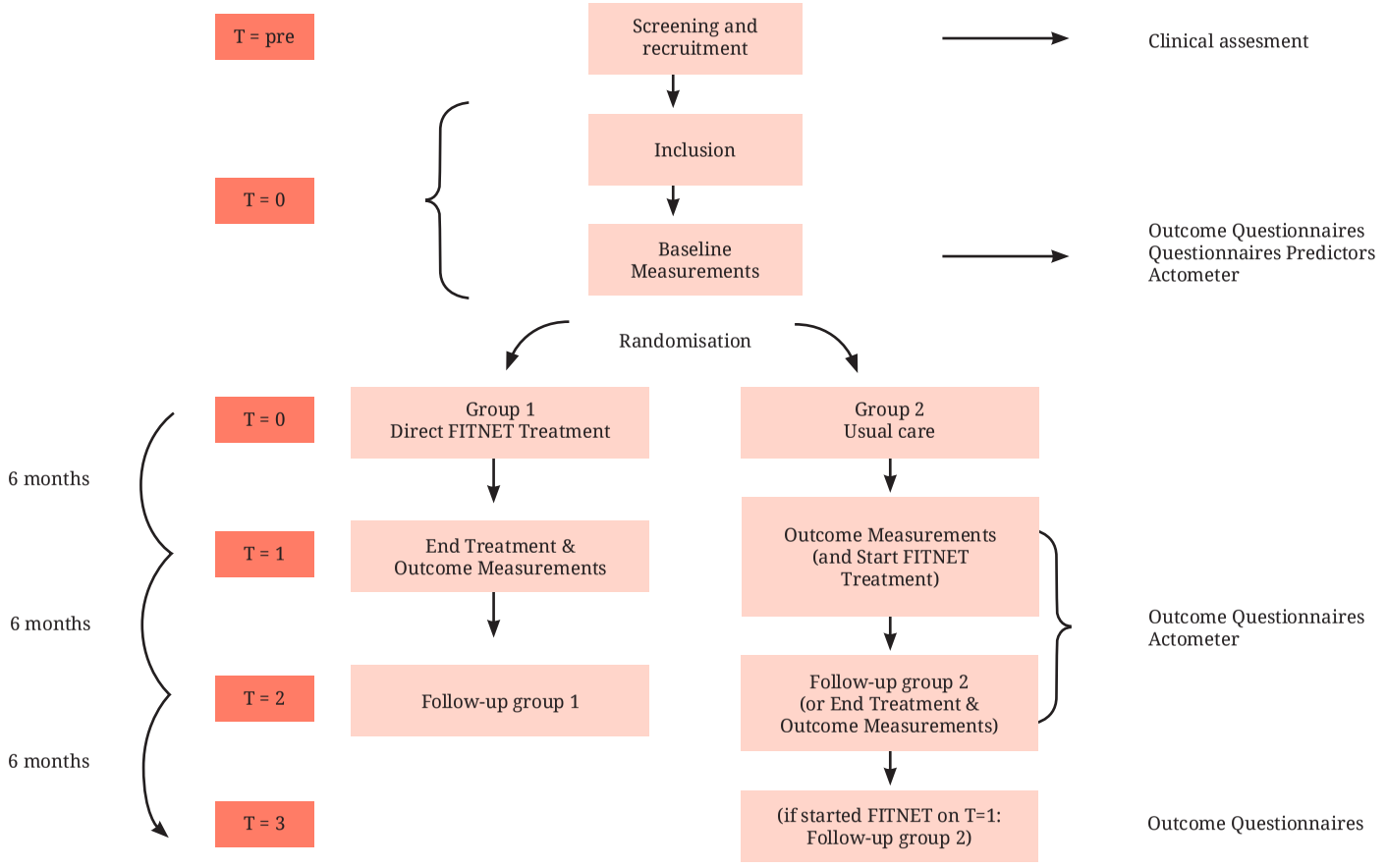


FIGURE 1: Flowchart of trial design

addition, on the website of the 'CVS-ME Stichting' (a Dutch CFS Foundation) a direct call to participate in this study will be published.

Ethical approval

This study has been reviewed and approved by the Medical Ethical Committee of the University Medical Centre Utrecht (reference 07/196-K) and the Medical Ethical Committee of the Radboud University Nijmegen Medical Centre (reference AMO nr. 07/105). Patients and their parents receive verbal and written information about the study and informed consent will be obtained before randomisation.

Randomization and blinding

Concealed randomisation will be performed by the datamanagement section of the Julius Centre for Health Sciences and Primary Care Utrecht. This randomization is computer-generated by creating 'blocks' with a size of 6, ensuring that the same number of participants will be allocated to each group. The investigators who are responsible for the inclusion will be blinded. Primary outcome parameters will be assessed by computer.

Inclusion criteria

1. The participant has given written informed consent
2. CFS diagnosis according to the CDC criteria [1]
3. Adolescent between 12-18 years old at inclusion
4. Fatigue severity subscale (CIS-20) score ≥ 40 (healthy population's mean plus two SD) [19]
5. Physical functioning (Child Health Questionnaire) score < 85 (healthy population's mean minus two SD) and/or school participation ≤ 85% (healthy population's mean minus two SD) in last two weeks [20]

Exclusion criteria

1. Inadequate control of Dutch language by child or parent
2. No availability of computer hardware and internet connection
3. Suicide risk as assessed on the Children's Depression Inventory (CDI) [21]
4. Cognitive retardation (when indicated an IQ-test will be conducted; IQ < 85 will be excluded)
5. Score greater than or equal to 44 (healthy population's mean plus two SD) on the State-Trait Anxiety Inventory for Children (STAIC) [23]
6. Score greater than or equal to 16 (healthy population's mean minus two SD) on the Children's Depression Inventory (CDI) [21]

TABLE 1: Inclusion and exclusion criteria

Interventions

Usual care

The patients in the control group will receive the usual care available in the region where the patient lives. The available usual care for adolescents with CFS in the Netherlands includes: individual/group based rehabilitation programs, psychological support including CBT face-to-face, graded exercise therapy by a physiotherapist, etc. All care received will be monitored during the study.

Web-based Cognitive Behavioural Therapy (FITNET)

FITNET is a web-based cognitive-behavioural treatment accessible to patients and both parents, based on the existing face-to-face CBT protocol for adolescents developed by the ECCF.[3,17] Trained cognitive behavioural psychotherapists from the ECCF will support the patients by e-consults. There will be no face-to-face contact between the therapists and patients at all.

The web portal is designed by the UMCU in collaboration with the ECCF, and has been developed in cooperation with adolescents with CFS who critically appraised text, lay-out and structure. Two authors of children books (Mr. and Mrs. van Hagen) revised the textual content on readability for adolescents. All therapists receive a special half a day training in the application of written language for this target group.

The programme consists of a psycho-educational and a CBT section. The psycho-educational section will be readily available, after receiving log in codes. The CBT section consists of 21 interactive modules (see appendix 1), accessible upon activation by the therapist. The webbased therapy comprises about 20 internet-sessions over 6 months. Meanwhile, the parents will follow a parallel program. All users will have a unique username and password, ensuring private communication with the therapist. Both parents and adolescents will have a regular e-consult (email contact) with the therapist, wherein results so far are discussed and new assignments can be given. The therapist will reply on a fixed weekday. The patient will have the ability to send an emergency email, on which a prompt reply will be made. For emergency situations, telephone contact details are available for the patient.

The FITNET treatment programme is implemented in a portal with a lay-out especially designed for adolescents, combining different applications such as: e-consult, personal diaries, questionnaires, psycho-education, all treatment steps and the possibility to review previous communications and assignments. Patient data and emails will be encrypted and securely stored on the UMCU mainframes to guarantee privacy and confidentiality. The treatment protocol is described in more detail in the appendix.

Compliance and attrition

Therapy compliance will be assessed by recording the number of treatment-modules (CBT) that have been completed. When applicable, participants will be asked for their reasons for poor compliance. In the case of therapy drop-out, patients will be asked for the reason of non compliance and stimulated to continue participation in the assessments until the last follow-up.

OUTCOMES

Outcome measures and predictors of outcome are listed in table 2. The primary outcome measures are: (1) Fatigue as measured by the subscale fatigue severity (8 items, 7-points Likert Scale) of the Checklist Individual Strength-20[19] with a severity range from 8-56. The questionnaire has good reliability and discriminative validity. (2) Physical functioning as measured by the subscale physical functioning (9 items) of the validated Dutch translation of the Child Health Questionnaire (CHQ-CF87) (0-100%),[20] and (3) School presence (expressed in attended hours/obliged hours * 100%) as assessed in prior intervention studies in adolescents with CFS[3]. Secondary outcome measure is

	Instruments	T0	T1	T2	T3
Primary outcome parameters					
Fatigue severity	Checklist Individual Strength (CIS subscale fatigue) [19]	x	x	x	x
Physical Functioning	Child Health Questionnaire (CHQ-CF87 subscale physical functioning) [20]	x	x	x	x
School presence	Last two weeks school presence expressed in attended hours/obliged hours * 100% [3]	x	x	x	x
Secondary outcome parameters					
Self rated improvement	short questionnaire consisting of 3 items [3]		x	x	x
Possible patient's predictors of treatment outcome					
Depression score	Child Depression Inventory (CDI) [21,22]	x			
Anxiety score	Spielberger State-Trait Anxiety Inventory for Children, STAIC [23,24]	x			
Somatisation score	Children's Somatisation Inventory (CSI) [25,26]	x			
Physical activity	Actometer and Self-observation list daily functioning [27,28]	x	x	x	
Self-efficacy	Self Efficacy Scale-28 [2]	x			
Perceptions of parental rearing behaviours	EMBU-A [29]	x			
Possible parental predictors of treatment outcome					
Fatigue severity	Checklist Individual Strength (CIS subscale fatigue) [19]	x			
Psychological distress	Symptom Checklist (SCL-90) [30,31]	x			
Focussing on bodily symptoms	subscale private body consciousness of the Body Consciousness Scale [32,33]	x			
Perceptions of rearing behaviours	EMBU-P [34]	x			
Causal attributions	CAL [19]	x			

TABLE 2 Outcome measures, predictors of outcome and instrumentation

self-rated improvement, measured using a short questionnaire consisting of 4 items as assessed in prior intervention studies in adolescents with CFS[3] : patients indicate whether they have completely recovered, feel much better, have the same complaints of have become worse compared with the previous measurement.

Outcome measures will be obtained at the UMCU at the start of the study period (T0), after the intervention 6 months later (T1) and after 6 months follow-up (T2). For those adolescents primarily allocated to usual care who will start with FITNET at T1 - in case of no recovery - there will be an extra follow-up moment after 12 months (T3), see figure 1.

At the first measurements (T0) demographic data and the following predictors of response to treatment and measures of processes of change will be obtained by the primary investigator (SN) both for adolescent and parent(s) (see table 2). Possible predictors of response to treatment in adolescents are: (a) Depression score (validated Dutch translation of the Child Depression Inventory, CDI),[21,22] (b) Anxiety (Dutch translation of the Spielberger State-Trait Anxiety Inventory for Children, STAIC),[23,24] (c) Number and severity of other somatic symptoms measured by a validated Dutch translation of the Children's Somatisation Inventory (CSI),[25,26] (d) Physical performance as measured with the actometer. This is a motion-sensing device worn at the ankle that registers and quantifies physical activity. The actometer is worn day and night during a period of twelve consecutive days.[27] During the same days patients rate fatigue, pain and activity levels on a prescheduled diary four times daily on a scale of 0 (not at all) to 4 (very much). Daily registration of hours being at school is registered as well. The psychometric qualities are good,[28] (e) Self-efficacy (Self Efficacy Scale- 28),[2] (f) Perceptions of parental rearing behaviours (the adolescent version of the Egna Minnen Beträffende Uppfostran, EMBU-A).[29]

Possible parental predictors of response to treatment are: (a) Parental fatigue (Checklist Individual Strength- 20),[19] (b) Parental psychological distress measured by the Symptom Checklist (SCL-90),[30,31] (c) Parental focussing on bodily symptoms by the subscale private body consciousness of the Body Consciousness Scale,[32,33] (d) EMBU-P, the parental version of the Egna Minnen Beträffende Uppfostran,[34] (e) parental causal attributions to the origin of CFS (Causal Attribution List, CAL).[19,28]

Finally, the patients and parent(s) treated with FITNET (including the drop-outs) will be interviewed (responsive evaluation) about their experiences with the FITNET intervention. The interviews are semi-structured, with open questions guided by a topic list (10 point scale, questionnaire especially developed for this study). Different aspects of this web-based programme will be evaluated: text, lay-out, feedback by the therapist, scheduling of modules, technical experience, etc.

Adverse events

The delivery of CBT to adolescents and adults is considered safe. All adverse events reported spontaneously by the participants or observed by the therapists will be recorded. All adverse events will be followed until they have aborted, or until a stable situation has been reached.

Statistical Analysis

One-hundred-forty newly diagnosed CFS patients will be included in two years. The data will be analysed on an intention to treat basis. Prognostically important baseline characteristics will be tabulated by treatment modality in order to evaluate success of randomisation. The main efficacy analysis will pertain to the data obtained after a 6 months FITNET or usual care condition. Differences between treatment groups concerning the primary outcome measures will be expressed as relative risks and 95% confidence intervals or as central estimators and variance measures where appropriate. In case of baseline differences in prognosis between groups, treatment effects in primary outcome will additionally be adjusted for these differences using logistic regression for binary outcome data and linear regression for continuous outcome measures. At 12 months follow-up after randomization, a repeated measurement of the primary outcome measures will be undertaken as well as an evaluation of participants' experiences with the FITNET intervention. The latter measurements will have a descriptive nature.

Concerning the predictors of outcome, the study will be merely exploratory because statistical power is not calculated for subgroup analyses. To that end, linear regression analysis will be used with primary continuous outcome measures as dependent variables and interaction terms of putative response predictors and treatment modality as independent variables. Separate analyses will be run for predictors in adolescents and predictors in parents respectively.

Power

We estimate that under care as usual the estimated average percentages of school absence, our primary endpoint, at the end of follow-up, will be 40%. Given the efficacy of face to face CBT in adolescence[3] we consider a reduction of school absence of 15% in the e- intervention group to be realistic and highly relevant. In order to statistically detect such a reduction, given a 2 sided-alpha of 0.05 and with 90% power, we will need to allocate 60 patients to each group. In order to accommodate a small anticipated percentage of non-participation we will include 140 diagnosed patients.

DISCUSSION

To the best of our knowledge, the FITNET study will be the first randomized clinical trial which evaluates the effect of web-based treatment versus usual care in adolescents with CFS.

This study has several strengths. Firstly, the FITNET treatment is based on a theoretical model of a proven effective face-to-face CBT for adolescents[3] and will be compared with usual care in a randomized design. This will enable to determine the additional value of FITNET in the current therapeutical spectrum. Secondly, FITNET involves parents in the treatment of adolescent CFS. Earlier studies from Chalder et al showed the importance of family-focused CBT to achieve treatment success in adolescents.[4,35] Furthermore, the advantage of making treatment available at any time by internet is considerable. Online treatment can reduce face-to-face treatment barriers (i.e., inconvenience of scheduling appointments, missing school/work, travelling to and from a clinician's office),[36,37] increase adherence[38] and reduce treatment time and costs.[37] We hope that a web-based treatment will increase the therapeutic accessibility. A limitation of the study is that the design is not appropriate to compare the efficacy of web-based CBT with face-to-face CBT. That would have asked for a non-inferiority design with comparison of the two interventions.

In conclusion, the FITNET study will provide greater insight on evidence-based treatment options for adolescents with CFS. If web-based CBT is more effective than usual care, this web-based program would greatly improve the prognosis of the adolescents with CBT.

APPENDIX

Overview of FITNET web-based CBT treatment for adolescents with CFS

Psycho-educational part

- What is CFS?
- CFS in the Netherlands
- CFS in my family
- Causes of CFS
- CFS, anxiety, depression and other illnesses
- How is the diagnosis confirmed?
- What is the treatment for CFS?
- Talking about CFS/How do I explain what CFS is?
- Prognosis

Cognitive Behavioural Treatment Modules

1. To introduce myself
2. How does this treatment work?
3. Assessing my present possibilities
4. My parents
5. My goals
6. My sleep routine
7. My thoughts
8. Changing my attention to fatigue
9. Step up my physical activities *(passive patients)*
10. Balance between activity and rest *(relative active patients)*
11. Step up my physical activities *(relative active patients)*
12. Recognizable problems with the treatment
13. Step up my mental activities
14. My schedule for school
15. My social activities
16. To reach goals
17. My schedule for work
18. To have a night out
19. Do I still see myself as a patient with CFS?
20. My evaluation
21. Follow-up

FITNET is derived from the protocol for CBT that was developed on the basis of a model of perpetuating factors of CFS.[2] It has been tested in several studies[3,17,39] and is aimed at changing fatigue related cognitions and a gradual increase of activities.

Typically, treatment involves (a) formulation of treatment goals, (b) establishing a sleep routine, (c) encouraging the participant to achieve a balance between activity and rest, (d) gradually increasing activities including home, social and school life, (e) addressing cognitions about fatigue, (f) gaining independence from surroundings and parents, (g) reducing the focus on fatigue, and (h) paying attention to relapse prevention.

Addressing physical activity patterns is important in CBT for adolescent CFS. The CBT modules are adapted for two levels of physical activity: relative active and passive, based on the existing protocols.[3,16,17] An actometer, a motion sensing device that can quantify physical activity, will be used to assess the activity pattern.[27,32] Adolescents with a *relatively high physical activity pattern* alternate between periods of activity and periods of rest.[16] For these patients the therapy focuses on learning to recognise and accept their current state of fatigue and impairment. Then they learn to distribute their activities more evenly. After this, the patient will start to build up activity levels. In contrast, patients with a *low physical activity pattern* spend most time lying down and go out infrequently. Most do not attend school at all. For them, the treatment program starts with a systematic build up of activity as soon as possible, while addressing and challenging their beliefs that activity would aggravate symptoms.

Modules 1, 2 and 4 introduce CBT and explain the role of the therapists, and the context of the family. A rationale based on a multi-factorial model of CFS that distinguished predisposing, precipitating and maintaining factors is presented. Parents will be actively involved in supporting their child and parents' beliefs and behaviours regarding the condition of their child will be explored and addressed. The aims of therapy take into account the specific developmental tasks of adolescents. In children younger than 15 years, parents often act as a coach; for older participants, parents have to step back and encourage their child to take responsibility for the treatment.

Modules 3 and 5 are focused on treatment goals. Return to full time education is always a goal of treatment, and a plan for returning to school will be discussed early with everyone involved.

Modules 6 to 19 focus on cognitive behavioural strategies and include instructions and exercises on how to identify, challenge and change cognitive processes that contribute to CFS. There are two treatment protocols, depending on the pattern of

physical activity of the patient.[16]

Module 20 evaluates treatment success.

Module 21 is a relapse preventing module focusing on maintaining gains and staying healthy.

Diaries

Sleep diary, Helpful Thoughts, My goals, Activity schedule, School schedule.

REFERENCES

1. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A: The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994, 121(12):953-959.

2. Vercoulen JH, Swanink CM, Galama JM, Fennis JF, Jongen PJ, Hommes OR, van der Meer JW, Bleijenberg G: The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: development of a model. J Psychosom Res 1998, 45(6):507-517.

3. Stulemeijer M, de Jong LW, Fiselier TJ, Hoogveld SW, Bleijenberg G: Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. BMJ 2005, 330(7481):14.

4. Chalder T, Tong J, Deary V: Family cognitive behaviour therapy for chronic fatigue syndrome: an uncontrolled study. Arch Dis Child 2002, 86(2):95-97.

5. ter Wolbeek M, van Doornen LJ, Kavelaars A, Heijnen CJ: Severe fatigue in adolescents: a common phenomenon? Pediatrics 2006, 117(6): e1078-e1086.

6. Bell DS, Jordan K, Robinson M: Thirteen-year follow-up of children and adolescents with chronic fatigue syndrome. Pediatrics 2001, 107(5):994-998.

7. Tummers M, Knoop H, Bleijenberg G: Effectiveness of stepped care for chronic fatigue syndrome: a randomized noninferiority trial. J Consult Clin Psychol 2010, 78(5):724-731.

8. Emmelkamp PM: Technological innovations in clinical assessment and psychotherapy. Psychother Psychosom 2005, 74(6):336-343.

9. Cuijpers P, van SA, Andersson G: Internet-administered cognitive behavior therapy for health problems: a systematic review. J Behav Med 2008, 31(2):169-177.

10. Williamson DA, Martin PD, White MA, Newton R, Walden H, York-Crowe E, Alfonso A, Gordon S, Ryan D: Efficacy of an internet-based behavioral weight loss program for overweight adolescent African-American girls. Eat Weight Disord 2005, 10(3):193-203.

11. O'Kearney R, Gibson M, Christensen H, Griffiths KM: Effects of a

cognitive- behavioural internet program on depression, vulnerability to depression and stigma in adolescent males: a school-based controlled trial. Cogn Behav Ther 2006, 35(1):43-54.

12. Spence SH, Holmes JM, March S, Lipp OV: The feasibility and outcome of clinic plus internet delivery of cognitive-behavior therapy for childhood anxiety. J Consult Clin Psychol 2006, 74(3):614-621.

13. Trautmann E, Kroner-Herwig B: A randomized controlled trial of Internet- based self-help training for recurrent headache in childhood and adolescence. Behav Res Ther 2009.

14. Patten CA, Croghan IT, Meis TM, Decker PA, Pingree S, Colligan RC, Dornelas EA, Offord KP, Boberg EW, Baumberger RK, Hurt RD, Gustafson DH: Randomized clinical trial of an Internet-based versus brief office intervention for adolescent smoking cessation. Patient Educ Couns 2006, 64(1-3):249-258.

15. Cuijpers P, Marks IM, van Straten A, Cavanagh K, Gega L, Andersson G: Computer-aided psychotherapy for anxiety disorders: a meta-analytic review. Cogn Behav Ther 2009, 38(2):66-82.

16. Bleijenberg G, Prins J, Bazelmans E: Cognitive behavioral therapies. In Handbook of Chronic Fatigue Syndrome. Edited by: Jason LA, Fennel PA, Taylor RR. Wiley 2003:493-526.

17. Prins JB, Bleijenberg G, Bazelmans E, Elving LD, de Boo TM, Severens JL, van der Wilt GJ, Spinhoven P, van der Meer JW: Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. Lancet 2001, 357(9259):841-847.

18. Hira Sing RA, Rodrigues PR: [The Dutch Pediatric Surveillance System; a quality focused instrument for prevention and research]. Ned Tijdschr Geneeskd 2002, 146(50):2409-2414.

19. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G: Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994, 38(5):383-392.

20. Raat H, Landgraf JM, Bonsel GJ, Gemke RJ, Essink-Bot ML: Reliability and validity of the child health questionnaire-child form (CHQ-CF87) in a Dutch adolescent population. Qual Life Res 2002, 11(6):575-581.

21. Kovacs M: The Children's Depression, Inventory (CDI). Psychopharmacol Bull 1985, 21(4):995-998.

22. Timbremont B, Braet C: Psychometrische evaluatie van de Nederlandstalige Children's Depression Inventory. Gedragstherapie 2001, 34(3):229-242.

23. Papay JP, Spielberger CD: Assessment of anxiety and achievement in kindergarten and first- and second-grade children. J Abnorm Child Psychol 1986, 14(2):279-286.

24. Houtman IL, Bakker FC: The anxiety thermometer: a validation study. J Pers Assess 1989, 53(3):575-582.

25. Meesters C, Muris P, Ghys A, Reumerman T, Rooijmans M: The Children's Somatization Inventory: further evidence for its reliability and validity in a pediatric and a community sample of Dutch children and adolescents. J Pediatr Psychol 2003, 28(6):413-422.

26. van de Putte EM, Engelbert RH, Kuis W, Sinnema G, Kimpen JL, Uiterwaal CS: Chronic fatigue syndrome and health control in adolescents and parents. Arch Dis Child 2005, 90(10):1020-1024.

27. van der Werf SP, Prins JB, Vercoulen JH, van der Meer JW, Bleijenberg G: Identifying physical activity patterns in chronic fatigue syndrome using actigraphic assessment. J Psychosom Res 2000, 49(5):373-379.

28. Vercoulen JH, Hommes OR, Swanink CM, Jongen PJ, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G: The measurement of fatigue in patients with multiple sclerosis. A multidimensional comparison with patients with chronic fatigue syndrome and healthy subjects. Arch Neurol 1996, 53(7):642-649.

29. Gerlsma C, Arrindell WA, Veen van der N, Emmelkamp PM: A parental rearing style questionnaire for use with adolescents: Psychometric evaluation of the EMBU-A. Personality and Individual Differences 1991, 12:1245-1253.

30. van de Putte EM, van Doornen LJ, Engelbert RH, Kuis W, Kimpen JL, Uiterwaal CS: Mirrored symptoms in mother and child with chronic fatigue syndrome. Pediatrics 2006, 117(6):2074-2079.

31. Derogatis LR: SCL-90-R administration, scoring & procedures. Manual I. For the R(evised) version and other instruments of the psychopathology

rating scale series. Clinical Psychometric Research 1977.

32. Bazelmans E, Bleijenberg G, Voeten MJ, van der Meer JW, Folgering H: Impact of a maximal exercise test on symptoms and activity in chronic fatigue syndrome 2. J Psychosom Res 2005, 59(4):201-208.

33. van der Werf SP, de Vree B, Der Meer JW, Bleijenberg G: The relations among body consciousness, somatic symptom report, and information processing speed in chronic fatigue syndrome. Neuropsychiatry Neuropsychol Behav Neurol 2002, 15(1):2-9.

34. Arrindell WA, Perris C, Van der EJ, Gaszner P, Eisemann M, Perris H: Cross- national generalizability of dimensions of perceived parental rearing practices: Hungary and The Netherlands; a correction and repetition with healthy adolescents. Psychol Rep 1989, 65(3 Pt 2):1079-1088.

35. Chalder T, Deary V, Husain K, Walwyn R: Family-focused cognitive behaviour therapy versus psycho-education for chronic fatigue syndrome in 11- to 18-year-olds: a randomized controlled treatment trial. Psychol Med 2010, 40(8):1269-1279.

36. Ritterband LM, Thorndike FP, Cox DJ, Kovatchev BP, Gonder-Frederick LA: A behavior change model for internet interventions. Ann Behav Med 2009, 38(1):18-27.

37. Tate DF, Finkelstein EA, Khavjou O, Gustafson A: Cost effectiveness of internet interventions: review and recommendations. Ann Behav Med 2009, 38(1):40-45.

38. Celio AA, Winzelberg AJ, Wilfley DE, Eppstein-Herald D, Springer EA, Dev P, Taylor CB: Reducing risk factors for eating disorders: comparison of an Internet- and a classroom-delivered psychoeducational program. J Consult Clin Psychol 2000, 68(4):650-657.

39. Knoop H, Bleijenberg G, Gielissen MF, van der Meer JW, White PD: Is a full recovery possible after cognitive behavioural therapy for chronic fatigue syndrome? Psychother Psychosom 2007, 76(3):171-176.

4
Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET)

A randomised controlled trial

Sanne L. Nijhof, Gijs Bleijenberg, Cuno S.P.M. Uiterwaal,
Jan L.L. Kimpen and Elise M. van de Putte

Lancet 2012; 379(9824): 1412-8

ABSTRACT

Background

Chronic fatigue syndrome is characterised by persistent fatigue and severe disability. Cognitive behavioural therapy seems to be a promising treatment, but its availability is restricted. We developed Fatigue In Teenagers on the interNET (FITNET), the first dedicated internet-based therapeutic program for adolescents with this disorder, and compared its effectiveness with that of usual care.

Methods

Adolescents aged 12–18 years with chronic fatigue syndrome were assigned to FITNET or usual care in a 1:1 ratio at one tertiary treatment centre in the Netherlands by use of a computer-generated blocked randomisation allocation schedule. The study was open label. Primary outcomes were school attendance, fatigue severity, and physical functioning, and were assessed at 6 months with computerised questionnaires. Analysis was by intention to treat. Thereafter, all patients were offered FITNET if needed. This trial is registered, number ISRCTN59878666.

Findings

68 of 135 adolescents were assigned to FITNET and 67 to usual care, and 67 and 64, respectively, were analysed. FITNET was significantly more effective than was usual care for all dichotomised primary outcomes at 6 months—full school attendance (50 [75%] vs 10 [16%], relative risk 4.8, 95% CI 2.7–8.9; p<0.0001), absence of severe fatigue (57 [85%] vs 17 [27%], 3.2, 2.1–4.9; p<0.0001), and normal physical functioning (52 [78%] vs 13 [20%], 3.8, 2.3–6.3; p<0.0001). No serious adverse events were reported.

Interpretation

FITNET offers a readily accessible and highly effective treatment for adolescents with chronic fatigue syndrome. The results of this study justify implementation on a broader scale.

Funding

Netherlands Organisation for Health Research and Development.

INTRODUCTION

Chronic fatigue syndrome, also known as myalgic encephalomyelitis or myalgic encephalopathy, is characterised by disabling persistent (>6 months) or relapsing severe unexplained fatigue that is not the result of ongoing exertion and cannot be alleviated by rest. This fatigue is accompanied by other symptoms such as muscle pain and difficulty concentrating.[1] In adolescents, chronic fatigue syndrome often has a protracted course that can lead to much absence from school and long term detrimental effects on their academic and social development.[2–5]

The prevalence of chronic fatigue syndrome has been estimated to be between 0.11% and 1.29% in Dutch, British, and US adolescent populations, with a female-to-male ratio from 2:1 to 5:1.[6–11] Most recent estimations of incidence and prevalence based on diagnosis by the physician are lower than those based on population surveys.[6] The lack of treatment options might contribute to physicians being reticent about diagnosing chronic fatigue syndrome.

The results of a 13 years' followup study showed that most adolescents had persistent mild to moderate symptoms and disruption of school attendance.[11] Although untreated chronic fatigue syndrome has a better prognosis in adolescents than in adults, the risk of disruption to social development and education in adolescents requires prompt diagnosis of the syndrome and an effective and accessible treatment.[11–13]

The cause of chronic fatigue syndrome is not known, but research has shown that differentiation of triggering, sustaining, and precipitating factors at the biological and psychosocial levels, especially for treatment, would be useful.[12,14] Patients' cognition of perpetuating factors is used in cognitive behavioural therapy, which seems promising in adolescents. Until now, cognitive behavioural therapy for adolescents with chronic fatigue syndrome has only been compared with patients being on a waiting list or receiving psychoeducation, but not treatment as usual, and resulted in a clinically significant improvement of 60–70% directly after treatment.[12,15] The biggest challenge associated with cognitive behavioural therapy is its restricted availability due to the requirement for specialised skills,[12,15] leading to unequal access for adolescent patients. Therefore, alternative ways to enhance the availability of cognitive behavioural therapy are of paramount importance.

Internet-based cognitive behavioural therapy might improve access to treatment.[16,17] It was shown to be effective in patients with illnesses other than chronic fatigue syndrome, but mostly in adults. For adolescents, it has been developed for disorders such as depression,[18] anxiety,[19] and headache,[20] and for smoking cessation,[21] but not

for chronic fatigue syndrome.

We developed Fatigue In Teenagers on the interNET (FITNET), a comprehensive internet-based application based on existing protocols and a theoretical model of effective face-to-face cognitive behavioural therapy for adolescents,[12,22,23] specifically for those with chronic fatigue syndrome and their parents. In this program, a skilled therapist would provide support through regular e-mail consultations (e-consultations). We compared the short term effectiveness of the FITNET program with usual care in reduction of fatigue, school absence, and physical dysfunction in adolescents with chronic fatigue syndrome.

METHODS

Study population

A detailed description of the study protocol and FITNET program has been reported elsewhere.[24] This trial was undertaken at the Wilhelmina Children's Hospital, University Medical Centre Utrecht (UMCU), Utrecht, and the Expert Centre for Chronic Fatigue (ECCF, treatment coordinating centre), Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands. All children were referred to, examined, and randomly assigned at the UMCU.

To achieve nationwide referral, all Dutch paediatricians were personally informed about the FITNET trial and referral options.[24] All adolescents with fatigue who were referred to the outpatient clinic of the Department of Paediatrics, UMCU, and the outpatient clinic of ECCF were assessed in the UMCU by a paediatrician specialised in chronic fatigue syndrome. They under went a uniform diagnostic workup, consisting of a detailed history and physical and laboratory examinations. Once the diagnosis of chronic fatigue syndrome was established, study eligibility was assessed with computerised questionnaires. Patients were eligible if they were aged 12–18 years, could read and write Dutch, had access to a computer with internet connection, and met the criteria for chronic fatigue syndrome as defined by the Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA.[1] We chose the CDC criteria because these are the most used in the Netherlands by paediatricians.[6] Severe fatigue was defined as a score of 40 or more on the fatigue severity subscale of the checklist individual strength-20 (CIS-20),[12,25] and functional impairment as a score of 85 or less on the child health questionnaire (CHQ-CF87) physical functioning subscale,[26] or a school attendance of 85% or less.[24] Exclusion criteria were primary depression, anxiety disorder, or suicidal risk, as assessed with computerised self-reported questionnaires (Dutch translation of the child depression inventory[27] and statetrait anxiety inventory for children[28]). If scores were abnormal,[24] a skilled psychologist undertook a clinical assessment to exclude primary depression or anxiety.

The study protocol was approved by the ethics boards of both institutions. Oral and written consent was obtained from patients who were willing to participate and their parents (one or both), according to the Declaration of Helsinki.

Randomisation and masking

The random allocation sequence was computer-generated with a block size of six by the data management section of the Julius Centre for Health Sciences and Primary

Care, Utrecht, Netherlands. Participants were randomly assigned in a 1:1 ratio. The study was open label and the primary investigator, who was not the treating physician, informed the participants about their allocated treatment. Data for primary outcomes were assessed by use of a computer.

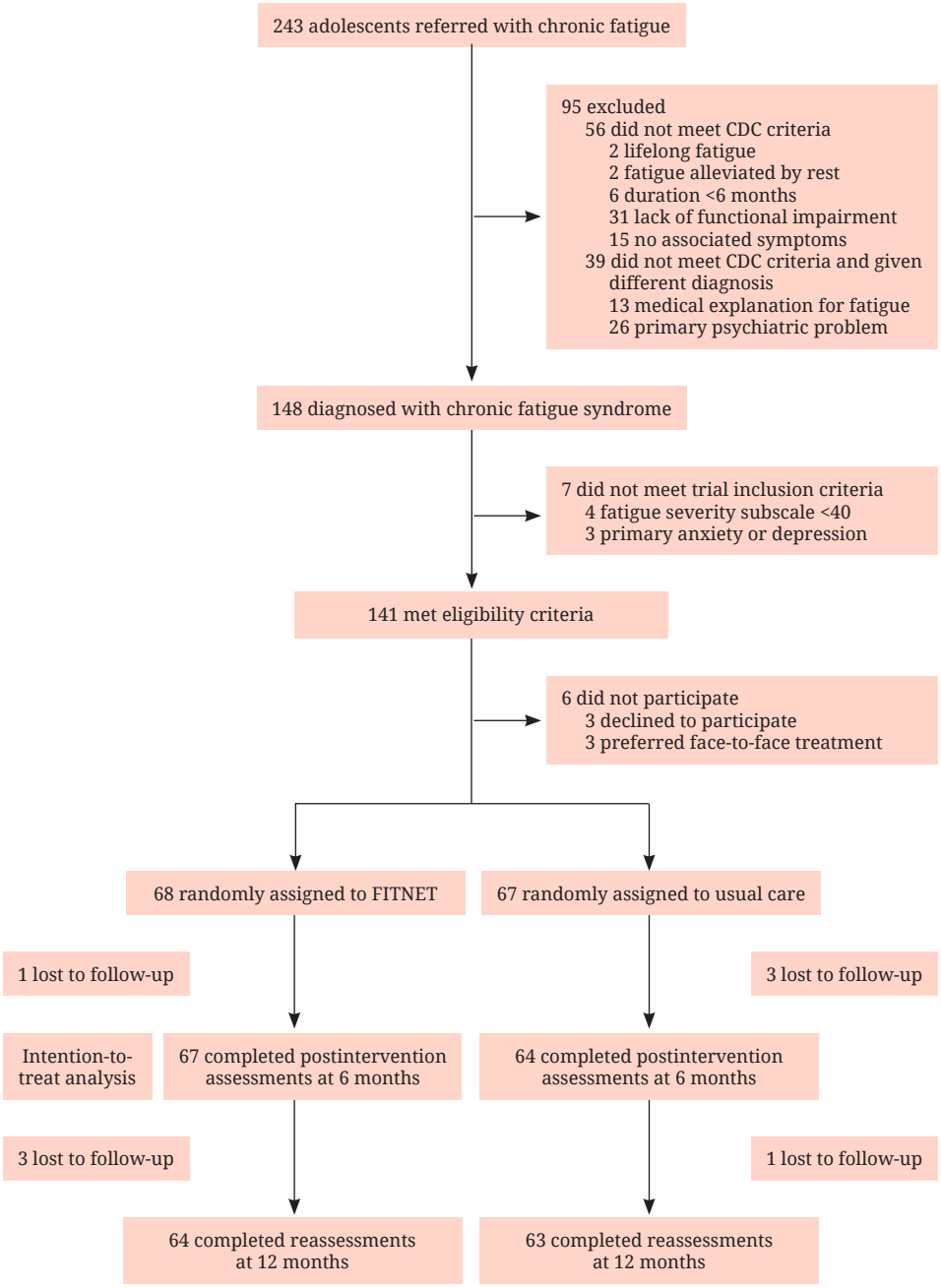
Interventions

The FITNET program was run on a dedicated hospital network (in Dutch). The portal layout for the program was specifically designed for adolescents. Patients' data and emails were encrypted and securely stored on the UMCU mainframes to guarantee privacy and confidentiality.

The FITNET program consisted of two sections. The psycho-educational section could be accessed after the adolescents received their login codes. The cognitive behavioural therapy section consisted of 21 interactive modules,[22,24] accessible after activation by the therapist. The patients received support from trained cognitive behavioural psychotherapists from the ECCF, solely through e-consults. At the start of the trial, two therapists had several years of experience as behavioural therapists (5 years and 10 years), and three were in the first year of their practical training as behavioural therapists. All five were given equal caseloads of patients. The FITNET therapists were not involved in usual care.

Patients were able to log in and compose and send emails at any time. According to an individually tailored treatment, therapists responded to the e-consults on a set day once a week and thereafter once every 2 weeks. The patient would receive an immediate response to an emergency email. Additionally, for emergency situations, telephone contact details were available to the patients.

Parents followed a parallel program, and had the same frequency of email contacts wherein results so far were discussed and new assignments were given. The parents' portal consisted of the module's content, psycho-education, and an e-consult application. The patients' portal was more detailed than was the parents' with diaries, questionnaires, and a review function of all passed modules. Patients and parents had separate accounts with unique usernames and passwords, and were not able to see each other's e-consult responses, ensuring confidentiality in communication with the therapist. The parents of patients younger than 15 years were instructed to coach their children, whereas those of older patients were asked to encourage their children to take responsibility for their treatment. Return to fulltime education was the primary aim of treatment and was discussed early in therapy. Patients assigned to FITNET agreed not to undergo any further medical examinations or to receive other treatments for fatigue while under going treatment.



CDC=Centers for Disease Control and Prevention. FITNET=Fatigue In Teenagers on the interNET.

FIGURE 1 Trial profile

The FITNET therapist and school mentor had at least one communication about school attendance and the school's effort to encourage treatment compliance. The school mentor acted as a coach, adviser, or tutor when needed. School mentors were sent a standard letter at the commencement of treatment asking them for their cooperation and consideration.

The patients in the control group were given usual care, which included individual or groupbased rehabilitation programmes, cognitive behavioural therapy face-to-face, or graded exercise treatment, or both, by a physical therapist. Records were kept of all the care given. Adolescents assigned to usual care were given the opportunity to attend FITNET after 6 months.

Outcomes

The primary outcomes were school attendance, fatigue, and physical functioning, and were assessed at 6 months and then reassessed at 12 months. School attendance was measured as the proportion of classes attended, expressed as a percentage of the normal school schedule. It was recorded daily on a 24 h timetable of the selfobservation list 12 days before testing.[29] On the day of testing, the past 2 weeks of school attendance were validated with a general questionnaire and checked with the parents. During FITNET treatment, the therapist and school mentor were in contact about the school plan and attendance when needed. Fatigue was measured with the subscale fatigue severity of the CIS20 (range 8–56). The questionnaire has good reliability and discriminative validity with good internal consistency (Cronbach's α=0.93).[12,25] Physical functioning was measured with the subscale physical functioning of the CHQ-CF87 (0–100%). This assessment method is reported to be reliable and has been validated with a good internal consistency (Cronbach's α=0.86).[26]

The secondary outcome was selfrated improvement, for which patients could indicate whether they were completely recovered, felt much better, had the same complaints, or had become worse than with the previous measurement.[12,29] It was measured at 6 months and then at the 12 months' reassessment.

Recovery

Recovery was defined post hoc, in relation to healthy peers (±2 SD), as having a fatigue severity score of less than 40,[6,12,30] physical functioning score of 85% or more,[6,26] and school absence of 10% or less in the past 2 weeks,[6] all assessed at 6 months. Additionally, patients were only judged to be recovered if they had rated themselves as being completely recovered or as feeling much better according to the secondary outcome questionnaire.[12]

Semistructured interview

All patients treated with FITNET and their parents (one or both) were interviewed about their experiences and satisfaction with the intervention. The interviews were semistructured, with open questions guided by a topic list (scale of 10 points, questionnaire especially developed for this study). Different aspects of this internet-based program were assessed to evaluate and improve the FITNET program, such as text, layout, feedback by the therapist, scheduling of modules, and technical experience.

Statistical analysis

With an estimated school absence after usual care of 40%, sample size calculations showed that 60 patients would have to be allocated to each group to detect an increase in school attendance of 15% in the FITNET group, with a two-sided α of 0.05 and 90% power. To compensate for a small anticipated proportion of patients and their parents not participating, we aimed to include 140 patients diagnosed with chronic fatigue syndrome. No interim analysis of the data was planned or undertaken. Data were analysed on an intention-to-treat basis.

The analysis of effectiveness was done with data obtained after 6 months of treatment with FITNET therapy or usual care. Effects on main outcomes were expressed as relative risks and mean group differences, each with 95% CIs. Differences between groups in the amount of change in the primary outcome variables were calculated with independent samples Student's t test. Additionally, linear regression was used to adjust for possible confounding factors, like age, sex, and baseline scores of anxiety, depression, and primary outcomes. All analyses were done with SPSS (version 16.0).

After completion of the randomly assigned treatment at 6 months, the patients who had not recovered were offered a crossover to either FITNET or usual care. All randomly assigned patients were invited for reassessments of primary outcomes at 12 months. Data for these reassess ments are described without statistical analysis. This trial is registered, number ISRCTN59878666.

Role of the funding source

The sponsor of the study had no role in study design, data gathering, data analysis, and data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

148 adolescents who were diagnosed with chronic fatigue syndrome were screened for eligibility between January, 2008, and February, 2010. 135 (96%) of 141 eligible patients were enrolled (figure). The baseline charac teristics of the enrolled adolescents (n=135) and those who did not want to participate (n=6) did not differ (data not shown). No patients were excluded after random isation. Table 1 shows the baseline charac-

	FITNET (n=68)	Usual care (n=67)
Age at entry (years)	15.9 (1.3)	15.8 (1.3)
Girls	54 (79%)	57 (85%)
Education level*		
Low	16 (24%)	25 (37%)
Medium	24 (35%)	21 (31%)
High	28 (41%)	21 (31%)
Duration of symptoms at entry (months)	16.0 (6–84)	19.0 (6–108)
Onset of disease		
Acute	11 (16%)	7 (10%)
Gradual	38 (56%)	43 (64%)
After infection	19 (28%)	17 (25%)
School attendance		
Continuous	39.5% (29.4)	45.1% (32.6)
≥85%	4 (6%)	9 (13%)
<85%	64 (94%)	58 (87%)
Fatigue severity (CIS-20, range 8–56)	51.2 (4.4)	51.6 (4.6)
Physical functioning (CHQ-CF87, range 0–100)	60.7 (14.5)	56.8 (20.9)
Somatic complaints (CSI, range 0–132)	33.3 (13.6)	34.7 (12.9)
Depression score (CDI, range 0–54)	11.6 (5.2)	11.0 (5.2)
≥16	14 (21%)	9 (13%)
Anxiety score (STAIC, range 20–60)	32.7 (8.8)	32.3 (8.0)
≥44	9 (13%)	6 (9%)

Data are number (%), mean (SD), or median (range). FITNET=Fatigue In Teenagers on the interNET. CIS-20=checklist individual strength-20. CHQ-CF87=child health questionnaire. CSI=children's somatisation inventory. CDI=children's depression inventory. STAIC=state-trait anxiety inventory for children. *After 6 years of general primary school, at the age of 12 years, students enter low (4 years), medium (5 years), or high (6 years) secondary education.

TABLE 1: Baseline characteristics of the study population in FITNET and usual care groups

	FITNET (n=67)	Usual care (n=64)	Mean difference (95% CI)	p-value
School attendance	84.3% (29.5)	51.7% (34.1)	32.6% (21.5 to 43.6)	<0.0001
Fatigue severity (CIS-20, range 8–56)	24.0 (13.4)	42.3 (13.1)	–18.3 (–22.9 to –13.7)	<0.0001
Physical functioning (CHQ-CF87, range 0–100)	88.5 (13.8)	70.1 (17.6)	18.4 (12.9 to 23.9)	<0.0001

Data are mean (SD), unless otherwise indicated. FITNET=Fatigue In Teenagers on the interNET. CIS-20=checklist individual strength-20. CHQ-CF87=child health questionnaire.

TABLE 2: Effect of treatment at 6 months on fatigue severity, functional impairment, and school attendance in FITNET and usual care groups

teristics of both groups. All patients started the treatment they were assigned to. The baseline characteristics of four of 135 patients who were lost to follow-up did not differ from those of patients who adhered to the study schedule. Of the patients lost to follow-up (telephone interview), two had reported that they had recovered and no longer wanted to be reminded of chronic fatigue syndrome (one assigned to FITNET and one to usual care), and two who were not recovered wanted to continue the treatment but felt no need to come back for the postintervention assessment (both assigned to usual care).

In the usual care group, 38 (57%) of 67 participants received more than one treatment. Usual care involved cognitive behavioural therapy (44 [66%]), rehabilitation treatment (inpatient or outpatient treatment, individual or group programme; 15 [22%]), physical treatment (mostly graded exercise therapy; 33 [49%]), or alternative treatment (16 [24%]). Only seven (10%) adolescents did not receive any treatment because treatment was not available within an acceptable travelling distance.

Increase in school attendance was significantly higher in the FITNET group than in the usual care group, and patients in the FITNET group were significantly less fatigued and functionally impaired (table 2). A significantly greater proportion of adolescents in the FITNET group reported improvement—ie, answered “yes” to the statement “I have completely recovered” or “I feel much better but still experience some symptoms” and more achieved recovery than did those in the usual care group (table 3). The number needed to treat to achieve recovery at both primary and secondary outcomes was 1.8 (table 3).

Additional analyses with adjustments for possible confounding factors, like age, sex, baseline scores for anxiety, depression, and primary outcomes, had no effects on the results (data not shown). Analysis at other cutoff points for recovery (–1 SD) did not

	FITNET (n=67)	Usual care (n=64)	Relative risk (95% CI)	Number needed to treat	p-value
Primary outcomes					
Full school attendance*	50 (75%)	10 (16%)	4.8 (2.7–8.9)	1.7	<0.0001
Fatigue severity (CIS-20)**	57 (85%)	17 (27%)	3.2 (2.1–4.9)	1.7	<0.0001
Physical functioning (CHQ-CF87)***	52 (78%)	13 (20%)	3.8 (2.3–6.3)	1.8	<0.0001
Secondary outcome					
Self-rated improvements ****	52 (78%)	17 (27%)	2.9 (1.9–4.5)	2.0	<0.0001
Combined					
Primary outcomes	44 (66%)	5 (8%)	8.4 (3.6–19.8)	1.7	<0.0001
Primary and secondary outcomes	42 (63%)	5 (8%)	8.0 (3.4–19.0)	1.8	<0.0001

Data are number (%), unless otherwise indicated. FITNET=Fatigue In Teenagers on the interNET. CIS-20=checklist individual strength-20. CHQ-CF87=child health questionnaire. *School absence of 10% or less. **Cutoff score of less than 40. ***Cutoff score of 85% or more. ****Answer "yes" to statement "I have completely recovered" or "I feel much better but still experience some symptoms".

TABLE 3: Recovery at 6 months in FITNET and usual care groups

change our findings with respect to treatment effects (appendix).

No serious adverse events were reported. Of 68 adolescents assigned to the FITNET program, only four (6%) stopped treatment early, according to both patient and therapist. Reasons for stopping were that the internet was too impersonal (n=1), communication difficulties (n=1), and not enough selfdiscipline to log in frequently to the FITNET program (n=2). These four patients completed the post treatment assessment at 6 months. Most patients and parents were satisfied with FITNET treatment; details of the experience and satisfaction with the FITNET treatment will be reported elsewhere.

The FITNET treatment lasted a mean of 26.2 weeks (SD 7.3). The mean number of times patients and parents logged in was 255.0; to maintain confidentiality, we could not differentiate between users. Treatment progression was monitored by regular econsult contact between thera pists, patients, and parents. The mean number of econsults sent by patients was 66.6 (SD 16.3) and by parents 22.8 (10.3). The mean number of econsults sent by the therapist was 28.7 (10.3) per patient and 19.5 (10.5) per parent. No significant differences were noted in treatment effects between the five FITNET therapists (recovery rates 61.1%, 61.5%, 66.7%, 68.4%, and 70.6%, p=0.917).

During the trial, three patients (one assigned to usual care and two to FITNET) were given new diagnoses - school phobia, personality disorder or gender identity disorder, and posttraumatic stress disorder due to family violence - by the therapist of their allocated group that were given treatment priority. We did not exclude these patients from the analysis because of the intention to treat principle.

	Number*	School attendance	Fatigue severity (CIS-20, range 8–56)	Physical functioning (CHQ-CF87, range 0–100)
FITNET (at 6 months)	64	89.1% (22.2)	26.2 (13.5)	86.7 (18.7)
Recovered	41	96.3% (8.6)	21.0 (10.6)	89.8 (18.6)
Not recovered continued FITNET	12	89.8% (17.6)	31.3 (12.9)	86.7 (14.0)
Not recovered crossed over to usual care	11	59.3% (37.8)	39.8 (13.5)	75.0 (20.3)
Usual care (at 6 months)	63	75.9% (33.9)	29.2 (14.7)	84.4 (16.7)
Recovered	5	99.6% (0.9)	14.4 (6.1)	92.5 (2.6)
Not recovered continued usual care	27	60.6% (36.3)	32.9 (12.5)	83.1 (16.2)
Not recovered crossed over to FITNET	31	85.7% (28.6)	28.4 (16.0)	84.2 (18.3)

Data are mean (SD), unless otherwise indicated. FITNET=Fatigue In Teenagers on the interNET. CIS-20=checklist individual strength-20. CHQ-CF87=child health questionnaire. *Adjusted for loss to follow-up.

TABLE 4: Results of reassessment at 12 months (n=127)

127 (97%) of 131 adolescents completed the reassessment at 12 months. Patients who had recovered after FITNET showed sustainable treatment effects. Mean school attendance improved further (tables 2, 4). 12 patients, who had not recovered at the 6 months' assessment, continued FITNET and improved at 12 months (table 4). 32 patients (including one lost to follow-up) not recovered after 6 months of usual care crossed over to FITNET. Their treatment results at 12 months were similar to the primary FITNET group (table 4).

DISCUSSION

Internet-based cognitive behavioural therapy was much more effective than was usual care, resulting in higher school attendance, diminished severity of fatigue, improved physical functioning, and better selfrated improvement. In patients who recovered with FITNET, treatment success persisted at the 12 months' reassessment. Patients who continued FITNET treatment or switched to FITNET had similar success by 12 months. FITNET is the first randomised controlled trial in which the effectiveness of internet-based treatment for chronic fatigue syndrome was compared with usual care. Also, the cohort of adolescents followed up is the largest described for chronic fatigue syndrome so far (panel).

Some issues need further consideration. We chose a pragmatic study design that enabled us to assess the value of FITNET therapy relative to currently available treatments for chronic fatigue syndrome. Because of the vulnerable age, high risk of disruption to development, and general cognitive behavioural therapy lasting 5–6 months, we thought that all treatments should be assessed after 6 months. This design meant that we could not provide detailed data about the specific interventions in the usual care group because the quality and quantity of cognitive behavioural therapy differed according to local availability and adolescents often combined cognitive behavioural therapy with other treatments such as graded exercise, but it answers the most relevant question of whether FITNET treatment is indeed an effective alternative to the heterogeneous treatments that are available.

Chronic fatigue syndrome was diagnosed or confirmed in a tertiary academic hospital setting. Since referrals were obtained nationwide and from various sources (family doctors and paediatricians),[24] we think that our study population is representative of the adolescent Dutch population with chronic fatigue syndrome. Physicians referring patients seemed to find the diagnosis of chronic fatigue syndrome difficult, judging by the high numbers of other primary diagnoses and patients who did not meet CDC criteria (figure). In our tertiary centre, only three adolescents were given a different diagnosis during treatment. We expect that this number will increase if FITNET treatment is made available to physicians who refer patients without assessment at a specialised tertiary centre.

There is no universal definition of recovery in patients with chronic fatigue syndrome during therapy. We constructed a posthoc definition of recovery based on four components (fatigue, physical functioning, school participation, and selfrated improvement) that we believe are inseparable. Self-rated improvement is particularly

Panel: Research in context

Systematic review

We searched the PubMed and Cochrane databases up to June 29, 2011, for full reports of randomised controlled trials, systematic reviews, and meta-analyses with the search terms "chronic fatigue syndrome", "myalgic encephalomyelitis", or "myalgic encephalopathy"; "adolesc*" or "childr*"; and "treatment", "cognitive behaviour therapy", "exercise", "pacing", or "internet". There were no language restrictions. We excluded trials of adults and education and group interventions. The reports we included in the references are key pieces of evidence. Our search identified two randomised controlled trials.[12,31] Cognitive behavioural therapy for adolescents with chronic fatigue syndrome has only been compared with patients being on a waiting list[12] or receiving psychoeducation,[31] and resulted in a clinically significant improvement of 60–70% directly after treatment. Results of both studies also showed the importance of family-focused cognitive behavioural therapy to treatment success in adolescents. Limitations of these trials were their fairly small sizes and high dropout rates. The biggest practical challenge of cognitive behavioural therapy is its restricted availability because its administration requires specialised therapeutic skills,[12,15] to which there is unequal access for adolescents with chronic fatigue syndrome. Cognitive behavioural therapy has not been compared with treatment as usual in adolescents with chronic fatigue syndrome in controlled studies. No randomised trials of internet interventions or recent reviews of children and adolescents with chronic fatigue syndrome that included discussions of other randomised controlled trials of treatment, in particular cognitive behavioural therapy, were identified.

Interpretation

Very little evidence exists for treatment of children and adolescents with chronic fatigue syndrome. We provide new evidence in this randomised controlled trial (Fatigue In Teenagers on the interNET [FITNET]) that internet-based cognitive behavioural therapy was much more effective than was usual care within a timeframe of 6 months, resulting in higher school attendance, diminished severity of fatigue, improved physical functioning, and better self-rated improvement. In patients recovered with FITNET, treatment success persisted at the reassessment at 12 months. Patients who continued FITNET or switched to FITNET reached similar levels of success at 12 months. The sustainability of FITNET treatment success at 12 months and FITNET results after usual care reassured us of its intrinsic effectiveness. Findings from FITNET allow the following interpretations: cognitive behavioural therapy for adolescents with chronic fatigue syndrome can now be broadly made available as FITNET, and thus remove former accessibility issues and thereby improve the prognosis of chronic fatigue syndrome in adolescents. These findings emphasise the need for proper and rapid diagnosis and of making medical professionals aware of chronic fatigue syndrome in adolescents and the available treatment options.

crucial for recovery since it combines having a normal amount of fatigue and not being disabled, according to the patient's own perception.

This study had several strengths. First, the FITNET program involved parents in their children's treatment. The results of earlier studies have shown the importance of familyfocused cognitive behavioural therapy in the successful treatment of adolescents.[12,15,31] Furthermore, hardly any loss to follow-up occurred, thus reducing the risk of bias. Only 3% of patients were lost to follow-up, which is low compared with previous studies[12,15,31] and other internet-based interventions.[16–21] The high participation rate (96% of eligible adolescents entered the study) is a sign of the low threshold and high acceptance of internet-based health care. A particular strength is that the main outcome (school attendance) was checked and double checked by the investigators, parents, teachers, and therapists.

Internet-based treatment has general advantages: it is available at any time, avoids face-to-face treatment barriers (ie, treatment delay due to poor accessibility, inconvenience of scheduling appointments, missing school or work, travelling to and from a clinician's office),[32,33] and reduces treatment time and costs.[33] This unique cognitive behavioural therapy seems to appeal to modern youth, who grow-up using the internet as their main source of information. Specialised internet-based cognitive behavioural therapy for adolescents with chronic fatigue syndrome was more effective than were the more general approaches applied in usual care, but it is not known which aspect, such as being readily accessible soon after diagnosis, 24 h availability, anonymity, or professional feedback by a trained psychotherapist, is the reason for this increased effectiveness. Our results warrant a proper costbenefit assessment of FITNET, focusing on the factors contributing to treatment success, especially the added value of a psychotherapist. We did not note any significant differences in treatment effects between the therapists despite differences in their work experiences. The same orientation and training within a specialised treatment centre in a shared supervised environment might have contributed to this equivalent effectiveness. Ultimately, knowledge of whether internet-based treatment of chronic fatigue syndrome can achieve equal results without or with less professional guidance is important.[34]

Chronic fatigue syndrome can only be diagnosed after 6 months of disabling fatigue.[1] Our patients had symptoms for almost 2 years before chronic fatigue syndrome was diagnosed and treated, and thus the FITNET program is a promising treatment because so many patients showed improvement within 6 months of treatment. The effectiveness of FITNET was confirmed by the sustained success of the treatment at 12 months and when it was given after usual care. Prompt initiation of treatment might even further reduce the rate of morbidity, with subsequent positive effects on educational and social

development. With FITNET, effective treatment is within reach for any adolescent with chronic fatigue syndrome. These findings stress the need for proper and rapid diagnosis and making medical professionals aware of adolescent chronic fatigue syndrome and the treatment options.[6]

Cognitive behavioural therapy for adolescents with chronic fatigue syndrome can now be broadly made available as FITNET and thus remove previous accessibility issues and thereby improve the prognosis of this disorder in adolescents.

	FITNET (%)	Usual Care (%)	Relative Risk (95% CI)	NNT	p-value
Main outcomes					
Full school attendance*	50/67 (75)	10/64 (16)	4.8 (2.7-8.9)	1.7	<0.0001
Fatigue severity (CIS)**	57/67 (85)	17/64 (27)	3.2 (2.1-4.9)	1.7	<0.0001
Physical functioning (CHQ)***	52/67 (78)	13/64 (20)	3.8 (2.3-6.3)	1.8	<0.0001
Secondary outcomes					
Self rated improvement (SRI)****	52/67 (78)	17/64 (27)	2.9 (1.9-4.5)	2.0	<0.0001
Combined					
Main outcomes	44/67 (66)	5/64 (8)	8.4 (3.6-19.8)	1.7	<0.0001
Main and secondary outcomes	42/67 (63)	5/64 (8)	8.0 (3.4-19.0)	1.8	<0.0001

* Full school attendance means school absence ≤ 10%.
** CIS-fatigue improvement cut off score < 40
*** CHQ cut off score ≥ 85%.
**** Answer "yes" to statement "I have completely recovered" or "I feel much better but still experience some symptoms."
RR: Relative Risk; NNT: Number needed to treat

TABLE 3a. Recovery at 6 months by treatment group (mean +/- 2 SD)

	FITNET (%)	Usual Care (%)	Relative Risk (95% CI)	NNT	p-value
Main outcomes					
Full school attendance*	44/67 (66)	8/64 (13)	5.3 (2.7-10.3)	1.9	<0.0001
Fatigue severity (CIS)**	54/67 (81)	13/64 (20)	4.0 (2.4-6.5)	1.7	<0.0001
Physical functioning (CHQ)***	49/67 (73)	12/64 (19)	3.9 (2.3-6.6)	1.8	<0.0001
Secondary outcomes					
Self rated improvement (SRI)****	26/67 (39)	5/64 (8)	5.0 (2.0-12.1)	3.2	<0.0001
Combined					
Main outcomes	37/67 (55)	5/64 (8)	7.1 (3.0-16.9)	2.1	<0.0001
Main and secondary outcomes	24/67 (36)	3/64 (5)	7.6 (2.4-24.1)	3.2	<0.0001

* Full school attendance means school absence ≤ 6%.
** CIS-fatigue improvement cut off score < 35
*** CHQ cut off score ≥ 90%.
**** Answer "yes" to statement "I have completely recovered"
RR: Relative Risk; NNT: Number needed to treat

TABLE 3b. Recovery at 6 months by treatment group (mean +/- 1 SD)

REFERENCES

1. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994; 121: 953–59.

2. Crawley E, Sterne JA. Association between school absence and physical function in paediatric chronic fatigue syndrome/myalgic encephalopathy. Arch Dis Child 2009; 94: 752–56.

3. Marshall GS. Report of a workshop on the epidemiology, natural history, and pathogenesis of chronic fatigue syndrome in adolescents. J Pediatr 1999; 134: 395–405.

4. Dowsett EG, Colby J. Longterm sickness absence due to ME/CFS in UK schools—an epidemiological study with medical and educational implications. J Chronic Fatigue Syndr 1997; 3: 29–42.

5. Rangel L, Garralda ME, Levin M, Roberts H. The course of severe chronic fatigue syndrome in childhood. J R Soc Med 2000; 93: 129–34.

6. Nijhof SL, Maijer K, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Adolescent Chronic Fatigue Syndrome: Prevalence, Incidence, and Morbidity. Pediatrics 2011; 127: e1169–75.

7. Rimes KA, Goodman R, Hotopf M, Wessely S, Meltzer H, Chalder T. Incidence, prognosis, and risk factors for fatigue and chronic fatigue syndrome in adolescents: a prospective community study. Pediatrics 2007; 119: e603–09.

8. Chalder T, Goodman R, Wessely S, Hotopf M, Meltzer H. Epidemiology of chronic fatigue syndrome and self reported myalgic encephalomyelitis in 5–15 year olds: cross sectional study. BMJ 2003; 327: 654–55.

9. Farmer A, Fowler T, Scourfield J, Thapar A. Prevalence of chronic disabling fatigue in children and adolescents. Br J Psychiatry 2004; 184: 477–81.

10. Jones JF, Nisenbaum R, Solomon L, Reyes M, Reeves WC. Chronic fatigue syndrome and other fatiguing illnesses in adolescents: a populationbased study. J Adolesc Health 2004; 35: 34–40.

11. Bell DS, Jordan K, Robinson M. Thirteenyear followup of children and adolescents with chronic fatigue syndrome. Pediatrics 2001; 107: 994–98.

12. Stulemeijer M, de Jong LW, Fiselier TJ, Hoogveld SW, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. BMJ 2005; 330: 14.

13. van Geelen SM, Sinnema G, Hermans HJ, Kuis W. Personality andchronic fatigue syndrome: methodological and conceptual issues. Clin Psychol Rev 2007; 27: 885–903.

14. Vercoulen JH, Swanink CM, Galama JM, *et al.* The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: development of a model. J Psychosom Res 1998; 45: 507–17.

15. Chalder T, Tong J, Deary V. Family cognitive behaviour therapy for chronic fatigue syndrome: an uncontrolled study. Arch Dis Child 2002; 86: 95–97.

16. Emmelkamp PM. Technological innovations in clinical assessment and psychotherapy. Psychother Psychosom 2005; 74: 336–43.

17. Cuijpers P, van Straten A, Andersson G. Internetadministered cognitive behavior therapy for health problems: a systematic review. J Behav Med 2008; 31: 169–77.

18. O'Kearney R, Gibson M, Christensen H, Griffiths KM. Effects of a cognitivebehavioural internet program on depression, vulnerability to depression and stigma in adolescent males: a schoolbased controlled trial. Cogn Behav Ther 2006; 35: 43–54.

19. Spence SH, Holmes JM, March S, Lipp OV. The feasibility and outcome of clinic plus internet delivery of cognitivebehavior therapy for childhood anxiety. J Consult Clin Psychol 2006; 74: 614–21.

20. Trautmann E, KronerHerwig B. A randomized controlled trial of Internetbased selfhelp training for recurrent headache in childhood and adolescence. Behav Res Ther 2010; 48: 28–37.

21. Patten CA, Croghan IT, Meis TM, *et al.* Randomized clinical trial of an Internetbased versus brief office intervention for adolescent smoking cessation. Patient Educ Couns 2006; 64: 249–58.

22. Prins JB, Bleijenberg G, Bazelmans E, *et al.* Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. Lancet 2001; 357: 841–47.

23. Bleijenberg G, Prins J, Bazelmans E. Cognitive behavioral therapies. In: Jason LA, Fennel PA, Taylor RR, eds. Handbook of chronic fatigue syndrome. Hoboken: Wiley and Sons, 2003: 493–526.

24. Nijhof SL, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Fatigue In Teenagers on the interNET—the FITNET Trial. A randomized clinical trial of webbased cognitive behavioural therapy for adolescents with chronic fatigue syndrome: study protocol. [ISRCTN59878666]. BMC Neurol 2011; 11: 23.

25. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38: 383–92.

26. Raat H, Landgraf JM, Bonsel GJ, Gemke RJ, EssinkBot ML. Reliability and validity of the child health questionnairechild form (CHQCF87) in a Dutch adolescent population. Qual Life Res 2002; 11: 575–81.

27. Kovacs M. The Children's Depression, Inventory (CDI). Psychopharmacol Bull 1985; 21: 995–98.

28. Papay JP, Spielberger CD. Assessment of anxiety and achievement in kindergarten and first and secondgrade children. J Abnorm Child Psychol 1986; 14: 279–86.

29. Vercoulen JHMM, Hoofs MPE, Bleijenberg G, *et al.* Randomised, doubleblind, placebocontrolled study of fluoxetine in chronic fatigue syndrome. Lancet 1996; 347: 858–61.

30. van Geelen SM, Bakker RJ, Kuis W, van de Putte EM. Adolescent chronic fatigue syndrome: a followup study. Arch Pediatr Adolesc Med 2010; 164: 810–14.

31. Chalder T, Deary V, Husain K, Walwyn R. Familyfocused cognitive behaviour therapy versus psychoeducation for chronic fatigue syndrome in 11 to 18yearolds: a randomized controlled treatment trial. Psychol Med 2010; 40: 1269–79.

32. Ritterband LM, Thorndike FP, Cox DJ, Kovatchev BP, GonderFrederick LA. A behavior change model for internet interventions. Ann Behav Med 2009; 38: 18–27.

33. Tate DF, Finkelstein EA, Khavjou O, Gustafson A. Cost effectiveness of internet interventions: review and recommendations. Ann Behav Med 2009; 38: 40–45.

34. Tummers M, Knoop H, Bleijenberg G. Effectiveness of stepped care for chronic fatigue syndrome: a randomized noninferiority trial. J Consult Clin Psychol 2010; 78: 724–31.

5

Internet-Based Therapy for Adolescents With Chronic Fatigue Syndrome: Long-term Follow-up

Sanne L. Nijhof*, Loudy P. Priesterbach*, Cuno S.P.M. Uiterwaal, Gijs Bleijenberg, Jan L.L. Kimpen and Elise M. van de Putte
* Both authors contributed equally

Pediatrics 2013; 131(6): e1788-95

ABSTRACT

Objective

Cognitive behavioral therapy (CBT) is known to be an effective treatment of adolescents with chronic fatigue syndrome (CFS), but its availability is limited. Fatigue in Teenagers on the Internet (FITNET), an Internet-based CBT program for adolescents with CFS, has been developed as an alternative to face-to-face CBT. Recently, its short-term effectiveness has been proven in a randomized clinical trial. Here we aimed to assess the long-term outcome of CFS in adolescents after FITNET treatment and after usual care. In addition, factors related to recovery at long-term follow-up (LTFU) for adolescents treated with the FITNET program were investigated.

Methods

The study was an LTFU of participants of the FITNET trial. Data were completed for 112 (88.2%) of 127 approached FITNET study participants. Primary outcomes were fatigue severity (Checklist Individual Strength–20), physical functioning (87-item Child Health Questionnaire), and school/work attendance.

Results

After a mean follow-up of 2.7 years, 66 (58.9%) adolescents had recovered from CFS. Most adolescents who recovered directly after treatment with FITNET were still recovered at LTFU. At LTFU there was no difference between the recovery rates for the different treatment strategies (original randomization: FITNET [64%] versus any form of usual care [52.8%]). Per additional month of "pretreatment disease duration," the odds for recovery were 4% lower (odds ratio: 0.96; 95% confidence interval: 0.93–0.99; P = .016), and per added point on "focus on bodily symptoms" (Body Consciousness Scale) of the mother (0–20 points) the odds for recovery were 11% lower (odds ratio: 0.89; 95% confidence interval: 0.80–0.99; P = .029).

Conclusions

The short-term effectiveness of Internet-based CBT on adolescent CFS is maintained at LTFU. At LTFU, usual care led to similar recovery rates, although these rates were achieved at a slower pace.

INTRODUCTION

Chronic fatigue syndrome (CFS) is characterized by debilitating fatigue that persists for longer than 6 months (according to the definition by the US Centers for Disease Control and Prevention [CDC]), is not alleviated by rest or sleep, and is often accompanied by other symptoms such as muscle pain and unrefreshing sleep.[1–3] Adolescent CFS is uncommon compared with chronic fatigue in adolescents[4–6] but leads to high disability and subsequent negative effects on physical, educational, and social development.[6,7]

One of the most successful potential treatments for adolescents with CFS is cognitive behavioral therapy (CBT), which has been shown to be effective in two-thirds of adolescents with CFS.[8–10] CBT is considered a safe treatment of CFS[11,12] but requires specialized therapeutic skills that are not always available within driving distance.[8,10] Fatigue in Teenagers on the InterNET (FITNET), an Internet-based CBT program for adolescents with CFS, has been developed as an alternative to face-to-face CBT.[10,13] The FITNET program was found to be successful in the treatment of CFS in adolescents, because it led to an 8 times higher chance of short-term recovery compared with usual care.[10] FITNET is the first internet-based therapy for CFS. It makes CBT more accessible to patients who live in an area without a specialized therapist and teenagers seem to prefer internet-based therapy.[10]

Untreated CFS in adolescents seems to have a better prognosis than CFS in adults; however, the disruption of development and education requires prompt recognition and treatment.[8,10,14] Reports on long-term prospects after treatment are variable. Study results of significant improvement vary between 50% (mean follow-up period of 2.2 years)[15] and 70% in adolescents who were initially treated with face-to-face CBT (mean follow-up period of 2.1 years).[16]

The factors that influence treatment outcomes in adolescent CFS are largely unknown. Several patient and parental factors have been suggested to be associated, such as age at inclusion,[15] presence of pain,[15] mental health,[15] self-esteem,[15] and general health perception[15] and the fatigue severity of the mother.[16,17] An earlier study has suggested the role of family, especially the mother, as a factor related to treatment success.[16] If factors related to long-term recovery from CFS in adolescents treated with FITNET can be established, results can be used to adjust content, focus, and duration of treatment of both the adolescent and/ or parent(s) to enhance recovery rates and to determine which adolescents are most likely to benefit.

The primary goal of this study was to determine long-term recovery rates of adolescent CFS patients who participated in the FITNET trial. In addition, factors related to recovery were assessed.

METHODS

Design and Participants

This study was designed to assess the long-term outcome of participants of the FITNET study. The FITNET study design[13] and short-term outcomes[10] were published elsewhere.

Between January 2008 and February 2010, 135 CFS patients aged 12 to 18 years were enrolled in the original FITNET trial.[13] All patients complied with CDC criteria for CFS diagnosis[3] and were randomly assigned to either FITNET (n = 68) or usual care (n = 67). Usual care consisted mainly of individual or group-based rehabilitation programs, face-to-face CBT, and graded exercise therapy with a physical therapist.

After 6 months of treatment, the randomized part of the trial ended and nonrecovered patients were offered to cross over to either FITNET or usual care. Thirty-two adolescents who were initially randomly assigned to usual care treatment (n = 67), and had not recovered after 6 months, decided to cross over to FITNET. Eleven nonrecovered adolescents initially randomly assigned to FITNET (n = 68) crossed over to usual care. All randomly assigned patients were invited for assessment of primary outcomes at 12 months postrandomization. These outcomes were published with the initial FITNET results.[10]

For the current long-term follow-up (LTFU) study, 127 potential participants received a written invitation for follow-up assessment between August and October 2011. Of the 135 initial FITNET trial participants, 8 participants dropped out of the trial before the initiation of this LTFU study. These 8 participants were not contacted. This LTFU measurement was performed within a fixed period, resulting in a follow-up period of different lengths for each participant (with a minimum of 1.7 years and a maximum of 3.8 years).

All primary and secondary outcome measures were obtained through written questionnaires that were sent to the participant by post and e-mail. Reminders to take part in the LTFU assessment were sent by e-mail and provided through phone calls. The medical ethics committee of the University Medical Centre Utrecht approved the study. Written informed consent for follow-up assessment was obtained from patients and parent(s). Figure 1 illustrates the relation of the LTFU study to the FITNET trial and clarifies the flow of participants.

Outcome Variables

The primary outcomes of this study were the same as the outcome measures of the

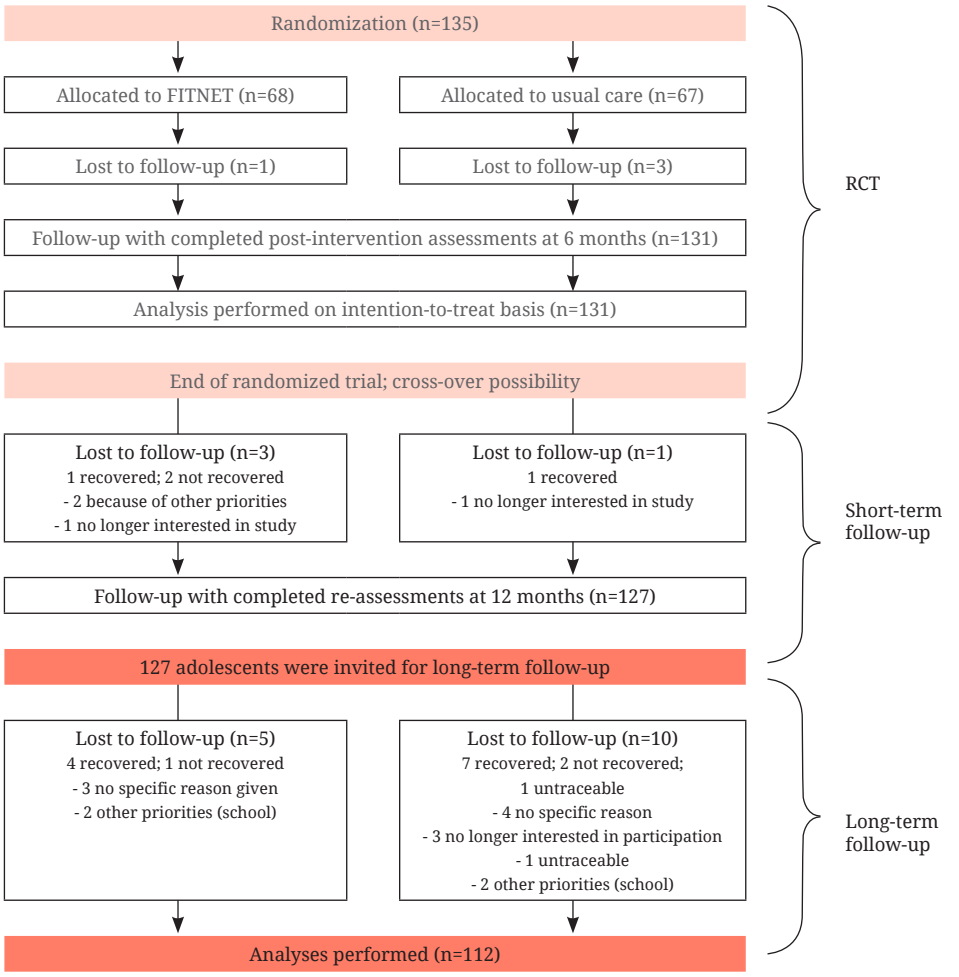


FIGURE 1 Design RCT and LTFU with flow of participants in FITNET trial

original FITNET trial and were as follows: (1) fatigue, as measured by the subscale "fatigue severity" (8 items) of the Checklist Individual Strength–20 (CIS-20; range: 8–56), which has good reliability and discriminative validity[8,18,19]; (2) physical functioning, as measured by the subscale "physical functioning" (9 items) of the 87-item Child Health Questionnaire (CHQ-CF87; range: 0%–100%)[20]; and (3) school attendance, measured retrospectively as the proportion of classes attended the 6 months before filling out the questionnaire, was expressed as a percentage of the normal school schedule. Considering that some of the adolescents were now beyond school age, the alternative primary outcome to school attendance was work attendance.

The secondary outcome measure was "self-rated improvement" (SRI), measured by using a 4-item tool in which patients can indicate whether they have completely recovered, feel much better, have the same complaints, or have become worse compared with the measurement before commencement of CFS treatment.[8,10]

Factors Related to Treatment Outcome

Potential factors related to nonrecovery, assessed at baseline for the original randomized clinical trial (RCT),[13] were as follows: age at the time of CFS diagnosis, gender, disease duration, fatigue score (CIS-20),[8,18,19] somatization score (Child Somatization Inventory),[21,22] physical functioning (CHQ-CF87),[20] depression score (Child Depression Inventory),[23,24] anxiety score (Spielberger State-Trait Anxiety Inventory for Children),[25,26] self-efficacy (Self-Efficacy Scale–28),[27] and focus on (fatigue) symptoms (Illness Management Scale).[28] Possible parental factors taken into account were as follows: parental fatigue score (CIS-20),[18] psychological stress [Brief Symptom Inventory, short version of Symptom Checklist (SCL)-90],[29] and focus on bodily symptoms (Body Consciousness Scale).[30,31]

All participants completed a general questionnaire with items relating to school, work, medication use, and participation in sports/exercise.

Definition of Recovery

Recovery from CFS was defined in relation to healthy peers (±2 SD) and in accordance with the FITNET trial.[10] This combined end point consisted of a fatigue-severity score of <40, a physical functioning score of ≥85%, school/ work presence of ≥90%, and an SRI answered with (1) "I have completely recovered" or (2) "I feel much better."

Statistical Analysis

Baseline characteristics of LTFU participants and nonparticipants were tested for dissimilarity by using independent samples t tests. Of all relevant variables, group-specific means and SDs or proportions were calculated for 12-month assessment and LTFU. After labeling of participants as recovered or nonrecovered, a X^2 test was used to assess the difference in recovery rates between the 2 groups on the basis of original randomization at LTFU.

The possible relationships between the adolescent/parental factors and the long-term outcome were quantified by estimating odds ratios (ORs) and 95% confidence intervals (CIs) by using binary logistic regression, with outcome (recovery: yes or no) as the dependent variable and the assessed factors as independent variables. Separate analyses were performed for adolescent factors and parental factors. Because the LTFU

period varied, time between inclusion and LTFU assessment was taken into account as a covariate. All analyses were performed by using PASW Statistics 20.0.

Data Presentation

For the presentation of recovery rates in Fig 2, the participants were distributed in 3 groups. The group "Direct Start FITNET" (FN group) consisted of adolescents initially randomly assigned to FITNET therapy (n = 68 at RCT initiation; n = 64 at 12 months assessment; n = 59 at LTFU). The group "FITNET Cross-over After Usual Care" (XO group) consisted of adolescents initially randomly assigned to usual-care treatment, who were not recovered after 6 months, and who decided to cross over to the FITNET therapy (n = 32 crossed over at RCT ending at the 6-month assessment; n = 31 completed 12-month assessment; n = 25 completed LTFU). The group "Usual Care Only" (UC group) consisted of adolescents initially randomly assigned to usual-care treatment, and who remained in usual care after 6 months of treatment (n = 35 at RCT ending at the 6-month assessment; n = 32 completed 12-month assessment; n = 28 completed LTFU).

RESULTS

Study Population

One-hundred twelve of 127 adolescents (88.2%) completed LTFU assessment (Fig 1). Of the 15 nonparticipants (telephone interview), 11 reported recovery, 3 reported nonrecovery, and 1 was untraceable (Fig 1). There were no significant differences in baseline characteristics between participants and nonparticipants (Table 1). Table 1 also shows baseline characteristics of this cohort and the severity of disease at study entry.

LTFU of Treatment Effects

The mean (±SD) follow-up period was 2.7 ± 0.5 years (range: 1.7–3.8 years). The mean age of the participants at LTFU was 18.5 ± 1.5 years.

Table 2 shows the outcomes at LTFU compared with the 12-month assessment for

	Participants	Non-participants*	p-value
N	112	15	
Age (years), mean (SD)	15.8 (1.4)	16.0 (1.4)	.58
Gender (% girls)	81.3	93.3	.47
Disease duration (months, mean (SD))	21.4 (14.8)	31.7 (31.6)	.23
Initial randomization (% FITNET)	52.7	33.3	.18
Total FITNET participation incl. crossovers	75.0	73.3	1.00
School attendance (% mean (SD))	43.9 (30.7)	41.4 (32.7)	.78
Questionnaire scores (mean, SD)			
Fatigue severity (CIS-20), range: 8-56	51.3 (4.4)	52.0 (5.0)	.62
Physical functioning (CHQ-CF87), range: 0-100	59.5 (17.5)	53.1 (22.3)	.30
Somatic complaints (CSI), range: 0-132	33.2 (12.6)	34.3 (16.0)	.79
Depression score (CDI), range: 0-54	11.3 (5.3)	10.5 (4.8)	.54
Anxiety score (STAIC), range: 20-60	32.8 (8.4)	29.5 (8.8)	.19
Self-efficacy (SES-28), range: 0-28	18.0 (2.9)	16.9 (3.6)	.31
Focus on fatigue (IMQ), range: 0-54	3.5 (0.8)	3.7 (0.8)	.52

*There were no significant differences in characteristics between the two study groups, equal variance not assumed, 2-tailed significance.

CIS = checklist individual strength; SES = Self efficacy Scale; IMQ = Illness Management Questionnaire; CHQ-CF87 = Child Health Questionnaire; CSI = Children's Somatisation Inventory; CDI = Children's Depression Inventory; STAIC = State-Trait Anxiety Inventory for Children

TABLE 1. Baseline characteristics of participating and non-participating adolescents

	12 month assessment			LTFU 2.7 (±0.5) years		
	Total	**Recovered**	**Not recovered**	**Total**	**Recovered**	**Not recovered**
N	112	62	50	112	66	46
School/work attendance*	84.5 (27.3)	98.5 (3.1)	66.0 (33.5)	84.0 (30.8)	98.0 (2.9)	63.9 (40.4)
Fatigue severity (CIS-20, range 8-56)	26.5 (13.9)	17.7 (6.4)	37.3 (13.1)	26.2 (14.4)	17.2 (7.1)	39.2 (12.0)
Physical functioning (CHQ-CF87, range 0-100)	86.2 (17.8)	95.4 (4.1)	74.8 (21.3)	89.4 (14.3)	97.2 (4.2)	78.2 (16.2)
Self-rated improvement** (SRI, no. (%))	87 (77.7)	62 (100)	25 (50)	87 (68.5)	66 (100)	21 (45.7)

Data are mean (SD), unless otherwise indicated. LTFU = Long term follow-up; CIS-20 = Checklist Individual Strength-20; CHF-CF87 = Child Health Questionnaire; SRI = Self Rated Improvement

* Measured as follows: at 12 month assessment a 2 week prospective diary was used; at LTFU a 6 months retrospective questionnaire was used.

**SRI answered with 'yes' to the statements 'I have completely recovered' or 'I feel much better'.

TABLE 2. Follow-up results at 12 month- and LTFU assessment (n=112)

all 112 LTFU participants, irrespective of initial randomization or treatment during the RCT. Thus, these adolescents received either FITNET therapy, usual care, or both. LTFU assessment showed sustained treatment effects in comparison with the 12-month assessment; mean scores on fatigue, physical functioning, school/work attendance, and SRI were similar. Analyses at other cutoff points (-1 SD) obviously changed the number of recovered patients (57 instead of 66) but did not materially change our findings concerning the relative effects (FITNET compared with usual care; data not shown).

Recovery rates per group (FN/XO/UC) from the start of the RCT through the current follow-up are shown in Fig 2. All participants at the 4 different times of assessment are included in the graph: 135 at RCT initiation, 131 at 6-month assessment, 127 at 12-month assess- ment, and 112 at LTFU. The FN group (n = 59 at LTFU) showed stable recovery rates (64%) at all follow-up moments. The XO group (n = 25 at LTFU) showed an increased and subsequent stable recovery rate after crossing over to FITNET (52%). The UC group (n = 28 at LTFU) showed comparable recovery rates (53.6%) at LTFU, although these were achieved at a slower pace.

Of the FN group, 18 (30.5%) LTFU participants followed ≥1 forms of usual care between 12-month follow-up and LTFU. The recovery percentage in this group was 61.1% at LTFU. Recovery percentages at LTFU for the 2 groups based on original randomization (FITNET versus usual care) were not significantly different (64.4% vs 52.8%; x2 test, P = .251). At LTFU, receiving FITNET therapy did not significantly

influence recovery rates (followed FITNET [58.2%] versus no FITNET [53.6%], P = .515). Per protocol analysis of just the 112 respondents to the LTFU study for all moments of assessment did not change these findings.

A number of adolescents experienced a relapse during the follow-up period. Within the FN group, 5 (8.5%) adolescents, who were recovered at 12-month assessment, no longer met recovery criteria at LTFU. Within the XO group, 4 (16%) relapses occurred, and 3 were within the UC group (10.7%).

Most adolescents were still going to school at the time of LTFU, although some adolescents had started their working careers (n = 10). Only 3 (30%) of the adolescents with a job were currently working full-time. However, 70% of the adolescents were satisfied with working a part-time job and worked as many hours as they liked, unrestrained by CFS (results from general questionnaire, work-related items).

Factors Relating to Recovery

Baseline factors related to recovery at LTFU after following the FITNET program are presented in Table 3. Of 112 LTFU participants, 84 (59 from the FN group and 25 from the XO group) followed FITNET and were included in this analysis. Only 2 factors were related to recovery; every additional month of pretreatment disease duration led to 4% lower odds of recovery (adolescent factor; OR: 0.96; 95% CI: 0.93–0.99; P =

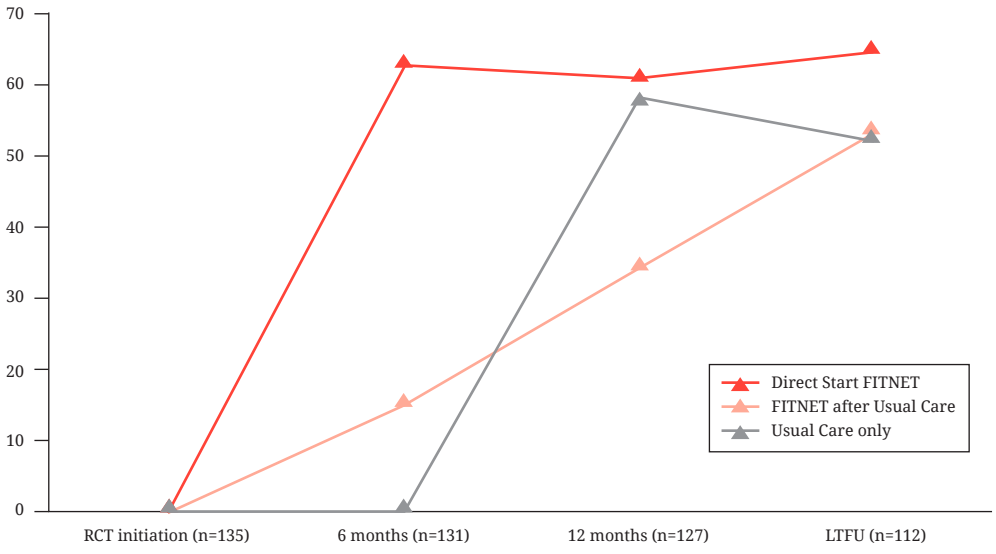


FIGURE 2 Percentage of participants meeting criteria for recovery per group. Baseline group counts: 'Direct Start FITNET n=68', FITNET after Usual Care n=32', 'Usual Care only n=35' (Detailed info in Methods section).

.016), and every additional point scored on maternal focus on bodily symptoms (Body Consciousness Scale) led to 11% lower odds of recovery (parental factor; OR: 0.89, 95% CI: 0.80–0.98; P = .029). Adjustment for follow-up time did not change the findings.

DISCUSSION

The long-term outcome of CFS in adolescents in this study was mostly favorable. On average, 2.7 years after commencing treatment and 4.5 years after onset of disease, ± 60% of the adolescents recovered, irrespective of the type of treatment. It was encouraging to see that the short-term treatment effects of FITNET therapy appeared stable and were sustained at LTFU. The number of relapses was limited. Patients who only followed usual-care treatment eventually achieved comparable outcomes at LTFU. However, the pace of recovery was remarkably slower; it took this group considerably more months to achieve similar recovery rates.

Nonetheless, a substantial number of adolescents did not recover and were unable to attend all required hours of school or work full-time. Factors related to recovery after FITNET treatment at LTFU were disease duration before treatment commencement and maternal focus on bodily symptoms.

Strengths and Limitations

The cohort of adolescents followed in our study population is, to our knowledge, the largest described for CFS thus far. Moreover, it is a wellcharacterized group, representative of the Dutch CFS population and strictly diagnosed with the CDC criteria.

Another particular strength is the high participation rate of 88.2%, reducing the risk of selection bias.

An additional strength is our definition of recovery, which used a combined end point of 4 criteria, which is fairly strict compared with other studies.[8,9,14,15] The combination of the primary measures of disease severity with the patient's own perception of recovery (SRI) generally creates lower recovery rates than the primary measures alone.

Some issues need additional consideration.The scope of the LTFU was to assess the sustainability of FITNET treatment, rather than to compare FITNET with usual care. Our original pragmatic study design enabled us to demonstrate the value of FITNET relative to currently locally available therapies. Availability, of course, is defined locally and differs from region to region, even in a small country such as The Netherlands. This design meant that we could and cannot provide detailed data about the specific interventions in the UC group because the quality and quantity of treatments (mostly CBT) differed according to local availability, and adolescents often combined CBT with other treatments such as graded exercise. Nonetheless, we wanted to provide insight into the long-term results of the UC group as well. A considerable number of usual-care

patients received FITNET therapy using the cross-over opportunity (n = 32), which means that only 35 adolescents received solely usual care treatment.

At LTFU, school presence was scored by using retrospective questionnaires. These are less precise than the prospective diaries used during the FITNET trial and at the 12-month assessment.

Results in the Context of Previous Literature

Despite significant methodologic differences and definitions of recovery with previous studies on this topic, the outcomes found in our study are in accordance with previous reports on the prognosis of adolescent CFS.[14,32,33] The longest follow-up study of natural course (13 years) showed that the majority of adolescents with CFS have mild to moderate persisting symptoms with a considerable duration of school absence.[16] Previous study results of significant improvement after treatment vary between 50% and 70% (mean follow-up period of 2.2 and 2.1 years, respectively).[15,16]

Because a significant group of adolescents remain impaired by CFS symptoms, it is important to characterize this group to change content or choice of treatment. In previous studies, a number of predictors for outcome of CFS in adolescents have been suggested. Both patient and parental factors have been revealed to be associated with unfavorable outcome after regular care[15] or after CBT.[16] We could not confirm an association between older age, poor mental health,[15] or higher maternal fatigue severity[16] with an inferior outcome. However, our finding that maternal focus on bodily symptoms was associated with long-term recovery of the child suggests that an intergenerational vulnerability and interaction between mother and child may exist.[17] More research focused on this topic is required.

Clinical Implications

Compared with usual care, internet-based CBT treatment of adolescents led to earlier recovery from CFS. This shortened recovery period is crucial during adolescence, when school attendance and social contacts are crucial for social and academic development. Extensive absence from school is associated with poorer educational outcome and may increase the risk of unemployment.[34] Previous literature has shown that delays in diagnosis of CFS and absenteeism because of CFS in adolescents are unfortunately (still) substantial.[10,35] FITNET treatment supported quick improvement of school attendance and thereby contributed to diminishing these detrimental effects of school absence during this critical time.

The finding that longer disease duration was related to long-term nonrecovery underlines the necessity for prompt diagnosis and treatment of CFS. Although

attention to bodily symptoms is one of the main themes in the FITNET treatment, both for the adolescent and for the parent(s), this is apparently insufficient for a subgroup of patients characterized by high maternal scores on the focus on bodily symptoms. In the FITNET program, adolescents and parents are treated simultaneously, both in a bilateral contact with the therapist. The possible implication of this finding is that a face- to-face dynamic family approach is needed for a subgroup of adolescent CFS patients.[8–10]

CONCLUSIONS

The treatment effects of internet-based CBT persist at LTFU. Its therapeutic gain lies largely in rapid recovery. A challenge remains to offer internet-based CBT in those cases that are most likely to benefit from it and to recognize situations that might require more intense forms of (family) therapy.

REFERENCES

1. Smith WR, White PD, Buchwald D. A case control study of premorbid and currently reported physical activity levels in chronic fatigue syndrome. BMC Psychiatry. 2006;6: 53. doi:10.1186/1471-244X-6-53

2. Priebe S, Fakhoury WK, Henningsen P. Functional incapacity and physical and psychological symptoms: how they interconnect in chronic fatigue syndrome. Psychopathology. 2008;41(6):339–345

3. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A; International Chronic Fatigue Syndrome Study Group. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med. 1994;121(12):953–959

4. Chalder T, Goodman R, Wessely S, Hotopf M, Meltzer H. Epidemiology of chronic fatigue syndrome and self reported myalgic encephalomyelitis in 5-15 year olds: cross sectional study. BMJ. 2003;327(7416):654–655

5. Farmer A, Fowler T, Scourfield J, Thapar A. Prevalence of chronic disabling fatigue in children and adolescents. Br J Psychiatry. 2004;184:477–481

6. Nijhof SL, Maijer K, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Adolescent chronic fatigue syndrome: prevalence, incidence, and morbidity. Pediatrics. 2011; 127(5). Available at: www.pediatrics.org/ cgi/content/full/127/5/e1169

7. Crawley E, Sterne JA. Association between school absence and physical function in paediatric chronic fatigue syndrome/ myalgic encephalopathy. Arch Dis Child. 2009;94(10):752–756

8. Stulemeijer M, de Jong LW, Fiselier TJ, Hoogveld SW, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. BMJ. 2005;330(7481):14

9. Chalder T, Deary V, Husain K, Walwyn R. Family-focused cognitive behaviour therapy versus psycho-education for chronic fatigue syndrome in 11- to 18-year-olds: a randomized controlled treatment trial. Psychol Med. 2010;40(8):1269–1279

10. Nijhof SL, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic

fatigue syndrome (FITNET): a randomised controlled trial. Lancet. 2012;379(9824):1412–1418

11. Heins MJ, Knoop H, Prins JB, Stulemeijer M, van der Meer JW, Bleijenberg G. Possible detrimental effects of cognitive behaviour therapy for chronic fatigue syndrome. Psychother Psychosom. 2010;79(4):249–256

12. White PD, Goldsmith KA, Johnson AL, et al; PACE trial management group. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet. 2011;377(9768):823–836

13. Nijhof SL, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Fatigue in teenagers on the internet—the FITNET trial. A randomized clinical trial of web-based cognitive behavioural therapy for adolescents with chronic fatigue syndrome: study protocol [ISRCTN59878666]. BMC Neurol. 2011;11:23. doi:10.1186/1471-2377-11-23

14. Bell DS, Jordan K, Robinson M. Thirteen-year follow-up of children and adolescents with chronic fatigue syndrome. Pediatrics. 2001; 107(5):994–998

15. van Geelen SM, Bakker RJ, Kuis W, van de Putte EM. Adolescent chronic fatigue syndrome: a follow-up study. Arch Pediatr Adolesc Med. 2010;164(9):810–814

16. Knoop H, Stulemeijer M, de Jong LW, Fiselier TJ, Bleijenberg G. Efficacy of cognitive behavioral therapy for adolescents with chronic fatigue syndrome: long-term follow-up of a randomized, controlled trial. Pediatrics. 2008;121(3). Available at: www. pediatrics.org/cgi/content/full/121/3/e619

17. van de Putte EM, van Doornen LJ, Engelbert RH, Kuis W, Kimpen JL, Uiterwaal CS. Mirrored symptoms in mother and child with chronic fatigue syndrome. Pediatrics. 2006; 117(6):2074–2079

18. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res. 1994; 38(5):383–392

19. Vercoulen JHMM, Alberts M, Bleijenberg G. De checklist individual strength (CIS). Gedragstherapie. 1999;32:131–136

20. Raat H, Landgraf JM, Bonsel GJ, Gemke RJ, Essink-Bot ML. Reliability and validity of the Child Health Questionnaire-Child Form (CHQ-CF87) in a Dutch adolescent population. Qual Life Res. 2002;11(6):575–581

21. Meesters C, Muris P, Ghys A, Reumerman T, Rooijmans M. The Children's Somatization Inventory: further evidence for its reliability and validity in a pediatric and a community sample of Dutch children and adolescents. J Pediatr Psychol. 2003;28(6):413–422

22. van de Putte EM, Engelbert RH, Kuis W, Sinnema G, Kimpen JL, Uiterwaal CS. Chronic fatigue syndrome and health control in adolescents and parents. Arch Dis Child. 2005;90(10):1020–1024

23. Kovacs M. The Children's Depression Inventory (CDI). Psychopharmacol Bull. 1985; 21(4):995–998

24. Timbremont B, Braet C. Psychometrische evaluatie van de nederlandstalige Children's Depression Inventory. Gedragstherapie. 2001;34:229–242

25. Papay JP, Spielberger CD. Assessment of anxiety and achievement in kindergarten and first- and second-grade children. J Abnorm Child Psychol. 1986;14(2):279–286

26. Houtman IL, Bakker FC. The anxiety thermometer: a validation study. J Pers Assess. 1989;53(3):575–582

27. Vercoulen JH, Swanink CM, Galama JM, *et al.* The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: development of a model. J Psychosom Res. 1998;45(6):507–517

28. Ray C, Weir W, Stewart D, Miller P, Hyde G. Ways of coping with chronic fatigue syndrome: development of an illness management questionnaire. Soc Sci Med. 1993; 37(3):385–391

29. Arrindell WA, Perris C, Van Der Ende J, Gaszner P, Eisemann M, Perris H. Crossnational generalizability of dimensions of perceived parental rearing practices: Hungary and The Netherlands; a correction and repetition with healthy adolescents. Psychol Rep. 1989;65(3 pt 2):1079–1088

30. Bazelmans E, Bleijenberg G, Voeten MJ, van der Meer JW, Folgering H. Impact of a maximal exercise test on symptoms and activity in chronic fatigue syndrome. J Psychosom Res. 2005;59(4):201–208

31. van der Werf SP, de Vree B, van Der Meer JWM, Bleijenberg G. The relations among body consciousness, somatic symptom report, and information processing speed in chronic fatigue syndrome. Neuropsychiatry Neuropsychol Behav Neurol. 2002;15(1):2–9

32. Patel MX, Smith DG, Chalder T, Wessely S. Chronic fatigue syndrome in children: a cross sectional survey. Arch Dis Child. 2003;88(10):894–898

33. Smith MS. Adolescent chronic fatigue syndrome. Arch Pediatr Adolesc Med. 2004;158 (3):207–208

34. Weitzman M, Klerman LV, Lamb G, Menary J, Alpert JJ. School absence: a problem for the pediatrician. Pediatrics. 1982;69(6): 739–746

35. Webb CM, Collin SM, Deave T, Haig-Ferguson A, Spatz A, Crawley E. What stops children with a chronic illness accessing health care: a mixed methods study in children with chronic fatigue syndrome/ myalgic encephalomyelitis (CFS/ME). BMC Health Serv Res. 2011;11:308. doi:10.1186/1472-6963-11-308

6

Functional Improvement Is Accompanied by Reduced Pain in Adolescent Chronic Fatigue Syndrome

Sanne L. Nijhof, Loudy P. Priesterbach, Gijs Bleijenberg,
Raoul H. Engelbert and Elise M. van de Putte

Pain Med. 2013; 14 (9): 1435-8

INTRODUCTION

Chronic fatigue syndrome (CFS) in adolescents is a complex, disabling condition characterized by severe and unexplained fatigue lasting more than 6 months, and often accompanied by pain symptoms. CFS in adolescents has substantial long-term consequences for educational and social development.[1,2] Chronic pain symptoms in CFS are disabling and affect physical and social functioning.[3] Adult patients with CFS show lower pain thresholds than healthy subjects.[4] In a recently published review about pain in patients with CFS, Nijs *et al.* stated that pain appears to be one out of many symptoms related to central sensitization in adult CFS.[5] They concluded that pain-catastrophizing thoughts and depression partly account for these pain symptoms. They suggested that it is important to understand the symptoms of pain in CFS better in order to assess whether it requires a specific treatment approach other than the main treatment focused on fatigue.[5] Previous research has suggested to view the pathophysiological state of pain in CFS as an increase in the excitability and synaptic efficacy of neurons in central nociceptive pathways.[5,6] We present original data on pain symptoms in adolescent CFS and their relation to treatment focused on fatigue. We hypothesized that adolescent CFS patients have a lowered pain threshold at the time of diagnosis and that both pain experience and pain threshold improve when CFS is successfully treated.

METHODS

Between November 2008 and February 2010, 83 adolescents (12–18 years) participating in the Fatigue In Teenagers on the interNET (FITNET) trial[7] were invited to participate in this longitudinal study on pain in adolescents with CFS, when attending their initial assessment at the University Medical Center Utrecht for the original FITNET trial.[8] All patients agreed to participate (100%). They all complied with the U.S. Centers for Disease Control and Prevention criteria for CFS diagnosis[9] at the time of inclusion. In the original FITNET trial, patients were randomly assigned to either FITNET or usual care. FITNET, an internet-based cognition behavioral therapy (CBT) program for adolescents with CFS, was developed as an alternative to face-to-face CBT.[7,8] Usual care consisted mainly of individual or groupbased rehabilitation programs, face-to-face CBT, and graded exercise therapy with a physical therapist. After 6 months of treatment, the randomized part of the FITNET trial ended, and non-recovered patients were offered the opportunity to cross over to either FITNET or usual care. In the FITNET trial, CFS adolescents were treated primarily to target their fatigue.[7,8] All participants in this pain study were treated with CBT, either internet-based (55 of 72 of the participating patients) or face to face.

Pain threshold was measured at four sites using an analog algometer: two bony sites (right femur lateral condyle and right elbow lateral condyle) and two muscle sites (musculus deltoideus right upper arm and musculus vastus medialis right leg). Using the algometer, increasing pressure was applied to these four reference points. The force was gradually increased at a rate of 1 kg/s by silently counting seconds while increasing pressure. The subjects were asked to react verbally when the level of pressure is perceived as pain. The score was then read from the algometer (range: 0–11) and was designated as the pain threshold.[7,10] Algometry has an excellent test–retest reliability.[11] The rater was blind to the scores of the subjects at previous measurements. Subjective pain experience was measured by the self-reporting of a mean daily observed pain (DOP) score (range 0–16) over the course of 12 days.[7]

Questionnaires were used to assess baseline characteristics and recovery of CFS after treatment. Participants were asked to fill out these questionnaires without assistance from their parent(s) or the researcher. Fatigue and activity level were assessed with the self-report questionnaire Checklist Individual Strength (CIS-20) subscales “fatigue severity” (range 8–56) and “activity level” (range 3–21). The CIS-20 is a reliable assessment tool with excellent internal consistency (Cronbach’s a 0.93) and discriminative validity for CFS.[12] Physical functioning was measured by the subscale

"physical functioning" (range 0–100%) of the Child Health Questionnaire (CHQ-CF87). This assessment method is reported to be reliable and has been validated with good internal consistency (Cronbach's a = 0.86).[13]

Assessment of trait anxiety in adolescents was performed with a validated Dutch translation of the Spielberger State-Trait Anxiety Inventory for Children, consisting of 20 statements on a 3-point scale (range 20–60).[14] Depression in adolescents was measured with a validated Dutch translation of the Children's Depression Inventory,[15] which has a high degree of internal consistency, with Cronbach's alpha ranging between 0.71 and 0.89. Somatic complaints were assessed with a validated Dutch translation of the Children's Somatization Inventory, a self-report questionnaire rating the presence of 35 somatic symptoms in the last 2 weeks using a 5-point Likert scale (range 0–140).[16] Finally, "self-rated improvement" (SRI) was measured using a four-item tool in which patients can indicate whether they have completely recovered, feel much better, have the same complaints, or have become worse compared with the measurement before commencement of CFS treatment.[8]

All measurements were carried out twice: at diagnosis and at 12-month follow-up.

Group analyses were performed on the basis of whether the adolescents had recovered (yes/no) from CFS at 12-month follow-up. Recovery from CFS was defined, in relation to healthy peers (±2 standard deviation [SD]) in accordance with the FITNET trial as a combination of fatigue scores (CIS-20 fatigue scale <40), physical functioning (CHQ physical functioning scale ≥85%), school attendance within normal limits (>90%), and if the patient rates himself or herself as having recovered (SRI: "I have completely recovered" or "I feel much better").[8] The data were analyzed with linear regression using both pain outcome measures (DOP and pain threshold) as a dependent variable and a group indicator (recovered = 1, non-recovered = 0) as an independent variable. The results are presented as linear regression coefficients representing mean differences between the recovered and the non-recovered adolescent for the parameter investigated, with their corresponding 95% confidence intervals. The same models were used to adjust for confounding factors, such as age, gender, anxiety, depression, and pain threshold/DOP at baseline in which variables with a P value of <0.15 were retained for further analysis.[17] The medical ethics committee of the University Medical Center Utrecht approved this study. Written informed consent was obtained from the adolescent and their parents.

RESULTS

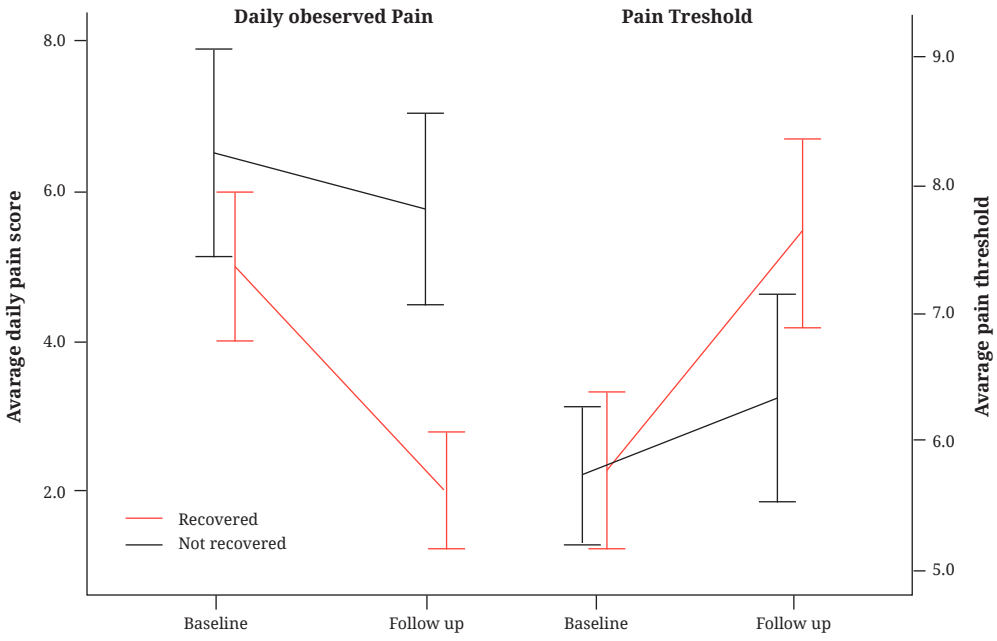
For 72 out of 83 (86.7%) participants of the algometry study, algometry and DOP data were complete (valid measurements at baseline and 12-month follow-up). The baseline characteristics of the 11 remaining adolescents did not differ significantly from the adolescents included in the analyses. The mean age of the participants was 15.8 years

	Recovered (mean; SD)	**Not Recovered** (mean; SD)	p*	**Mean difference** (95% CI)	**Adjusted Difference** (95% CI)**
N	39	33			
Baseline					
Age at entry (yrs)	15.6 (1.4)	16.2 (1.3)	0.071		
Gender (% female)	79.5	78.8	0.942**		
Body Mass Index	21.0 (2.6)	21.8 (3.6)	0.247		
Disease duration (months)	22.1 (20.4)	24.9 (15.9)	0.532		
Fatigue score (CIS20, range 8-56)	51.0 (4.6)	51.8 (4.0)	0.461		
Activity level (CIS20, range 3-21)	15.4 (4.0)	16.6 (4.5)	0.226		
Physical functioning (CHQ, range 0-100%)	59.5 (18.4)	57.9 (17.2)	0.701		
Depression score (CDI, range 0-54)	10.1 (4.1)	12.4 (6.3)	0.064		
Anxiety score (STAIC, range 20-60)	32.3 (7.9)	31.9 (7.3)	0.850		
Somatization score (CSI, range 0-140)	35.9 (12.5)	33.5 (13.4)	0.439		
Pain scores at Baseline					
Average pain threshold (0-11kg)	5.8 (1.9)	5.7 (1.5)	0.901	0.1 (-0.7 to 0.9)	0.0 (-0.9 to 0.8)
Average Daily Observed Pain (score range 0-16)	5.0 (3.0)	6.5 (3.9)	0.072	-1.5 (-3.2 to 0.1)	-1.2 (-2.9 to 0.4)
Pain scores at 12 months FU					
Average pain threshold (0-11kg)	7.6 (2.3)	6.3 (2.3)	0.019	1.3 (0.2 to 2.4)	1.2 (0.2 to 2.2)
Average Daily Observed Pain (score range 0-16)	2.0 (2.4)	5.8 (3.6)	<0.001	-3.8 (-5.2 to -2.3)	-2.9 (-4.2 to -1.6)

* Independent T-tests, equal variance not assumed, sig. 2 tailed
** Pearson Chi-square test
*** Adjusted for age, gender, anxiety, depression, average pain threshold at baseline and average DOP at baseline

TABLE 1. Baseline characteristics and pain scores at 12-month follow-up

(SD ± 1.4), 79.2% were female, and mean disease duration was 23.4 months (SD ± 18.4). In Table 1, the baseline characteristic and outcome measures of this study are presented. Measurements of recovered and non-recovered were similar at baseline, as well as the pain threshold scores and the DOP scores. As can be deduced from both Table 1 and Figure 1, the recovered group scored significantly higher on pain threshold measurements and significantly lower on DOP scores at follow-up than the baseline (P value < 0.001). Also, the average pain threshold of the recovered group was found to be significantly higher and the DOP scores significantly lower at follow-up compared with the non-recovered adolescents, which indicated a lower experience of daily pain in the recovered group. Mean pain thresholds and symptoms in the recovered group were between 1 and 2 SD of the population mean (healthy controls: average pain threshold of 9.8 [SD 1.4][8]; mean DOP scores adults: 1.0 [SD 1.3];[18] mean DOP scores adolescents: 0.73 (SD 0.86), unpublished data). Adjusting for age, gender, pain threshold, and DOP at baseline, as well depression, did not materially change these findings.



Error bars represent 95% confidence intervals

FIGURE 1. Pain threshold (kg) and daily observed pain (score 0–16) change between baseline and follow-up (12 months) for recovered and non-recovered group.

CONCLUSION

The subjective experience of pain is accompanied by an objectively lowered pain threshold in adolescents with CFS. Pain diminishes after successful treatment for CFS through cognitive behavioral therapy primarily focused on fatigue symptoms, as reflected in improved objective measurements of the pain threshold and self-reported pain scores in a diary. Even though CBT treatment was not targeted at pain symptoms, both the experience of pain and fatigue changed in recovered patients. Because this is not a controlled study, we can only conclude that an association exists between the reduction of pain and recovery from CFS. Depression has no influence on the pain threshold nor on the DOP scores. Adolescent CFS patients who did not recover by the 12-month follow-up still exhibited a low pain threshold and more selfreported pain symptoms, indicating that pain is an intrinsic feature of adolescent CFS consistent with the central sensitization hypothesis. Pain symptoms do not seem to require a specific treatment approach in adolescents with CFS, irrespective of the presence of concomitant depression. This is valuable information for adolescent CFS patients when they are informed about the prognosis of their disease.

REFERENCES

1. Nijhof SL, Maijer K, Bleijenberg G, *et al.* Adolescent chronic fatigue syndrome: Prevalence, incidence, and morbidity. Pediatrics 2011;127:e1169–75.

2. Crawley E, Sterne JA. Association between school absence and physical function in paediatric chronic fatigue syndrome/myalgic encephalopathy. Arch Dis Child 2009;94:752–6.

3. Meeus M, Nijs J, Meirleir KD. Chronic musculoskeletal pain in patients with the chronic fatigue syndrome: A systematic review. Eur J Pain 2007;11:377–86.

4. Meeus M, Roussel NA, Truijen S, Nijs J. Reduced pressure pain thresholds in response to exercise in chronic fatigue syndrome but not in chronic low backpain: An experimental study. J Rehabil Med 2010; 42:884–90.

5. Nijs J, Combrez G, Meeus M, *et al.* Pain in patients with chronic fatigue syndrome: Time for specific pain treatment? Pain Physician 2012;15:E677–86.

6. Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. Pain 2011;152:S2–15.

7. Nijhof SL, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Fatigue In Teenagers on the interNET–the FITNET Trial. A randomized clinical trial of web-based cognitive behavioural therapy for adolescents with chronic fatigue syndrome: Study protocol [ISRCTN59878666]. BMC Neurol 2011;11:23–30.

8. Nijhof SL, Bleijenberg G, Uiterwaal CSPM, Kimpen JLL, van de Putte EM. Effectiveness of internet-based cognitive behavioral treatment for adolescents with chronic fatigue syndrome (FITNET): A randomized clinical trial. Lancet 2012;379(9824):1412–8.

9. Fukuda K, Straus SE, Hickie I, *et al.* The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994;121(12): 953–9.

10. van de Putte EM, Uiterwaal CS, Bots ML, *et al.* Is chronic fatigue syndrome a connective tissue disorder? A cross-sectional study in adolescents. Pediatrics 2005;115:e415–22.

11. Hogeweg JA, Langereis MJ, Bernards AT, Faber JA, Helders PJ. Algometry. Measuring pain threshold, method and characteristics in healthy subjects. Scand J Rehabil Med 1992;24:99–103.

12. Vercoulen JH, Swanink CM, Fennis JF, *et al.* Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994;38(5):383–92.

13. Raat H, Landgraf JM, Bonsel GJ, Gemke RJ, Essink- Bot ML. Reliability and validity of the Child Health Questionnaire-Child Form (CHQ-CF87) in a Dutch adolescent population. Qual Life Res 2002;11(6):575–81.

14. Papay JP, Spielberger CD. Assessment of anxiety and achievement in kindergarten and first- and secondgrade children. J Abnorm Child Psychol 1986;14(2): 279–86.

15. Kovacs M. The Children's Depression Inventory (CDI). Psychopharmacol Bull 1985;21(4):995–8.

16. Meesters C, Muris P, Ghys A, Reumerman T, Rooijmans M. The Children's Somatization Inventory: Further evidence for its reliability and validity in a pediatric and a community sample of Dutch children and adolescents. J Pediatr Psychol 2003;28(6):413– 22.

17. Freedman DA. A note on screening regression equations. Am Stat 1983;37(1983):152–5.

18. Knoop H, Stulemeijer M, Prins JB, van der Meer JWM, Bleijenberg G. Is cognitive behaviour therapy for chronic fatigue syndrome also effective for pain symptoms? Behav Res Ther 2007;45:2034–43.

7

The role of intelligence in Chronic Fatigue Syndrome

Sanne L. Nijhof*, Linde N. Nijhof*, Gijs Bleijenberg, Rebecca K. Stellato, Jan L.L. Kimpen, Hilleke E. Hulshoff Pol and Elise M. van de Putte

* Both authors contributed equally

Submitted

ABSTRACT

Objective

Chronic Fatigue Syndrome (CFS) is characterized by persistent fatigue and severe disability. Most adolescent patients report attention and concentration problems, with subsequent poor performance at school. This study investigated the impact of CFS on intellectual capacity by (1) assessing discrepancies between current intelligence quotient (IQ) and school level, and (2) exploring differences in current IQ and pre-CFS school performance, compared with healthy individuals.

Method

Current data was gathered cross-sectionally in a tertiary hospital setting and compared with retrospective school performance data. 59 CFS adolescents and 40 controls were evaluated on performance on age-appropriate intelligence tests and school level. Current IQ scores were compared with present school level at an average age of 15.8 years, and with cognitive achievement at the age of 12 as measured by a standardized school performance assessment (CITO test).

Results

Current IQ scores of CFS adolescents were lower than expected on the basis of their school level. Furthermore, there was a difference in intelligence performance across time when current IQ scores were compared with CITO test results assessed at primary school age. Healthy controls did not show any discrepancies between their IQ, school level and CITO score.

Conclusions

CFS may be accompanied by a (temporary) decline in general cognitive functioning. According to their initial (pre-CFS) intelligence assessments, CFS patients started with appropriate secondary school levels at the age of 12. Decrease in intellectual capacity seems to be a result rather than a cause of CFS. Given the critical age for intellectual development, we recommend a timely diagnosis followed by appropriate treatment of CFS in adolescents.

INTRODUCTION

Chronic fatigue syndrome (CFS) in adolescents is a disabling condition characterized by severe and unexplained fatigue lasting for more than six months, with long-term consequences for educational and social development.[1,2] The fatigue is accompanied by additional symptoms such as headaches, myalgia, multiple joint pain, unrefreshing sleep, and memory and concentration problems. Somatic and psychiatric illnesses must be excluded to meet the criteria for CFS.[3]

The prevalence of CFS in adolescents has been estimated at between 0.19-1.29% in community studies in the US and the UK[4–7] and at 0.11% in a recent Dutch epidemiological study among general practitioners and pediatricians,[8] with a female-to-male ratio varying from 2:1 up to 5:1.[4–8]

Both adult and adolescent CFS patients frequently report cognitive problems associated with a perceived change in intellectual abilities.[9] Memory and concentration problems are reported by respectively 89% of adults[10] and 80% of adolescents.[11] Several studies, mainly focused on adults, have described impaired cognitive performance by CFS patients on neuropsychological tests. These tests measured information-processing speed, memory, motor speed and executive functioning.[12] Reduced speed of complex information processing is the impairment most consistently found.[9,12–14]

Our clinical observations confirm that CFS adolescents experience a change in intellectual capacity with subsequent poor performance at school. This often leads to a drop in school level during the illness, with subsequent feelings of frustration. We are interested in determining whether these observations could be validated by intelligence tests prior to the onset of CFS and during CFS compared with healthy controls.

In contrast to memory and concentration problems in CFS patients, the intellectual capacity in adolescents with CFS has rarely been investigated. One study measured the discrepancy between actual and perceived intelligence quotient (IQ) by parents of adolescents with CFS compared to those of parents of healthy peers in a cross-sectional design.[15] Parental expectations of IQ were significantly higher than the actual IQ for children with CFS. The authors concluded that high parental expectations might contribute to the development of CFS and that high expectations may need to be addressed within the context of treatment. However, because of the cross-sectional study design, it remained unclear whether these discrepancies in IQ were causal factors or consequences of the disease.

We hypothesize that the deterioration of cognitive performance in adolescent CFS

is a consequence, rather than a cause of the illness. One way to address this issue is to examine whether IQ in pre-adolescence (pre-CFS) was similar in children later diagnosed with CFS in comparison with healthy children. In the Netherlands the intellectual performance of every child is assessed in the last year of primary school, at the age of 12. This assessment, the so-called CITO-test, highly correlates with IQ performance[16] and plays an important advisory role in the choice of secondary school education.[17] In the Netherlands everyone receives the same primary education from 6 to 12 years of age. Thereafter, depending on general performance and assessment of intellectual capacity measured by the CITO-test, a child follows one of three levels of secondary education (VMBO, HAVO and VWO, corresponding respectively to 'average', 'above average' and 'high' levels of attainment). The general availability of CITO-test scores makes it possible to compare current cross-sectional data with retrospective intelligence data.

The aim of the study is to investigate whether adolescents with CFS show a discrepancy between current IQ and school level, compared with healthy controls. Secondly, we investigated differences in intelligence measured at twelve years (in the pre-CFS period) between children with CFS and healthy controls.

METHODS

Design and population

In this study current IQ data were cross-sectionally gathered and compared with retrospective standardized school performance assessments (CITO). This longitudinal design was used to compare adolescents with CFS and healthy adolescents. Between August 2009 and February 2010 64 adolescents (12-18 years) participating in the FITNET (Fatigue in Teenagers on the InterNET) trial[18,19] were invited to participate in this neurocognitive study when attending their initial assessment at the University Medical Center Utrecht. Fifty-nine patients agreed to participate (92%). All patients complied with CDC-criteria for CFS diagnosis.[3]

As a reference group, participants from a former control group were re-invited between August 2009 and February 2010.[8] Adolescents with neurological abnormalities, chronic illnesses, or under treatment from a psychiatrist or psychologist were excluded from participation. Forty of 58 eligible healthy adolescents (69%) completed age-appropriate intelligence tests. In view of the demographic characteristics and fatigue levels, both the CFS-patients and controls were representative samples of former studies.[8,19]

Outcome measures

(1) Intelligence. All subjects completed age-appropriate versions of the Wechsler intelligence scales. Full-scale IQ was estimated from four subtests (picture completion, information, block design and vocabulary).[20–24] Cronbach's alpha for the short version is 0.91, while for the full test it is 0.95.[24]

(2) CITO. Cognitive abilities and educational achievement in primary school were assessed using the Dutch CITO elementary test (Centraal Instituut Toets Ontwikkeling, www.cito.com). The CITO consists of 240 multiple-choice items assessing four different intellectual skills: language; mathematics; information processing; and world orientation. Taken together the performance scales result in a standardized score between 501 and 550. This assessment is not a formal IQ test, but highly correlates with IQ performance (correlation of 0.63 between CITO and IQ assessed at age 12).[16] The test is usually administered on three consecutive days in January or February when the children are in the final grade of primary school, and approximately 12 years old. Copies of the official CITO reports were collected by email from the adolescents themselves or from teachers after informed consent was obtained. Forty-nine CFS patients and 34 healthy controls (83% resp. 85% response) supplied a copy of their official CITO scores. None of these adolescents had symptoms of CFS at the time of completing the CITO test.

Self-reported questionnaires

Questionnaires were used to assess fatigue, concentration problems, anxiety, depression, and achievement motivation. Participants were asked to fill out these questionnaires without assistance from their parent(s) or the researcher.

Fatigue and concentration problems were assessed using the self-report questionnaire Checklist Individual Strength (CIS-20), subscales 'fatigue severity' (8 items) and 'concentration problems' (5 items). The CIS-20 is a reliable assessment tool with excellent internal consistency (Cronbach's α 0.93) and discriminative validity for CFS.[25] Assessment of trait anxiety in adolescents was performed with a validated Dutch translation of the Spielberger State-Trait Anxiety Inventory for Children (STAIC).[26] The STAIC consists of 20 statements on a 3-point scale. Depression in adolescents was measured using a validated Dutch translation of the Children's Depression Inventory (CDI).[27] The CDI quantifies depressive symptoms from the past 2 weeks and consists of 27 items rated on a 3-point scale. Fear of failure was determined in the adolescents by means of the Achievement Motivation Test for Children (PMTK), a validated Dutch questionnaire that expresses performance pressure, negative fear of failure, positive fear of failure, socially desirable behavior, and combined fear of failure in deciles (1-10).[28]

Ethics

The medical ethics committee of the University Medical Center Utrecht approved the study. Written informed consent was obtained from all adolescents and parent(s).

Data analysis

All variables were tested for normality and if normality was confirmed, parametric statistics were used. Differences between groups were assessed using the independent sample t-test and χ2-test. We divided the school educational levels into three groups: Level 1 (VMBO; average), Level 2 (HAVO; above average) and Level 3 (VWO; high level).

A two-way ANOVA model was used to explore a possible discrepancy between IQ and school level for CFS patients and healthy controls; the dependent variable was the IQ score and the independent variables were the group (CFS yes/no), the current school level and their interaction.

To examine the effect of CFS on IQ while correcting for potential confounders, linear regression models with CFS (yes/no), age, gender, and initial school level were used. Statistical significance was assumed at $p<0.05$. Statistical analyses were performed using IBM SPSS Statistics 20.

RESULTS

Descriptive statistics

The baseline characteristics of the participating adolescents (59 CFS patients and 40 healthy controls) and those who did not want to participate (5 CFS patients and 18 healthy controls) did not differ (data not shown).

Table 1 compares the demographic characteristics of CFS patients with healthy adolescents. The median duration of illness in CFS-patients was 20.0 months. Girls predominated both groups, but were significantly overrepresented in the CFS group. Adolescents with CFS reported more fatigue and concentration problems than healthy controls. Also, anxiety and depression levels were higher in the CFS group. There was no difference in achievement motivation. There was no statistically significant difference between CFS patients and the controls regarding initial school level (first grade secondary school) and current school level (current grade). Notably, 9 of 59 CFS patients (15.3%) already switched to a lower educational level during the course of the disease. This is in contrast to healthy peers who remained at the same level, or switched to a higher (n=2) school level.

Before disease onset, the CFS patients and the healthy peers did not differ in CITO scores. In contrast, current IQ was 8 points lower for CFS patients than for their healthy peers. Performance IQ contributed most to this difference in IQ since patients performed significantly worse on performance IQ than controls, while no significant difference was found for verbal IQ.

Match between school level and intelligence level (IQ)

The mean IQ scores per school level for both groups are shown in Table 2. Adolescents with CFS had lower mean IQ scores than the controls at all school levels. The main effect of CFS was significant ($p = 0.005$), as was the main effect of school level ($p = 0.001$). There was no significant interaction between group (CFS yes/no) and school level ($p = 0.960$).

Table 3 shows the mean differences for CITO score and IQ after adjustment for initial school level, gender and age. There was an unadjusted difference of nearly 8 points in IQ score, which persisted after adjustment (mean difference -6.5; 95% CI: -10.9 - -2.1). No difference in CITO scores after adjustment was found between patients and controls. Also, adjustment for initial school level, gender, age, as well current IQ had no significant effect on estimated CITO test outcomes (mean difference -1.0; 95% CI: -3.7 - 1.8).

	CFS (SD)* n=59	Healthy (SD)* n=40	Mean Difference (95% CI)	p-value
Demographic characteristics				
Gender - % girls	78	55	-	0.026
Age at entry (years)	15.8 (1.5)	15.7 (0.5)	-0.2 (-0.6; 0.2)	0.394
Duration of CFS symptoms at entry (months)****	20.0 (17.0)	-	-	-
School absence - %	52.9 (33.0)	1.5 (2.8)	51.3 (42.7; 60.0)	<0.001
Fatigue assessment				
CIS-score severity of fatigue (8-56)	51.5 (4.4)	21.2 (9.9)	30.3 (26.9; 33.6)	<0.001
CIS-score concentration problems (5-35)	29.3 (5.6)	16.0 (6.2)	13.3 (10.9; 15.7)	<0.001
Psychological Adjustment				
Anxiety disposition (STAIC; 20 items; 20-60)	32.3 (7.7)	27.9 (6.6)	4.3 (1.3; 7.3)	0.005
Depression disposition (CDI; 27 items; 0-54)	11.4 (5.7)	5.8 (4.0)	5.6 (3.5; 7.6)	<0.001
Achievement motivation				
PMT-K need to perform	4.6 (2.5)	4.1 (2,4)	0.6 (-0.4; 1.6)	0.268
PMT-K negative fear of failure	4.4 (2.7)	3.9 (2.6)	0.5 (-0.6; 1.6)	0.377
Initial secondary school level				
Level 1 - %	28.8	22.5		
Level 2 - %	28.8	35.0		0.721
Level 3 - %	42.4	42.5		
Current secondary school level				
Level 1 - %	32.2	22.5		
Level 2 - %	37.3	30.0		0.223
Level 3 - %	30.5	47.5		
CITO score (501-550)**	540.4 (7.0)	541.0 (6.6)	-0.6 (-3.6;2.4)	0.705
Intelligence level				
Measured IQ score***	103.3 (11.4)	111.2 (11.0)	-8.0 (12.6;-3.3)	**0.001**
Performance IQ				
Block design, (1-18)	10.3 (2.5)	11.8 (2.2)	1.5 (0.6;2.5)	**0.002**
Picture completion, (1-18)	9.1 (2.9)	10.7 (2.1)	1.6 (0.5;2.7)	**0.005**
Verbal IQ				
Information, (1-19)	11.0 (2.8)	11.7 (3.0)	0.7 (-0.6;2.0)	0.268
Vocabulary, (1-19)	11.1 (2.2)	11.3 (2.2)	0.2 (-0.8;1.1)	0.728

* Values are means (SD) unless otherwise stated. ** Intelligence index at the last year of the primary school (12 years old). *** Estimated IQ measured by subtests. IQ: CFS n=59, Controls n=39 (1 participant incomplete due to illness). **** Median (IQR)
CI, confidence interval.

TABLE 1. Demographic features and intelligence assessments scores of adolescents with CFS and healthy adolescents.

Intelligence Quotient (IQ)*	Educational level 1 (VMBO)	n	Educational level 2 (HAVO)	n	Educational level 3 (VWO)	n
CFS	96.8 (8.6)	19	104.8 (9.2)	22	108.2 (13.5)	18
Controls *	104.1 (14.0)	8	110.5 (6.9)	12	114.7 (10.8)	19

Values are means (SD). There are significant differences between groups at all school levels, p=0.005.
* CFS n=59, Controls n=39 (1 participant incomplete due to illness).

TABLE 2. Mean IQ score by school level of adolescents with CFS compared with healthy peers

	CFS (SD)	Healthy (SD)	Adjusted Difference (95% CI)*	p-value
CITO score	540.4 (7.0)	541.0 (6.6)	-1.0 (-3.1;1.1)	0.329
Intelligence level				
Measured IQ score***	103.3 (11.4)	111.2 (11.0)	-6.5 (-10.9;-2.1)	**0.004**
Performance IQ				
Block design, (1-18)	10.3 (2.5)	11.8 (2.2)	-1.4 (-2.4;-0.4)	**0.006**
Picture completion, (1-18)	9.1 (2.9)	10.7 (2.1)	-1.3 (-2.5;-0.1)	**0.036**
Verbal IQ				
Information, (1-19)	11.0 (2.8)	11.7 (3.0)	-0.3(-1.5;1.0)	0.663
Vocabulary, 1-19)	11.1 (2.2)	11.3 (2.2)	-0.3(-1.2;0.7)	0.572

Values are means (SD) unless otherwise stated
* Adjusted for age, sex and initial school level. **Intelligence index at the last year of the primary school. ***Estimated IQ measured by subtests

TABLE 3. CITO scores and intelligence level after adjustment for age, gender and initial school level

IQ	Depression (CDI)	Anxiety (STAIC)	Negative fear of failure	School absence
CFS	r = -0.06 (p = 0.68)	r = 0,14 (p = 0.31)	r = -0.12 (p = 0.39)	r = 0.15 (p = 0.25)
Controls	r = -0.17 (p = 0.32)	r = -0.22 (p = 0.19)	r = -0.18 (p = 0.27)	r = 0.25 (p = 0.13)

TABLE 4. Pearson correlation between IQ and depression, anxiety, negative fear of failure, and school absence per group

Associations between IQ and depression, anxiety, negative fear of failure, and school absence. Table 4 contains Pearson's correlations between IQ and possible confounders for patients with CFS and healthy peers. All correlations were weak, and none was statistically significant.

DISCUSSION

Our study found an overall lower IQ in CFS adolescents compared to healthy controls with an equivalent school level. Furthermore, IQ scores were lower than expected as compared with their pre-CFS intellectual performance assessment (CITO) score at the age of 12. Performance IQ was particularly affected. Healthy controls did not show any discrepancies between their IQ, initial or current school level and their CITO score.

Our study has limitations. We used CITO-scores as a pre-illness proxy of IQ-scores, while the CITO-test is not a formal IQ-test. However, it highly correlates with IQ scores assessed at the age of 12.[16] Moreover, the unique setting in The Netherlands, with a general availability of CITO-test scores, makes it possible to compare current cross-sectional data with retrospective intelligence data. Also, the controls were comparable to patients in terms of age and school level, but not for gender. We adjusted for these differences in our analysis. Further studies are required to replicate our findings and to determine the generalizability of these findings.

A strong aspect of our study is the longitudinal design; by assessing pre-illness intellectual performance, we have two time points, enabling the determination of causality of lowered IQ in CFS adolescents. Another strength of our study was the high participation rate: 92% of the eligible CFS patients entered the study, thus reducing the risk of bias. Accurately diagnosing CFS is complex and requires exclusion of other illnesses that could cause similar complaints, but require different treatment. In the FITNET study, CFS was strictly diagnosed using the CDC criteria, in a tertiary academic hospital setting. Since referrals were obtained nationwide, and from various sources (general practitioners as well as pediatricians) we consider our study population representative of the Dutch CFS population at large.[19] The control group was recruited for a number of sub-studies of the FITNET study, thus not specifically for a neurocognitive assessment or intelligence test, also reducing the risk of selection bias. In addition, the demographic data indicate that both groups are similar in terms of mean school level and in mean CITO scores before the onset of CFS. We think reliable conclusions can be drawn from these data.

The role of IQ in adults and adolescents with CFS has not been well studied. Godfrey *et al.* (2009) studied IQ in CFS adolescents in a cross-sectional study design.[15] Taking into account differences in methodology, our study agrees with Godfrey's in that actual IQ in CFS adolescents does not match expectations, which in our study were based

on their present school level and pre-CFS school performance. Godfrey *et al.* showed that parents' expectations regarding the IQ of adolescents with CFS were significantly higher than those of healthy controls. They concluded that the high expectations of parents could contribute to the development of CFS. Our longitudinal results make it more plausible that these parents had realistic expectations about their children's intellectual potential, but that IQ was affected during the course of the disease.

Many explanations for the discrepancy in IQ can be postulated. Firstly, it could imply that CFS adolescents regularly had to perform higher than their predicted level, leading to the emergence of CFS. However, our longitudinal data do not support this possible explanation. According to their initial intelligence assessments, they started with appropriate secondary school levels.

Secondly, CFS is often accompanied by considerable school absence. The discrepancy between IQ and school level could be explained by the high level of school absence, which leads to reduced knowledge. However, an IQ test should be independent of school attendance, and in this study we observed no correlation between IQ and school absence in the CFS or in the control group. We therefore postulate that CFS affects IQ score independently of absence from school. Also, no correlations between IQ and fear of failure, anxiety or depression were found. These findings are in accordance with the results of Cockshell *et al.* (2010), who undertook a meta-analysis on the cognitive performance of adults (>16) with CFS compared with healthy controls. Problems in neuropsychological functioning were found to be unrelated to depression, fatigue or anxiety.[12] Thus, neither school absence nor psychological functioning seems to be an adequate explanation for our findings.

Thirdly, an impaired neuropsychological test performance could be inherent to CFS. Previous studies, mostly in adults, showed a diminished performance in information-processing speed and in tasks requiring working memory over a sustained period of time.[9,12-14,29] These findings could be related to fatigue and concentration problems itself. This could imply that patients do not truly have a lowered IQ but rather achieve a low score on subtests that require fast processing. The fact that performance intelligence is particularly diminished in our study would fit this premise. If this assumption is true, IQ scores should normalize after treatment of and recovery from CFS.

Finally at this point, we can speculate that there is a neurobiological explanation for the reduced IQ scores. Adolescence is a critical phase of brain development. A recent study by Ramsden *et al.* (2011) and colleagues showed that measured IQ can fluctuate in healthy adolescents during the teenage years, over and above normal development.[30] Moreover, these fluctuations were related to changes in local brain structures. This

implies, according to the authors, that an individual's strengths and weaknesses in skills relevant to education and employment are still emerging or changing in the teenage years. These findings raise the question of whether there are factors, such as stress or illness, that influence these within-subject changes in measured IQ and brain structures in adolescence. Both Shaw *et al.* (2006) and Brans *et al.* (2010) found that the level of intelligence is related to the pattern of cortical development or changes during childhood, adolescence and in young adulthood, primarily in the frontal regions.[31] Notably, the studied age period corresponds with those of our patients at the time of illness. These findings were also congruent with functional magnetic resonance imaging (fMRI) studies showing that activation of the lateral prefrontal cortex is common for a range of intelligence tests, and that the magnitude of frontal cortical activation correlates highly with intelligence.[32,33] Strikingly, de Lange *et al.* (2005) detected lower cortical grey matter volume in adult CFS compared with healthy controls.[34] Crucially, CFS patients showed a significant increase in grey matter volume, localized in the lateral prefrontal cortex after effective treatment with CBT.[35] This change in cerebral volume was also related to improvements in cognitive speed in the CFS patients. De Lange *et al.* conclude that cortical plasticity in the adult human brain is responsible for the change in cerebral volume, demonstrating a surprisingly dynamic relation between behavioral state and cerebral anatomy.

Given this last possibility, CFS may affect brain development in adolescence and thus have a possible causal relationship with a reduced IQ. This hypothesis emphasizes the need to recognize CFS quickly and to treat it adequately, especially in adolescents.

In conclusion, adolescent CFS may be accompanied by a (temporary) decline in general cognitive functioning. Given the critical age for intellectual development, we recommend a timely diagnosis followed by appropriate treatment. In addition, our findings suggest that adjustment of school level prior to treatment is probably not the best choice for CFS adolescents. A diminished IQ can be an effect of the illness, and test outcomes may be unreliable in indicating which factors are prominent in causing reduced school performance. Follow-up research should reveal whether reduced performance on an IQ test is reversible after adequate CFS treatment and address its neurobiological and morphological explanations.

REFERENCES

1. Crawley E, Sterne JA. Association between school absence and physical function in paediatric chronic fatigue syndrome/myalgic encephalopathy. Arch Dis Child 2009; 94(10): 752-6.

2. Marshall GS. Report of a workshop on the epidemiology, natural history, and pathogenesis of chronic fatigue syndrome in adolescents. J Pediatr 1999; 134(4): 395-405.

3. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994; 121(12): 953-9.

4. Chalder T, Goodman R, Wessely S, Hotopf M, Meltzer H. Epidemiology of chronic fatigue syndrome and self reported myalgic encephalomyelitis in 5-15 year olds: cross sectional study. BMJ 2003; 327(7416): 654-5.

5. Farmer A, Fowler T, Scourfield J, Thapar A. Prevalence of chronic disabling fatigue in children and adolescents. Br J Psychiatry 2004; 184: 477-81.

6. Jones JF, Nisenbaum R, Solomon L, Reyes M, Reeves WC. Chronic fatigue syndrome and other fatiguing illnesses in adolescents: a population-based study. J Adolesc Health 2004; 35(1): 34-40.

7. Rimes KA, Goodman R, Hotopf M, Wessely S, Meltzer H, Chalder T. Incidence, prognosis, and risk factors for fatigue and chronic fatigue syndrome in adolescents: a prospective community study. Pediatrics 2007; 119(3): e603-9.

8. Nijhof SL, Maijer K, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Adolescent Chronic Fatigue Syndrome: Prevalence, Incidence, and Morbidity. Pediatrics 2011; 127: e1169-75.

9. Michiels V, Cluydts R. Neuropsychological functioning in chronic fatigue syndrome: a review. Acta Psychiatr Scand 2001; 103(2): 84-93.

10. Jason LA, Richman JA, Rademaker AW, *et al.* A community-based study of chronic fatigue syndrome. Arch Intern Med 1999; 159(18): 2129-37.

11. Davies S, Crawley E. Chronic fatigue syndrome in children aged 11 years

old and younger. Arch Dis Child 2008; 93(5): 419-21.

12. Cockshell SJ, Mathias JL. Cognitive functioning in chronic fatigue syndrome: a meta-analysis. Psychol Med 2010; : 1-15.

13. Moss-Morris R, Petrie KJ, Large RG, Kydd RR. Neuropsychological deficits in chronic fatigue syndrome: artifact or reality? J Neurol Neurosurg Psychiatry 1996; 60(5): 474-7.

14. Tiersky LA, Johnson SK, Lange G, Natelson BH, DeLuca J. Neuropsychology of chronic fatigue syndrome: a critical review. J Clin Exp Neuropsychol 1997; 19(4): 560-86.

15. Godfrey E, Cleare A, Coddington A, Roberts A, Weinman J, Chalder T. Chronic fatigue syndrome in adolescents: do parental expectations of their child's intellectual ability match the child's ability? J Psychosom Res 2009; 67(2): 165-8.

16. Bartels M, Rietveld MJ, Van Baal GC, Boomsma DI. Heritability of educational achievement in 12-year-olds and the overlap with cognitive ability. Twin Res 2002; 5(6): 544-53.

17. Polderman TJ, Bartels M, Verhulst FC, Huizink AC, van Beijsterveldt CE, Boomsma DI. No effect of classroom sharing on educational achievement in twins: a prospective, longitudinal cohort study. J Epidemiol Community Health 2010; 64(1): 36-40.

18. Nijhof SL, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Fatigue In Teenagers on the interNET--the FITNET Trial. A randomized clinical trial of web-based cognitive behavioural therapy for adolescents with chronic fatigue syndrome: study protocol. [ISRCTN59878666. BMC Neurol 2011; 11: 23,2377-11-23.

19. Nijhof SL, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. Lancet 2012; 379(9824): 1412-8.

20. Kulas JF, Axelrod BN. Comparison of seven-subtest and Satz-Mogel short forms of the WAIS-III. J Clin Psychol 2002; 58(7): 773-82. doi:10.1002/jclp.2009.

21. Shaw P, Greenstein D, Lerch J, *et al.* Intellectual ability and cortical development in children and adolescents. Nature 2006; 440(7084): 676-9. doi:10.1038/nature04513.

22. Sattler JM. Assessment of children: Cognitive applications (4th ed.). (2001).Assessment of children: Cognitive applications (4th ed.).xxvii, 931 pp.La Mesa, CA, US: Jerome M Sattler Publisher; US 2001.

23. Schrimsher GW, O'Bryant SE, O'Jile JR, Sutker PB. Comparison of tetradic WAIS-III short forms in predicting Full Scale IQ scores in neuropsychiatric clinic settings. Journal of Psychopathology and Behavioral Assessment 2008; 30(3): 235-40.

24. Gregoire J. Comparison of three short forms of the Wechsler Intelligence Scale for Children - third edition (WISC-III). European Review of Applied Psychology/ Revue Europeenne de Psychologie Appliquee 2000; 50(4): 437-41.

25. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38(5): 383-92.

26. Papay JP, Spielberger CD. Assessment of anxiety and achievement in kindergarten and first- and second-grade children. J Abnorm Child Psychol 1986; 14(2): 279-86.

27. Kovacs M. The Children's Depression, Inventory (CDI). Psychopharmacol Bull 1985; 21(4): 995-8.

28. Hermans HJ. A questionnaire measure of achievement motivation. J Appl Psychol 1970; 54(4): 353-63.

29. Cho HJ, Skowera A, Cleare A, Wessely S. Chronic fatigue syndrome: an update focusing on phenomenology and pathophysiology. Curr Opin Psychiatry 2006; 19(1): 67-73.

30. Ramsden S, Richardson FM, Josse G, *et al.* Verbal and non-verbal intelligence changes in the teenage brain. Nature 2011; 479(7371): 113-6.

31. Brans RG, Kahn RS, Schnack HG, *et al.* Brain plasticity and intellectual ability are influenced by shared genes. J Neurosci 2010; 30(16): 5519-24. 32. Gray JR, Chabris CF, Braver TS. Neural mechanisms of general fluid intelligence. Nat Neurosci 2003; 6(3): 316-22.

32. Duncan J, Seitz RJ, Kolodny J, *et al.* A neural basis for general intelligence. Science 2000; 289(5478): 457-60.

33. de Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JW, Toni I. Gray matter volume reduction in the chronic fatigue syndrome. Neuroimage 2005; 26(3): 777-81.

34. de Lange FP, Koers A, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JW, Toni I. Increase in prefrontal cortical volume following cognitive behavioural therapy in patients with chronic fatigue syndrome. Brain 2008; 131(Pt 8): 2172-80.

8

The role of hypocortisolism in Chronic Fatigue Syndrome

Sanne L. Nijhof, Juliette M.T.M. Rutten, Cuno S.P.M. Uiterwaal,
Gijs Bleijenberg, Jan L.L. Kimpen and Elise M. van de Putte

Submitted

ABSTRACT

Background

There is accumulating evidence of hypothalamic-pituitary-adrenal (HPA) axis disturbances in chronic fatigue syndrome (CFS). The clinical significance of this dysfunction however remains unclear. The objective of the current study was to assess the role of the HPA-axis in recovery from adolescent CFS. Additionally, factors which influence the association between HPA-axis dysfunction and CFS in adolescents, were identified.

Method

Salivary cortisol awakening response before and after treatment was measured in 118 adolescent patients diagnosed with CFS. At baseline, we compared CFS patients with a reference group of 39 healthy peers.

Results

Cortisol levels at baseline were significantly lower in CFS-patients than in healthy controls. After 6 months of treatment recovered patients had a significant rise in salivary cortisol output attaining normalization, whereas non-recovered patients improved slightly, but not significantly. The hypocortisolism found in CFS-patients was significantly correlated to the amount of sleep. Logistic regression analysis showed that one standard deviation higher change in the cortisol awakening response after treatment was significantly associated with a higher chance of recovery (adjusted OR 1.93 (1.12 -3.33), p=0.018). Baseline hypocortisolism was not associated with recovery.

Conclusions

Hypocortisolism is associated with adolescent CFS. It is not baseline cortisol but its change to normalization that predicts treatment success. We suggest that this finding may have clinical implications with regard to treatment possibilities.

BACKGROUND

Chronic fatigue syndrome (CFS) is characterized by unexplained persistent or relapsing disabling fatigue that lasts for at least 6 months and is accompanied by at least four out of eight possible symptoms (memory or concentration problems, sore throat, tender lymph nodes, muscle pain, multiple joint pain, headache, unrefreshing sleep, postexertional malaise).[1] CFS is found in adolescents as well as in adults. Its primary adverse impact in adolescents is extreme disability, associated with considerable school absence.[2]

Despite substantial research, a biological substrate for this syndrome has not yet been established. It is considered to be a multifactorial condition in which biological, psychological and social factors play a predisposing, precipitating or perpetuating role.

The most replicated biological finding in adult CFS-patients is a hypofunction of the hypothalamic-pituitary-adrenal (HPA)-axis, manifested in a low salivary cortisol awakening response (CAR).[3] The role of this hypofunction however remains unclear. It is not known whether this is a relevant biological factor in the aetiology of CFS. It has been hypothesized that lowered cortisol occurs, in part, secondarily to aspects of CFS such as disturbed sleep, inactivity or stress.[3,4] To date, hypocortisolism has been consistently shown in adult CFS-patients,[3–6] but it has not been longitudinally studied in adolescents with CFS.

In adolescents, CFS has to be identified and treated as soon as possible, regarding the risk of developmental and educational disturbances.[2,7] Cognitive behavioural therapy (CBT) is one of the most successful treatments for adolescents with CFS.[8–10] Perpetuating factors such as fatigue-related cognitions and behaviour, are addressed by CBT. However, not all patients suffering from CFS respond to CBT. It is of paramount importance to differentiate between responders and non-responders as early as possible in order to change content, duration, or choice of treatment.

The factors that influence treatment outcomes in adolescent CFS are largely unknown. In previous studies, a number of patient and parental factors have been revealed to be associated with an unfavourable outcome after treatment.[11-14] Most consistent factors are age at inclusion,[11] disease duration before start of treatment,[14] and maternal focus on fatigue or bodily symptoms.[12–14]

In adults, one study showed an association between HPA-axis hypofunction and a poor response to CBT,[15] suggesting that hypocortisolism could be a factor in the persistence of CFS.

No studies so far have looked at whether the amount of change in HPA-axis disturbances after treatment is related to recovery from CFS in adolescents. We hypothesized that HPA-axis hypofunction is a relevant biological factor in adolescent CFS, and that a subsequent association exists between recovery from CFS and a change in cortisol levels after treatment.

The primary aim of our study was to examine whether HPA-axis function, as measured with respect to differences in salivary cortisol response to awakening before and after treatment, is related to (recovery from) CFS. Additionally, we aimed to identify factors which influence the association between HPA-axis dysfunction and CFS in adolescents, including gender, medication use, co-morbid depressive disorder, sleep and physical activity.

METHODS

Subjects

One hundred and twenty-three adolescents (12-18 years) diagnosed with CFS participating in the FITNET (Fatigue In Teenagers on the interNET) trial[10,16] were invited to participate in this longitudinal study on cortisol between March, 2008 and February, 2010. 118 (96%) patients agreed to participate. They all complied with CDC-criteria for CFS diagnosis.[1] FITNET, an internet-based CBT program for adolescents with CFS, was developed as an alternative to face-to-face CBT.[10,16] A detailed description of the FITNET study protocol, methodology, and program has been reported elsewhere.[10,16] In the original trial, all patients were randomly assigned to either FITNET or usual care (T=0). Participants were reassessed after 6 months of treatment (T=1).

As a reference group, participants from a former control group were re-invited between March 2009 and February 2010.[2] Adolescents with neurological abnormalities, chronic illnesses, or under treatment by a psychiatrist of psychologist were excluded from participation. Thirty-nine of 58 eligible healthy adolescents (67%) completed the saliva-sampling protocol. In view of the demographic characteristics and fatigue levels, both the CFS-patients and controls were representative samples of former studies.[2,10]

The medical ethics committee of the University Medical Centre Utrecht (UMCU) approved this study. Written informed consent was obtained from the adolescents and their parent(s).

Questionnaires

Questionnaires were used to assess baseline characteristics and recovery from CFS after treatment.[10,16] Participants were asked to fill out these questionnaires without assistance from their parent(s) or the researcher. Length of illness was derived from the paediatrician's history.

Fatigue was assessed using the Checklist Individual Strength (CIS-20), subscale 'fatigue severity' (range 8-56). The CIS-20 has excellent internal consistency (Cronbach's α 0.93) and discriminative validity for CFS.[17] Physical functioning was measured using the Child Health Questionnaire (CHQ-CF87), subscale 'physical functioning' (range 0-100%). This scale has been validated as having a good internal consistency (Cronbach's α=0.86).[18] Actual physical activity was measured by an actometer: a motion-sensing device attached to the ankle and worn continuously for 12 days.[19] The mean hours of sleep registered by the actometer were used to assess the sleeping pattern. During these twelve days, school attendance was registered and calculated as the proportion

of classes attended, expressed as a percentage of the normal school schedule.[10]

Depression in adolescents was measured at baseline with a validated Dutch translation of the Children's Depression Inventory (CDI).[20] Cronbach's α reliability coefficients range from 0.71 to 0.89. Finally, 'self-rated improvement' (SRI) was measured at T=1 using a 4-item tool in which patients indicate whether they have completely recovered, feel much better, have the same complaints or have become worse compared to the previous measurement.[10]

Cortisol-sampling procedure and assay

The circadian rhythm of the HPA-axis develops within the first three to four years of life. After this period of time it reaches an adult, diurnal rhythm with the highest levels of cortisol in the morning and the lowest during the night.[21] Awakening is a mild physiological stressor for the HPA-axis, resulting in a rapid increase in cortisol, referred to as the cortisol awakening response (CAR).[22] The CAR is indicative of the HPA-axis responsivity.[23]

Measurement of salivary cortisol in children has been standard practice for more than 20 years. It is a non-invasive technique allowing cortisol to be measured without possible interference with the stress of intravenous cannulation and hospital attendance.[21]

Saliva was collected at home using the Salivette® sampling device (Sarstedt BV, The Netherlands). Participants were instructed to chew gently on sterile cotton wool swabs immediately after spontaneously awakening, and 15, 30 and 60 minutes thereafter while still lying in bed.[24,25] They were asked to sample on a weekday. During collection, subjects were instructed not to touch the samples with their hands. They were not allowed to brush their teeth, nor to eat or drink, except for water, during the sampling period. Furthermore, if possible, they were requested not to take any medication during the week before testing and were asked not to collect saliva when they were ill. Participants reported bedtimes and exact times of saliva collection. The CAR is sensitive to confounding factors, such as use of oral contraceptive, BMI, smoking, physical activity, and sleep-related factors.[23,26–28] Therefore, these factors were registered in order to check for potential influence on endocrine functioning.

Samples were stored in the refrigerator immediately after collection. Within two weeks they were returned to the laboratory of the UMCU, where they were stored at -20°C and analysed using a time-resolved immunoassay with fluorescence detection (DELFIA), with all intra-individual samples in the same batch. Cortisol is stable enough to endure these temperature shifts.[29]

Laboratory personnel were blinded to the clinical status of the subject and the study

design. The lower limit of detection was 1.0 nmol/L. Intra- and inter-assay variations were 4% and 5-9% respectively. Reference values for cortisol used by the endocrinological laboratory were 9-29 nmol/L for cortisol collected in the morning.

Statistical analyses

Subjects with a negative slope in cortisol concentration were excluded from analysis because a negative slope indicates that the samples were taken *after* the initial physiological rise in cortisol.[25] At T=0, ten (8.5%) patients and one healthy control showed a negative slope (2.6%). At T=1, five patients (4.5%) were for the same reason excluded from analysis.

If a cortisol measurement was missing, we imputed this missing value (19 missed sample points, 1.4%). No participant missed more than one individual cortisol measurement. With the assumption of randomly missing values, we applied the following imputation method: the mean cortisol levels of all participants at the five individual measuring points (0, 15, 30, 60 minutes after awakening) were calculated. Secondly, the degree of increase (percentage) in cortisol level between two measuring points (e.g. between 0 and 15 minutes after awakening, etc.) was calculated. This percentage of increase was then applied to the individual participant to calculate the missing value. This method was used to take into account the inter-individual differences in cortisol output.

All variables were tested for normality and if normality was confirmed, parametric statistics were applied. Differences between groups at the same moment of measuring were assessed by using the independent Student's t-test and χ2-test. Differences within groups at different points of measurement were tested using a paired-samples t-test.

Group analyses at T=1 were performed on the basis of whether the adolescents had recovered (yes/no) from CFS at the 6-month follow-up. Recovery from CFS was defined in accordance with the FITNET trial as a combination of fatigue scores (CIS-20 fatigue scale <40), physical functioning (CHQ physical functioning scale ≥85%), school attendance within normal limits (>90%), and whether the patient rates him- or herself as having recovered (SRI: "I have completely recovered" or "I feel much better").[10,16]

The primary outcome variable was the total cortisol response to awakening (nmol/L per hour), measured as the integrated area under the curve with respect to the ground (AUC_G). The trapezoidal method was used to calculate the AUC_G.[30,31] In addition, to analyse the effect of HPA-axis functionality on recovery, we calculated the change in the AUC_G after treatment (i.e. pre-treatment values subtracted from post-treatment values) and performed logistic regression with recovery (yes/no) as a dependent variable. Change in AUC_G (Δ AUC_G T1-T0) and AUC_G at baseline were entered as independent

variables. Data were expressed as absolute measures in nmol/L and z-scores.

Finally, to look for possible confounders in the relation of recovery and the AUC_G, we analysed differences at baseline of possible confounders based upon predefining the responsiveness of the HPA axis in 'low' or 'high'. The median of change in AUC_G was used as the cut-off point (96.8 nmol/L). To analyse the strength of linear dependence between AUC_G, clinical features and possible confounders, Pearson's correlation coefficients for all individual variables were determined (see appendix). We corrected for possible confounders, i.e. age and gender, in multiple regression analyses using the enter method. The significance level for all group comparisons was set at $p \leq 0.05$. Statistical analyses were performed using IBM SPSS Statistics 20.

RESULTS

Comparison of patients and controls

One hundred and twenty-three adolescents of the FITNET trial were invited to participate in cortisol sampling, of whom 118 (96%) agreed to participate. At follow-up (T=1) saliva specimens of 112 (95%) participants were obtained. After exclusion of cases with a negative slope, respectively 108 CFS-patients and 38 controls were included in the cortisol analyses at T=0, and 107 CFS-patients at T=1. Overall, 43 of these patients were recovered at T=1; 5 (9%) assigned to usual care and 38 (62%) assigned to FITNET. The baseline characteristics of excluded participants from analyses, did not differ from those who adhered to the study schedule.

The median duration of illness in CFS-patients was 16.5 months. CFS-patients reported significantly ($p < 0.01$) more fatigue (51.4 ± 4.3 vs. 20.5 ± 10.2), physical disabilities (59.0% ±16.7 vs. 96.0% ± 6.9), and school absence (56.7% ±31.1 vs. 1.2% ±3.8) than healthy controls. Details of patients and controls at baseline are shown in Table 1. Also, baseline characteristics of recovered vs. non-recovered patients, as well as both cortisol measurements, are shown in Table 1.

Medication use was significantly higher in the CFS group (50.4% vs. 21.6%), which is mostly attributable to the difference in gender and subsequent difference in contraceptive use. Within the group of CFS-patients using medication, 30 used oral contraceptives, 3 non-systemic corticosteroids (inhalation or cream), and 26 used other medication, such as paracetamol or melatonin (n=2). Within the control group 1 adolescent used other medication (paracetamol), the others contraceptives (n=8).

CFS-patients had significantly lower cortisol levels than healthy controls at 0, 15 and 30 minutes after awakening (Figure 1), resulting in a significantly lower AUCG (756.7 ±200.4 vs. 912.0 ±241.9, mean difference (95% CI): -155.3 (– 242.9, -67.7), $p = 0.001$). There were no significant differences between recovered and non-recovered patients at baseline (AUC_G: 749.3 ±174.3 vs. 761.9 ±218.0, mean difference (95% CI): -12.6 (– 89.0, 63.8), $p = 0.744$).

Recovered patients at T=1 showed significantly increased cortisol levels compared to baseline (AUC_G: mean difference (95% CI): 175.0 (98.1 – 251.8), $p < 0.001$) as well as compared to non-recovered patients at T=1 (AUC_G: mean difference (95% CI): 98.3 (6.3 – 190.3), $p = 0.037$), resulting in an improvement of the AUC_G of recovered patients to 'normal' levels (Figure 1 and Table 1). In contrast, cortisol levels of non-recovered

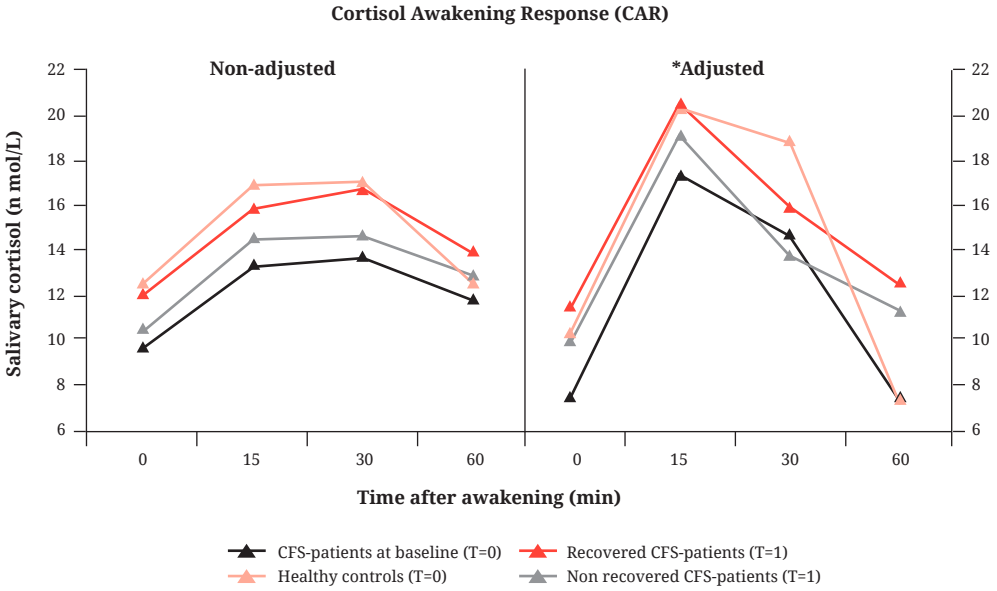
	Healthy controls (n=39)	CFS-patients T=0 (n=118)	p-value	Recovered CFS-patients T=0 (n=43)	Non-recovered CFS-patients T=0 (n=69)	p-value
Cortisol levels (nmol/L)						
AUC_G T=0 [a]	912.0 (241.9)	756.7 (200.4)	**0.001***	749.3 (174.3)	761.9 (218.0)	0.744*
AUC_G T=1 [a]	-	-	-	918.0 (235.8)	819.7 (227.5)	**0.037***
Characteristics						
Age (years) [a]	15.2 (0.5)	15.8 (1.4)	**0.005***	15.8 (1.4)	15.9 (1.4)	0.823*
Girls [b]	64.1	79.7	0.055**	72.1	84.5	0.148**
BMI (kg/m2) [a]	20.3 (2.9)	21.0 (2.8)	0.246*	21.3 (2.5)	20.8 (2.9)	0.364*
Illness duration (months) [c]	-	16.5 (11.0)	-	14.0 (9.0)	20.0 (11.0)	**0.013***
Psychopathology						
Depression [a]	6.1 (5.5)	11.3 (5.3)	< **0.001***	11.4 (4.8)	11.2 (5.5)	0.823*
Activity and sleep characteristics						
Physical activity [a]	85.4 (18.9)	62.7 (16.7)	< **0.001***	62.6 (11.5)	63.2 (19.4)	0.837*
Sleep during 2 weeks [a]	8h48 (0h33)	9h48 (1h14)	**0.001***	9h39 (1h05)	9h52 (1h19)	0.363*
Sleep duration before CAR [a]	8h46 (1h33)	9h26 (1h45)	**0.036***	9h30 (1h48)	9h24 (1h46)	0.781*
Awakening time [a]	8h43 (1h20)	8h43 (1h25)	**0.970***	8h39 (1h29)	8h47 (1h23)	0.666*
Bed time [a]	22h53 (0h46)	22h15 (1h33)	**0.001***	22h06 (2h02)	22h22 (1h13)	0.445*
Sample characteristics						
Medication use [b]	21.6	50.4	**0.002****	48.8	50.0	1.000**
Oral contraceptives (% of girls) [b]	28.0	40.9	0.345**	45.2	37.3	0.460**
Smoking [b]	2.8	2.6	1.000**	2.3	2.9	1.000**

[a] mean (SD) [b] percentage [c] Median (IQR) BMI= Body Mass Index
Depression score as measured with CDI score, physical activity as measured with an actometer, sleep during 2 weeks and before CAR in hours
* independent student t-test/ Mann-Whitney U-test
** χ2-test/ Fisher's Exact test

TABLE 1. Baseline characteristics and cortisol levels of healthy controls and CFS-patients

patients at T=1 improved slightly but not significantly; AUC_G: MD (95% CI): 47.2 (-13.6 – 108.0), p =0.123.

Additional adjustment for the possible confounders, age, gender, BMI, depression score, sleep duration, and activity level (actometer), had no effect on the results (data shown in Figure 1).



*Adjusted for gender, age, BMI, depression score, sleep duration and physical activity (actometer)

FIGURE 1. Cortisol Awakening Response in CFS patients and healthy controls at baseline (T=0), as well as in recovered and non-recovered patients at T=1.

Relation between cortisol dysfunction, possible confounders and outcome

CFS was significantly associated with a lower AUC_G at T=0 (β =-.31, $p < 0.001$). Age and gender did not explain this group effect (data not shown).

We examined associations between AUC_G and possible confounders for patients with CFS and healthy peers (see appendix). Longer sleep duration was significantly associated with a lower AUC_G (r= -.283, p =0.002), but adding sleep duration into the regression model did not materially change our findings. Notably, there were significant correlations between AUC_G and clinical features of CFS (fatigue, physical disabilities, and school absence), suggesting that lower cortisol was associated with higher levels of fatigue and disability.

There were no significant differences in any of the possible confounders between patients with less or more than 96.8 nmol/L difference in AUC_G at baseline (Table 2). Pre-treatment disease duration was significantly different between recovered and non-recovered patients at baseline (p=0.013, Table 1), but this was not reflected in changes in cortisol measurements after treatment. Treatment modality (FITNET vs. usual care) did not significantly affect the results.

	<Δ 96.8 nmol/L (n=49)	> Δ 96.8 nmol/L (n=50)	p-value
Age (years) [a]	15.6 (1.5)	16.0 (1.3)	0.172*
Girls [b]	75.5	78.0	0.815**
BMI (kg/m2) [a]	20.8 (3.0)	21.1 (2.4)	0.604*
Illness duration (months) [c]	21.6 (15.5)	24.0 (21.8)	0.534*
Randomization to FitNet at T0 [b]	49.0	56.0	0.548**
Activity and sleep characteristics			
Physical activity (actometer)[a]	61.5 (17.1)	64.7 (16.6)	0.357*
Δ Physical activity [a]	4.3 (16.9)	6.3 (14.5)	0.548*
Sleep during 2 weeks [a]	9h45 (1h20)	9h50 (1h05)	0.697*
Δ sleep during 2 weeks [a]	-0h29 (1h00)	-0h23 (1h15)	0.711*
Sleep duration before CAR [a]	9h23 (1h31)	9h46 (1h44)	0.236*
Δ sleep duration before CAR [a]	0h07 (1h38)	-0h11 (1h51)	0.403*
Sample characteristics			
Medication use [b]	45.8	54.0	0.545**
Oral contraceptives (% of girls) [b]	36.1	43.6	0.638**

[a] mean (SD) [b] percentage [c] Median (IQR) BMI= Body Mass Index
Depression score as measured with CDI score, physical activity as measured with an actometer, sleep during 2 weeks and before CAR in hours
* independent student t-test/ Mann-Whitney U-test ** χ2-test/ Fisher's Exact test

TABLE 2. Baseline characteristics of CFS-patients at T=0 represented in relation to the change in HPA-axis function

	Non-adjusted OR (95% CI)	p-value	Adjusted* OR (95% CI)	p-value
Δ AUC_G **	1.81 (1.13 - 2.90)	0.014	1.93 (1.12 - 3.33)	0.018
AUC_G at baseline **	1.00 (0.99 – 1.00)	0.753	1.00 (0.99 – 1.00)	0.802

OR = Odds Ratio, Δ: difference T1-T0
*Adjusted for age, gender, BMI, pre-treatment disease duration, difference in activity level between T1 and T0, and difference in hours of sleep between T1 and T0
** Data of AUC_G (absolute measures in nmol/L) were expressed as z-scores

TABLE 3. Relation of AUC_G to recovery

Table 3 shows that the change in HPA-axis function (Δ AUC_G T1-T0) was significantly associated with recovery, indicating that patients with a smaller change in cortisol levels after treatment showed a greater risk of non-recovery. Correction for all possible confounders did not materially change this finding.

There was no differential effect apparent in salivary cortisol measures at baseline between recovered or non-recovered adolescents (Table 1), corresponding to the finding that AUC_G at baseline was not a significant predictor of recovery (Table 2).

DISCUSSION

This study is the first in which HPA-axis functioning was assessed in a large group of adolescents with CFS, compared to healthy peers, with a 6-month follow-up. The data support our hypothesis that a normalization in HPA-axis function is associated with recovery of adolescent CFS. We identified a mild hypofunction of the HPA-axis at CFS diagnosis compared to healthy peers, manifesting itself in a significantly impaired salivary cortisol awakening response. This initial hypocortisolism was significantly reversed after recovery from CFS, whereas non-recovered adolescents had a persistent hypocortisolism. Furthermore, we found significant correlations between hypocortisolism and clinical features of CFS (fatigue, physical disabilities, and school absence), suggesting that lower cortisol was associated with the primary symptoms of CFS. Cortisol levels at baseline did not predict recovery. Hypocortisolism may thus represent an aspect of the illness, disappearing with its recovery.

Although the amount of sleep was significantly associated with hypocortisolism, we were not able to identify 'disease-behaviour' or pre-treatment variables as potential confounders of the association between HPA-axis dysfunction and CFS in adolescents. Pre-treatment disease duration differed significantly between recovered and non-recovered patients. However, there was no relationship between pre-treatment disease duration and the change in HPA-axis function after treatment, suggesting that disease duration is a predictor of recovery but has no influence on HPA-axis function.

Our study has limitations. The HPA-axis does not function in isolation, but interacts with other systems in the body, such as other parts of the central nervous system.[32,33] Because we studied cortisol output in response to awakening, we examined one part of the HPA-axis and should take this into account when interpreting the results of this study. Assessing awakening cortisol levels however has been accepted as a good indication of the functioning of the HPA-axis.[21,23] The fact that we only sampled on one day, instead of two or more consecutive days, might be considered a limitation.[34] However, it has been shown that the cortisol awakening response is stable over time, on both intra- and inter-individual levels.[23,24]

An evident strength of this study is the sample size of CFS-patients, which is large, relative to other studies.[3]

In our longitudinal study we have assessed all possible confounders simultaneously. The meta-analysis by Tak *et al.* suggests a multifactorial model of HPA axis dysfunction

in CFS in which levels of physical activity, presence of depression and use of medication did moderate the findings of low cortisol. Nevertheless, most studies have not assessed all these factors simultaneously; consequently, the degree to which factors affect the HPA axis remains unclear.[3] Other advantages of our study include a non-stressful method of assessing a biologically active hormone, and because patients acted as their own controls before and after treatment we excluded inter-individual factors that might complicate comparisons of HPA-axis assessments.

Our results concerning salivary hypocortisolism are in line with studies in adult CFS where hypocortisolism has consistently been demonstrated.[3,5] Our finding that a lower AUC_G was significantly associated with more hours of sleep the night prior to sampling, is in agreement with prior studies, except one[35] showing that cortisol increases when the amount of sleep decreases.[6,23,36] Also, the reversion of initial hypocortisolism, which could be attributed to recovery from CFS, is in concordance with a normalization in cortisol levels that has been shown after CBT in one study with adult CFS-patients.[37]

We could not confirm that CFS-patients with a more dysregulated HPA-axis at baseline, e.g. with lower levels of cortisol, responded less to treatment, as the adult study of Roberts *et al.* suggested.[15]

Instead, our data shows that normalization of cortisol levels predicts treatment success. This suggests that hypofunction of the HPA-axis in patients with CFS might be part of the symptom complex. This is consistent with the finding that HPA-axis hypofunction is associated not only with the diagnosis CFS but also with the clinical features of CFS. This supports the hypothesis that the HPA-axis disturbances develop as part of the CFS symptom complex rather than being of particular etiological significance.

In our study HPA-axis hypofunction is not explained by behavioural symptoms such as disturbed sleep pattern and physical activity. This HPA-axis hypofunction solely as a secondary response to the illness and its associated behaviour is therefore unlikely. Alternatively, low cortisol could represent an epiphenomenon of the illness, or a nonspecific response to a chronic illness.[38,39]

Regardless of whether disruption of the HPA axis is primary or secondary, a greater understanding of the complexities of CFS is gained from understanding the mechanisms by which HPA-axis changes occur. This knowledge could improve the treatment of CFS. CBT is the current mainstay of treatment of adolescent CFS, but not all patients recover. Identifying the individuals with a lower chance of treatment success is important,

since a delay in recovery has a severe impact on social and educational development. Assessing hypocortisolism at baseline did not identify these patients. More importantly, the change in hypocortisolism seemed to be a predictor of recovery. These findings emphasize that assessing HPA-axis functioning *during* treatment could earlier identify those likely not to recover. Cortisol might serve as a 'biomarker' for treatment success.

It has previously been demonstrated that cortisol-replacement therapy can lead to a significant, temporary, improvement of fatigue, disability and other features of CFS in adults.[40,41] However, it is not recommended as a treatment of choice in CFS, due to the observation that only a minority of patients gain benefit, and the long-term effects of cortisol-replacement are unknown. It is possible that only a subgroup of patients benefit.

Future research could be aimed at assessing HPA-axis function during therapy, and the subsequent role of additional low-dose hydrocortisone to enhance CBT effectiveness.

APPENDIX

	AUC_G	Age	Gender	BMI	Duration	CDI	CIS	CHQ	School	Acto	Sleep I	Sleep II	Medicati
AUC_G	NA	.02	.04	.02	.07	-.06	-.26**	.24**	.21**	.06	-.21*	-.28**	-.07
Age	.02	NA	.06	.15	.33**	.16	.19*	-.16*	.18*	-.20*	.08	.06	-.01
Gender	.04	.06	NA	.13	.01	.22**	.21**	-.23**	-.05	-.11	-.02	-.03	-.07
BMI	.02	.15	.13	NA	.02	.25**	.14	.01	-.03	-.05	-.11	-.15	.01
Duration	.07	.33**	.01	.02	NA	-.02	-.24*	.00	.09	-.11	-.04	-.11	.14
CDI	-.06	.16	.22**	.25**	-.02	NA	.46**	-.41**	.31**	-.17*	.00	.07	.10
CIS	-.26**	.19*	.21**	.14	-.24*	.46**	NA	-.76**	.60**	-.46**	-.25**	.09	.20*
CHQ	.24**	-.16*	-.23**	.01	.00	-.41**	-.76**	NA	-.52**	.39**	-.14	-.05	-.14
School	.21**	.18*	-.05	-.03	.09	.31**	.60**	-.52**	NA	-.45**	.26**	-.08	.23**
Acto	.06	-.20*	.11	-.05	-.11	-.17*	-.46**	.39**	-.45**	NA	-.17*	-.01	-.13
Sleep I	-.21*	.08	-.02	-.11	-.04	.00	-.25**	-.14	.26**	-.17*	NA	.59**	-.19*
Sleep II	-.28**	.06	-.03	-.15	-.11	.07	.09	-.05	-.08	-.01	.59**	NA	.06
Medicati	-.07	-.01	-.07	.01	.14	.10	.20*	-.14	.23**	-.13	-.19*	.06	NA

* P<0.05 ** P<0.01

Age in years, BMI (body mass index), Duration (Length of illness in months), CDI (depression), CIS (fatigue), CHQ (physical functioning), School absence, Actometer (physical activity), Sleep I (mean sleep during 2 weeks in hours), Sleep II (hours of sleep on the night prior to sampling day), Medication use on the day of sampling

To analyze predictors of the AUCG, Pearson's correlation coefficients for all individual variables measured in this study were determined, since these variables are possible confounders for the AUCG and recovery relationship. The more conservative significance level of p< 0.01 was used for these correlations analyses because of multiple comparisons.

SUPPLEMENTAL TABLE. Pearson's correlations at T=0 between AUCG, clinical features and possible confounding factors

REFERENCES

1. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994; 121(12): 953-9.

2. Nijhof SL, Maijer K, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Adolescent Chronic Fatigue Syndrome: Prevalence, Incidence, and Morbidity. Pediatrics 2011; 127: e1169-75.

3. Tak LM, Cleare AJ, Ormel J, Manoharan A, Kok IC, Wessely S, Rosmalen JG. Meta-analysis and meta-regression of hypothalamic-pituitary-adrenal axis activity in functional somatic disorders. Biol Psychol 2011; 87(2): 183-94.

4. Roberts AD, Wessely S, Chalder T, Papadopoulos A, Cleare AJ. Salivary cortisol response to awakening in chronic fatigue syndrome. Br J Psychiatry 2004; 184: 136-41.

5. Heim C, Ehlert U, Hellhammer DH. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. Psychoneuroendocrinology 2000; 25(1): 1-35.

6. Cleare AJ. The neuroendocrinology of chronic fatigue syndrome. Endocr Rev 2003; 24(2): 236-52.

7. Bell DS, Jordan K, Robinson M. Thirteen-year follow-up of children and adolescents with chronic fatigue syndrome. Pediatrics 2001; 107(5): 994-8.

8. Stulemeijer M, de Jong LW, Fiselier TJ, Hoogveld SW, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. BMJ 2005; 330(7481): 14.

9. Chalder T, Deary V, Husain K, Walwyn R. Family-focused cognitive behaviour therapy versus psycho-education for chronic fatigue syndrome in 11- to 18-year-olds: a randomized controlled treatment trial. Psychol Med 2010; 40(8): 1269-79.

10. Nijhof SL, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue

syndrome (FITNET): a randomised controlled trial. Lancet 2012; 379(9824): 1412-8.

11. van Geelen SM, Bakker RJ, Kuis W, van de Putte EM. Adolescent chronic fatigue syndrome: a follow-up study. Arch Pediatr Adolesc Med 2010; 164(9): 810-4.

12. van de Putte EM, van Doornen LJ, Engelbert RH, Kuis W, Kimpen JL, Uiterwaal CS. Mirrored symptoms in mother and child with chronic fatigue syndrome. Pediatrics 2006; 117(6): 2074-9.

13. Knoop H, Stulemeijer M, de Jong LW, Fiselier TJ, Bleijenberg G. Efficacy of cognitive behavioral therapy for adolescents with chronic fatigue syndrome: long-term follow-up of a randomized, controlled trial. Pediatrics 2008; 121(3): e619-25.

14. Nijhof SL, Priesterbach LP, Uiterwaal CS, Bleijenberg G, Kimpen JL, van de Putte EM. Internet-Based Therapy for Adolescents With Chronic Fatigue Syndrome: Long-term Follow-up. Pediatrics 2013; 131(6): e1788-95.

15. Roberts AD, Charler ML, Papadopoulos A, Wessely S, Chalder T, Cleare AJ. Does hypocortisolism predict a poor response to cognitive behavioural therapy in chronic fatigue syndrome? Psychol Med 2010; 40(3): 515-22.

16. Nijhof SL, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Fatigue In Teenagers on the interNET--the FITNET Trial. A randomized clinical trial of web-based cognitive behavioural therapy for adolescents with chronic fatigue syndrome: study protocol. [ISRCTN59878666. BMC Neurol 2011; 11: 23,2377-11-23.

17. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 1994; 38(5): 383-92.

18. Raat H, Landgraf JM, Bonsel GJ, Gemke RJ, Essink-Bot ML. Reliability and validity of the child health questionnaire-child form (CHQ-CF87) in a Dutch adolescent population. Qual Life Res 2002; 11(6): 575-81.

19. Scheeres K, Knoop H, Meer J, Bleijenberg G. Clinical assessment of the physical activity pattern of chronic fatigue syndrome patients: a validation of three methods. Health Qual Life Outcomes 2009; 7: 29.

20. Kovacs M. The Children's Depression, Inventory (CDI). Psychopharmacol Bull 1985; 21(4): 995-8.

21. Jessop DS, Turner-Cobb JM. Measurement and meaning of salivary cortisol: a focus on health and disease in children. Stress 2008; 11(1): 1-14.

22. Clow A, Thorn L, Evans P, Hucklebridge F. The awakening cortisol response: methodological issues and significance. Stress 2004; 7(1): 29-37.

23. Wust S, Wolf J, Hellhammer DH, Federenko I, Schommer N, Kirschbaum C. The cortisol awakening response - normal values and confounds. Noise Health 2000; 2(7): 79-88.

24. ter Wolbeek M., van Doornen LJ, Coffeng LE, Kavelaars A, Heijnen CJ. Cortisol and severe fatigue: a longitudinal study in adolescent girls. Psychoneuroendocrinology 2007; 32(2): 171-82.

25. Kupper N, de Geus EJ, van den Berg M, Kirschbaum C, Boomsma DI, Willemsen G. Familial influences on basal salivary cortisol in an adult population. Psychoneuroendocrinology 2005; 30(9): 857-68.

26. Steptoe A, Ussher M. Smoking, cortisol and nicotine. Int J Psychophysiol 2006; 59(3): 228-35. doi:10.1016/j.ijpsycho.2005.10.011.

27. Fries E, Dettenborn L, Kirschbaum C. The cortisol awakening response (CAR): facts and future directions. Int J Psychophysiol 2009; 72(1): 67-73.

28. Pruessner JC, Wolf OT, Hellhammer DH, *et al.* Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. Life Sci 1997; 61(26): 2539-49.

29. Tornhage CJ. Salivary cortisol for assessment of hypothalamic-pituitary-adrenal axis function. Neuroimmunomodulation 2009; 16(5): 284-9.

30. Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology 2003; 28(7): 916-31.

31. Fekedulegn DB, Andrew ME, Burchfiel CM, Violanti JM, Hartley TA, Charles LE, Miller DB. Area under the curve and other summary indicators of repeated waking

cortisol measurements. Psychosom Med 2007; 69(7): 651-9.

32. Cleare AJ. The HPA axis and the genesis of chronic fatigue syndrome. Trends Endocrinol Metab 2004; 15(2): 55-9.

33. Chrousos GP, Kino T, Charmandari E. Evaluation of the hypothalamic-pituitary-adrenal axis function in childhood and adolescence. Neuroimmunomodulation 2009; 16(5): 272-83.

34. Papadopoulos A, Ebrecht M, Roberts AD, Poon L, Rohleder N, Cleare AJ. Glucocorticoid receptor mediated negative feedback in chronic fatigue syndrome using the low dose (0.5 mg) dexamethasone suppression test. J Affect Disord 2009; 112(1-3): 289-94.

35. Federenko I, Wust S, Hellhammer DH, Dechoux R, Kumsta R, Kirschbaum C. Free cortisol awakening responses are influenced by awakening time. Psychoneuroendocrinology 2004; 29(2): 174-84.

36. Kudielka BM, Kirschbaum C. Awakening cortisol responses are influenced by health status and awakening time but not by menstrual cycle phase. Psychoneuroendocrinology 2003; 28(1): 35-47.

37. Roberts AD, Papadopoulos AS, Wessely S, Chalder T, Cleare AJ. Salivary cortisol output before and after cognitive behavioural therapy for chronic fatigue syndrome. J Affect Disord 2009; 115(1-2): 280-6.

38. Fries E, Hesse J, Hellhammer J, Hellhammer DH. A new view on hypocortisolism. Psychoneuroendocrinology 2005; 30(10): 1010-6.

39. Van Houdenhove B, Van Den Eede F, Luyten P. Does hypothalamic-pituitary-adrenal axis hypofunction in chronic fatigue syndrome reflect a 'crash' in the stress system? Med Hypotheses 2009; 72(6): 701-5.

40. Cleare AJ, Heap E, Malhi GS, Wessely S, O'Keane V, Miell J. Low-dose hydrocortisone in chronic fatigue syndrome: a randomised crossover trial. Lancet 1999; 353(9151): 455-8.

41. McKenzie R, O'Fallon A, Dale J, *et al.* Low-dose hydrocortisone for treatment of chronic fatigue syndrome: a randomized controlled trial. JAMA 1998; 280(12): 1061-6.

9
Summary and Discussion

Sanne L Nijhof

SUMMARY AND DISCUSSION

Despite the huge number of publications about chronic fatigue syndrome (CFS) in children in the past 25 years, starting with the first publication in the BMJ in 1989,[1] CFS remains a challenge to patients, clinicians and researchers. Novel findings regarding aetiology and treatment have generated at least as many questions as answers. In adolescents, the illness is characterized by profound, medically unexplained fatigue and extreme disability, which disrupts the social, emotional and academic development. This burden to the patient underlines not only the importance of research into this syndrome, but also the development of new, accessible treatment programs, since a quick diagnosis and recovery from CFS is of paramount importance.

In this thesis, studies were conducted on several aspects of adolescent CFS: epidemiology, treatment, and associated biological and psychological features. Its cornerstone is the FITNET-trial, where the effectiveness of web-based therapy for adolescent CFS was compared with usual care.

In this final chapter the main findings of this thesis are summarized and discussed. Implications of our findings and recommendations for future research directions are suggested.

EPIDEMIOLOGY

Knowledge about the prevalence and the incidence of adolescent CFS is important because it indicates the impact of this illness on society, and facilitates optimal treatment planning. The prevalence of adolescent CFS in community samples is highly variable, ranging from 0.19% to 1.29%,[2–6] depending on the ascertainment methods and definitions used. Most of these estimates were primarily established by self-reported questionnaires and telephone interviews.

Accurately diagnosing CFS is complex and requires the exclusion of other illnesses which could cause similar complaints, but require a different treatment. Therefore, we found it important to compute clinical estimations of incidence and prevalence based on a physician's diagnosis. *Chapter 2* shows the outcome of this research.

Our data supply nationwide cross-sectional prevalence data as well as prospective incidence data on adolescent CFS patients, in which CFS was diagnosed by either a general practitioner (GP) or a paediatrician. Adolescent CFS prevalence was estimated 0.11% with a yearly incidence of 0.01%. If prevalence and incidence data are valid, the mean illness duration can be calculated as 11 years, which means that the prevalence rate is overestimated or the incidence rate is underestimated as the known average illness duration in adolescent is shorter than 11 years.[7–10] These findings are lower than the aforementioned British and US population surveys. Reasons for possible underestimating are potential misclassification, sample selection bias or referral bias. Some physicians are reluctant to diagnose children with CFS, which leads to misclassification. The prevalence was calculated for a 10% sample of GPs with 48% responsiveness, which might have led to sample selection bias. The nationwide response rate for adolescent CFS incidence among pediatric departments was high (89%). Furthermore, the rate of adherence to CDC criteria (92%) suggested that Dutch pediatricians adequately diagnosed CFS in adolescents. In conclusion, there are more reasons for underestimation of the incidence than overestimation of the prevalence.

Our study additionally reports on physicians' attitudes towards CFS. An important difference is found between GPs and paediatricians. Awareness of the existence of and treatment options for adolescent CFS was much higher among paediatricians.

Some GPs questioned mentioned that they do not believe CFS in adolescents exists. The lack of locally available treatment options may enhance the reticence in diagnosing CFS. Nevertheless, when fatigue does not recover spontaneously and is accompanied by disabilities such as school absence, threatening the adolescent's social, emotional

and intellectual development, we recommend referral to a paediatrician. Overall, paediatricians were not reluctant to diagnose and refer for treatment of CFS. Correctly diagnosing CFS remains difficult though, as can be seen in the referrals for our FITNET trial; 39% of the referred patients with chronic fatigue in our FITNET study eventually did not comply with CDC criteria for CFS.[11]

This raises the important question of who should diagnose CFS in adolescents: the GP as primary healthcare professional, the paediatrician, or a team specializing in the diagnosis and treatment of CFS. We believe GPs should normalize fatigue in adolescents, in the absence of alarm symptoms and as long as it is not interfering with daily life. But adolescents with persistent or relapsing chronic debilitating fatigue should be referred to the paediatrician. The paediatrician is aware of CFS treatment options and should refer for treatment as soon as possible. The mean disease duration prior to diagnosis in this epidemiological study was 17 months, which could partly be explained by a doctor's delay in diagnosing or referral, combined with waiting lists for appropriate treatment. Prompt diagnosis and treatment is beneficial for the recovery of CFS, since long disease duration was a factor negatively associated with treatment outcome, as is shown in *Chapter 5*. These findings stress the need for proper and rapid diagnosis and creating awareness among medical professionals of adolescent chronic fatigue syndrome and its treatment options.

INTERVENTION

The FITNET study is the first randomized controlled trial to evaluate the effectiveness of web-based treatment in adolescents with CFS, compared with that of usual care. Details of trial design and FITNET treatment are given in *Chapter 3*. We found that web-based cognitive behaviour therapy (CBT) was effective, and significantly more successful than usual care after 6 months, with a 63% vs. 8% recovery rate. The number needed to treat for complete recovery was 1.8. In patients recovered with the help of FITNET, treatment success persisted at the 12 months' reassessment. Patients who continued FITNET treatment or switched to FITNET after 6 months of usual care reached similar levels of success at 12 months. Complete recovery implied that they were no longer severely fatigued, were attending school, were no longer physically impaired, and perceived themselves as (nearly) complete recovered. This favourable outcome is consistent with the results of earlier controlled studies regarding face-to-face CBT in adolescents given by specialist cognitive behavioural therapists.[12,13] Please see *Chapter 4* for a complete overview of FITNET trial results and *Chapter 5* for its long-term follow-up results.

Defining recovery of (adolescent) CFS is complex; no uniform international agreement exists. We defined *post hoc* a combined and comprehensive end-point, where four criteria had to be met: normalization of school attendance, recovery of fatigue scores and physical functioning to normal ranges, and a self-reported improvement, see *Chapter 4*. Normality was defined as being within two standard deviations (SD) of a healthy peer group.[11,14] Knoop and White *et al.* recently proposed to operationalize recovery criteria as scoring within 1 SD of the healthy (adult) population, but only regarding two criteria (fatigue and physical disability) instead of four.[15] In our opinion, school attendance is an important outcome in adolescents from a societal point of view; it is an objectively reliable marker of social and academic participation since school participation until 18 years of age is obligatory in most countries. This outcome measure becomes rather complicated when a patient has started working, since employment rates do not necessarily reflect one's capacity to work. We did perform analyses at other cut-off points for recovery (±1 SD).[11] This however did not change our findings with respect to treatment effects, but obviously changed the percentages of recovered patients. Bear in mind that the healthy peer groups in the FITNET study were selected for their good health, since adolescents who were suffering from a chronic illness or currently under psychological treatment were excluded.[14] Assuming a normal distribution, this implies

that a substantial part of the healthy subjects (scoring between 1 and 2 SD beyond the mean on only one of the four recovery criteria) have a score that would be considered as deviant from the norm.

International agreements on criteria for the recovery of (adolescent) CFS would greatly improve the comparability of trial outcomes.

We compared FITNET treatment with a heterogeneous usual care group, instead of assigning a standard usual care treatment or comparing with a non-active control group to control for the natural course of disease. With regard to a non-active control group, Stulemeijer *et al.* assessed the natural course of adolescent CFS without intervention, which was certainly unfavourable.[12] We used that knowledge for the design of our trial. Because of the vulnerable age with high risk of developmental disruption, we found it neither clinically relevant nor ethically acceptable to design a study with a waiting list, which would imply a 5- to 6-month delay of being treated. We could have chosen for a non-inferiority clinical trial with a comparison between face-to-face and internet-based CGT, but this was impracticable, because there is a restricted availability for face-to-face CGT for CFS adolescents. We chose a pragmatic study design to enable us to assess the value of FITNET therapy relative to the currently available treatments for CFS in the Netherlands. This intrinsic feature of our pragmatic trial design makes defining and controlling usual care options unfeasible; there was no detailed data on the content, intensity, and duration of the therapies offered in the usual care group. However the type of therapy was registered. The choice of multiple treatment options with considerable variations in accessibility and effectiveness is the reality for any CFS patient outside trial participation.

One of the novelties of our trial lies in its delivery of specialized psychotherapy treatment via the internet, with an obvious appeal to adolescents. Internet offers better accessibility, ease of delivery, and flexibility for patient, parents and therapist.

One major difference of face-to-face versus web-based treatment is that the latter can be 'consumed' at any moment, suiting the needs of every individual patient. This was reflected in the high consumption of FITNET therapy. From our server-logs we found that participants on average logged on 255 times to the programme modules, e-mailed the therapists 90 times and received 49 replies from the therapist. This implies much more therapy 'consumption' than attainable through face-to-face therapy. The results of a meta-analysis suggested that the dose of treatment (number of sessions of therapy) is a contributing factor to the response to CBT,[16] so a 'dose-effect relationship' could partly explain the difference in the short-term treatment outcome between

FITNET and usual care. Whether a potential increased uptake of therapy is indeed one of the factors contributing to FITNETs effectiveness should be part of future research. Ultimately, knowledge of whether internet-based treatment of CFS can achieve equal results with or without less professional guidance is important.

Additionally, an advantage of internet-based therapy could be that remarks and tips for formulating helpful thoughts are written down by the therapists and can be reviewed. Personal observations and reactions can be re-assessed as well. This potentially gives more insight into the progress one is making through therapy, although we did not quantify this effect.

A second major difference is the lack of face-to-face contact between therapist, patients and their parents. This was considered more a problem by the therapists and parents than the patients themselves. Adolescents nowadays seem completely adapted to a digital environment, fluent in social media and digital communication. They can be considered 'digital-natives'; born in a digital environment. All patients treated with FITNET and their parents (one or both) were interviewed about their experiences and satisfaction with the intervention. The interviews were semi-structured, with open questions guided by a topic list.[11] In contrast to their parents, the adolescents reported that they would prefer not to meet the therapist in person. Additionally, the rate of bonding with the therapist for adolescents was 4.7 on average. We analysed these attitude characteristics in the light of treatment effectiveness. See figures 1 (unpublished data). Not surprisingly, the recovered patients were more satisfied with

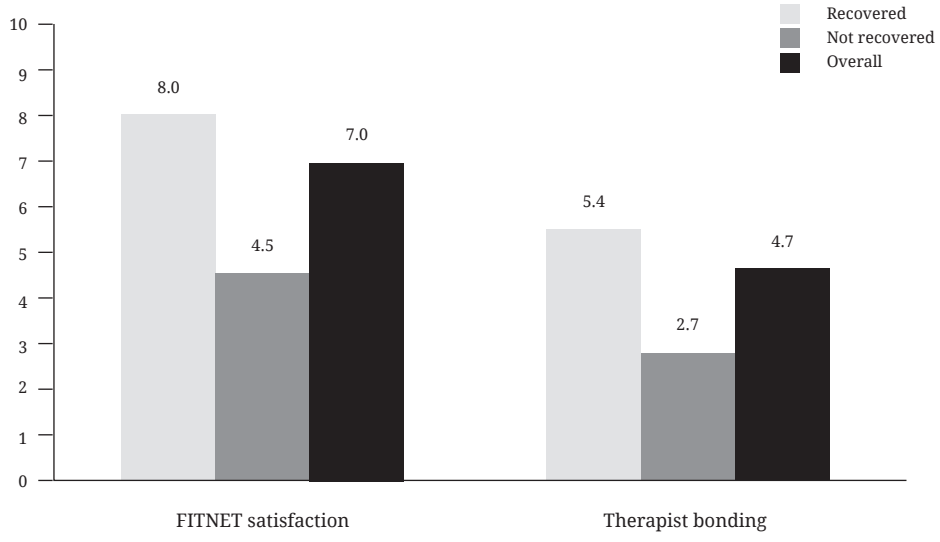


FIGURE 1. Association between adolescent treatment attitude and recovery

FITNET and had a somewhat better bonding with the therapist. Whether the reverse is true, that a more positive attitude towards FITNET promotes a greater chance of recovery, was not researched. It seems plausible though.

Therapists did appreciate the advantage of written communication: they were also able to review previous remarks and achievements. The personal aspect in digital communication remained very important for them though.

Effective (internet-based) CBT for CFS likely depends on the experience and specialization of the psychotherapist involved. Nevertheless, we did not note any significant differences in treatment effects between the therapists despite differences in their work experience. The same orientation and training within a specialised treatment centre, together with a shared supervised environment might have contributed to this equivalent effectiveness.

The long-term outcome of CFS in adolescents in our study was mostly favourable (*Chapter 5*). On average, 2.7 years after commencing treatment and 4.5 years after the onset of disease, ca. 60% of the adolescents had recovered, irrespective of the type of treatment. Short-term FITNET treatment effects were sustainable. Despite significant methodological differences and definitions of recovery with previous studies on this topic, the outcomes found in our study are in accordance with previous reports on the prognosis of adolescent CFS.[5,8–10] The fact that patients who only followed the usual care treatment in our study eventually achieved comparable outcomes at long-term follow-up, but at a much slower pace, underlines once more the importance of accessible and flexible treatment options in this vulnerable age group.

Chapter 5 furthermore examines in greater detail factors associated with (long-term) recovery. Because a significant group of adolescents remain impaired by CFS symptoms, it is important to differentiate between responders and non-responders as early as possible in order to change content, duration, or choice of treatment. The most important factors associated with non-recovery in our study are 'disease duration prior to treatment' and 'the maternal focus on bodily symptoms'. The latter is in line with previous research on the role of maternal factors in recovering from CFS. Knoop *et al.* (2008) demonstrated that severity of maternal fatigue was associated with the long-term recovery after face-to-face CBT.[10] Van de Putte *et al.* (2006) reported on mirrored fatigue severity between patients and their mothers,[17] and Chalder *et al.* (2003) found that maternal psychological distress was associated with parental report of CFS.[2] But given the cross-sectional nature of the data of the last two studies, it is impossible to determine the direction of causality. Paternal factors were investigated

but not identified in our study.

Both adolescents and parents were treated simultaneously in the FITNET programme, in a bilateral contact with the therapist. Our finding that long-term recovery was negatively associated with maternal focus on bodily symptoms suggests that an intergenerational vulnerability and interaction between mother and child exists. The possible implication of this finding is that a face-to-face dynamic family approach, or a separate treatment programme for the mother, is needed for a subgroup of adolescent CFS patients. More research focused on this topic is required.

The finding that disease duration prior to diagnosis is a predictor of treatment success again further underlines the importance of prompt diagnosis and treatment of CFS. Not only does it reduce the burden to the child with its detrimental effects on social and academic development, it also increases the chance of recovery.

FITNET is to date available in the Netherlands for adolescents with CFS (https://www.umcutrecht.nl/cvs and https://mijn.nkcv.nl) and will hopefully be translated soon in English in collaboration with colleagues from the UK.

CLINICAL FEATURES

Simultaneously with the FITNET intervention, several clinical features of adolescent CFS were assessed: pain sensation (*Chapter 6*), intellectual performance (*Chapter 7*), and the HPA-axis (*Chapter 8*).

One of the aims of this thesis was to provide insight into the complex interaction between these clinical features and the symptom complex of CFS as described in the CDC-criteria. Of particular interest was the question of whether the initial derivations of these clinical features are reversible after recovery from CFS.

The cause of adolescent CFS is not known, and it is generally assumed to be the result of a complex interaction between biological, psychological and social factors. Previous research has shown that it would be useful to differentiate in precipitating, predisposing, and perpetuating factors at the biological and psychosocial levels, especially for treatment; the so-called bio-psycho-social model.[18,19] This is more extensively discussed in *Chapter 1*. Precipitating and predisposing factors precede and facilitate chronic fatigue. Perpetuating factors impede recovery. Patients' cognition of perpetuating factors is used in CBT, which is the current mainstay of the treatment of adolescent CFS. Not all patients recover though. Identifying the individuals with a lower chance of treatment success is important, since therapy can be tailored, and a delay in recovery has a severe impact on social and educational development.

Regardless of whether disruption in clinical features is primary or secondary, a greater understanding of the complexities of CFS is gained from knowledge about the disruption, its reversibility and whether the clinical feature is part of the symptom complex CFS or rather may be viewed as a risk factor. This knowledge could improve the treatment of CFS, by providing new therapeutic clues or defining subgroups of patients who might need tailored treatment.

It is important therefore to identify the associations between these factors and CFS, both at diagnosis and after recovery. Our longitudinal trial design created the opportunity to assess the aforementioned factors at multiple points in time, which is valuable in establishing the reversibility of these factors. One strength of our studies is that the biological measurements can be interpreted in relation to physical activity, sleep disturbance and psycho-social variables such as depression and anxiety. All these parameters were cross-sectionally measured at multiple points in time as part of the intervention study. Another strength is the large treatment cohort size, with high

participation rates for the (biological) sub-studies. Nevertheless, it should be noted that our study was designed and powered on treatment outcomes and not on these clinical features. Moreover, this is not the ideal design for the assessment of etiological factors, while pre-diagnosis investigations are lacking. Investigating whether there is a primary causal role for e.g. HPA-axis dysfunction in the aetiology of adolescent CFS is only possible in very large cohort studies. Given the low incidence of adolescent CFS, this would require very large population samples, with only 0.01% of the adolescents developing CFS.

Pain

CFS is often accompanied by severe pain symptoms, and pain is an integral part of the CFS symptom complex. Five out of the eight additional CDC criteria for CFS are related to pain experience: a sore throat, tender cervical or axillary lymph nodes, muscle pain, multiple joint pain, and headaches.[20] The chronic pain symptoms in CFS are disabling and compromise physical and social functioning. Adolescents with CFS showed a lower pain threshold than healthy adolescents.[21] We wondered whether an effective treatment would lead to a normalization of pain symptoms and pain threshold.

In *Chapter 6*, we longitudinally assessed pain thresholds and subjective pain experiences at the time of CFS diagnosis and after treatment. We concluded that pain is an intrinsic feature of adolescent CFS, closely linked to the main symptom of fatigue, which seems to disappear upon recovery. Baseline pain score or pain threshold did not predict recovery (data not shown). Pain symptoms do not seem to require a specific treatment approach in adolescents with CFS, since the treatment administered was not specifically aimed at controlling pain symptoms. These outcomes were not influenced by the presence of a high co-morbid depression score. This is valuable information for adolescent CFS patients with pain symptoms when they are informed about treatment and the prognosis of their illness. In conclusion, pain is not viewed as a risk factor for CFS, but as an intrinsic feature of the symptom complex.

Intelligence

Most adolescent CFS patients report attention and concentration problems, with subsequent poor performance at school.[22,23] Several studies, mainly focused on adults, have described impaired cognitive performance by CFS patients on neuropsychological tests. Reduced speed of complex information processing is the impairment most consistently found.[22,24] In contrast to memory and concentration problems in CFS patients, the intellectual capacity in adolescents with CFS has rarely been

investigated. Only one study measured the discrepancy between actual and perceived IQ for adolescents with CFS compared to healthy peers in a cross-sectional design.[25] They showed that parents' expectations regarding the IQ of adolescents with CFS were significantly higher than those of healthy controls, and concluded that high parental expectations could contribute to the development of CFS. However, this discrepancy in actual and perceived IQ can be both a risk factor predisposing to CFS, or an effect of CFS. A recent cohort study by Kingma *et al.* (2011) showed that a lower childhood intelligence measured around 11 years of age was associated with functional somatic symptoms (not specifically CFS) during adolescence, especially in those adolescents perceiving high parental expectations.[26] This prompted the question of whether there are discrepancies in intelligence measurements before and after the commencement of CFS. In the Netherlands, intellectual performance of all children is measured at the age of 12, providing advice in the choice of their secondary school level: the CITO test. This unique setting, with a general availability of CITO–test scores, makes it possible to compare current cross-sectional data with retrospective (pre-CFS) intelligence data.

In *Chapter 7* we explored pre-morbid and actual intellectual performance in adolescents with CFS compared with healthy peers. We found that current IQ scores of CFS adolescents were lower than expected on the basis of their school level and when compared to healthy peers. Furthermore, there was a deterioration in intelligence performance across time when current IQ scores were compared with pre-morbid cognitive achievement. Importantly, CITO scores of CFS adolescents corresponded to their initial secondary school level, as was the case with their healthy controls. Healthy controls did not show any discrepancies between their current IQ score, school level and previous CITO score.

Since CITO tests were taken in a pre-morbid phase, our longitudinal results make it more plausible that the decline in intellectual performance could be considered a consequence of CFS. We elaborate on a possible explanation for the discrepancy in IQ scores before and during illness in *Chapter 7*.

An alternative explanation could be that adolescent CFS patients ‘grow into the deficit’. Although the CITO-test highly correlates with IQ scores assessed at the age of 12,[27] it is not a formal IQ-test. The CFS adolescents in our study underperformed in particular in the performance tasks, while no significant difference was found for verbal IQ between CFS and healthy adolescents. Does this relate to the reduced speed of complex information processing? Is it therefore why they perform worse on the, mostly time-bound, performance tasks? Is it possible that the CITO test potentially does not discriminate enough between these different entities?

In *Chapter 7* we conclude that CFS may be accompanied by a decline in general cognitive functioning. Based on their initial intelligence assessments, they started with appropriate secondary school levels. According to the CITO-scores, the decrease in intellectual capacity seems to be a consequence rather than a cause of CFS.

However, we cannot exclude that a pre-existent difference in performance and verbal IQ (which may not be measured with a CITO-test), could also be a feature, and therefore be a vulnerability factor, partly responsible for the development of CFS in adolescents.

Regardless of the aetiological role of intelligence in the emergence of CFS, we advise caution in interpreting intellectual performance tests measured during the course of the disease. It is currently not known whether lower IQ outcomes are due to concentration problems, a lowered processing speed, an initially lower (performance) IQ with a 'growing into the deficit', or CFS itself. Given the critical age for intellectual development, we recommend a timely diagnosis followed by appropriate treatment of CFS in adolescents.

At this moment we are performing a follow-up study in the adolescents that attended the FITNET study. This study repeats the intelligence performance testing and should answer the question of whether this lowered intellectual performance is reversible after successful treatment and address its possible neurobiological and morphological explanations. If the decrease in performance IQ persists after recovery, there is an argument for this being a predisposing factor in making children more at risk of developing CFS. If, on the other hand, the decreased performance IQ normalizes after recovery, we may conclude, together with the premorbid normal CITO scores, that decreased performance IQ is a feature of the symptom complex of CFS.

Cortisol

The most replicated biological finding in adult CFS-patients is a hypofunction of the hypothalamic-pituitary-adrenal (HPA)-axis, manifested in a low salivary cortisol awakening response (CAR).[28] The role of this hypofunction however remains unclear. It is not known whether this is a relevant biological factor in the aetiology of CFS. It has been hypothesized that lowered cortisol occurs, in part, secondarily to aspects of CFS such as disturbed sleep, inactivity or stress.[28,29] To date, hypocortisolism has been consistently shown in adult CFS-patients,[28–31] but it has not been studied longitudinally in adolescents with CFS.

In *Chapter 8* we assessed the HPA-axis functioning, as expressed by the CAR measured in saliva, in relation to recovery in adolescents with CFS. A mild but significant hypocortisolism was found in the adolescents diagnosed with CFS, which normalized after successful treatment. The absolute improvement in cortisol output was predictive for recovery, in that patients with a bigger change in cortisol levels after treatment show a better chance of recovery.

The association between the cortisol awakening response and (recovery of) CFS may be confounded by conditions or behaviour that influence cortisol levels, such as inactivity, sleep disturbance and psychiatric comorbidity. All these possible confounders were simultaneously assessed. Multiple regression analysis with adjustment for all possible confounders did not materially alter our findings.

These findings emphasize that the transient (mild) hypocortisolism could be regarded as part of the CFS symptom complex, supported by the fact that symptoms of CFS at diagnosis correlate with the degree of hypocortisolism. Assessing the cortisol awakening response cross-sectionally does not seem a suitable method for diagnosing or indicating recovery from CFS. The hypocortisolism demonstrated in our subjects was only mild, in the lower part of normal range, and would therefore not be distinctive enough. However, assessing HPA-axis functioning longitudinally during treatment could possibly identify earlier those likely not to recover. We suppose that assessing the change in cortisol levels during treatment might provide an early indication of treatment success or failure. Cortisol then might serve as a 'biomarker' for treatment success. This can have implications on future treatment strategies.

To conclude, the three clinical features discussed above together share the common factor that they are deviant in adolescents diagnosed with CFS, and so characterize the illness. Also, pre-treatment pain and hypocortisolism share that they do not predict recovery from CFS but are related to illness severity, and both features normalize after recovery. These findings suggest that pain and hypocortisolism are intrinsic features of the CFS symptom complex, regardless of whether they arose primarily (and causally) or secondarily (and consequentially) to the illness. The fact that both characteristics could not be explained by behavioural symptoms such as disturbed sleep pattern and physical activity, make it unlikely that these factors solely form an epiphenomenon of the illness.

Of course, these features are not exclusively linked to CFS, as for example adolescent post-traumatic stress disorder as a result of sexual trauma in female adolescents is also associated with dysregulation of the HPA-axis, expressed by lower levels of

cortisol.[32] Nor are both characteristics present in every individual patient in the same severity, nor do they seem to be a suitable method for cross-sectionally diagnosing or indicating recovery from CFS. However, they are helpful in describing 'the state' CFS, and could probably aid as a 'biomarker' for treatment success when measured during treatment.

A discrepancy in actual (and perceived) intelligence seems to be a vulnerability factor in the development of CFS. Follow-up research should reveal if IQ improves after recovery.

FUTURE DIRECTIONS

To further improve the treatment and prognosis of adolescent CFS it is important to identify the factors that contribute to treatment effectiveness and assess which factors are associated with non-recovery. Although FITNET is considered effective, still one third of patients do not recover. The fact that long-term recovery was negatively associated with maternal focus on bodily symptoms could be seen as an indication that during treatment the influence of this specific predictor has not been adequately addressed. The possible implication of this finding that a face-to-face dynamic family approach, or separate treatment programme for the mother, is needed for a subgroup of adolescent CFS patients, requires further research. Also, it might be necessary to distinguish different subgroups of CFS on the basis of assessing HPA-axis functioning *during* treatment. This could earlier identify those likely not to recover, and who subsequently might need tailored treatment. If this assumption can be confirmed in future research, a RCT that studies the effectiveness of additional low-dose hydrocortisone suppletion for a subgroup of patients to enhance CBT effectiveness would be very interesting.

The role of intelligence in (the development of) CFS deserves further study, especially with regard to the mechanisms responsible for the measured decline in intelligence in our study, and should also be aimed at a possible reversibility. Do recovered CFS patients catch up with their healthy peers in due time?

Taking together the above factors, we suppose that the intrinsic features of the CFS symptom complex can ideally be used for elucidating the basis of CFS and providing possible (additional) therapeutic options in future research. Furthermore, it is very important to inform the patient about the clinical features of the illness and its possible treatment options.

Concerning web-based treatment, our findings have contributed to the increasing evidence base that therapist-aided, internet-based CBT could be an effective treatment for many similar disorders.[33] Fatigue and disturbed sleep are also debilitating problems in many childhood diseases. These include auto-immune diseases, such as juvenile idiopathic arthritis, or adolescent post-cancer fatigue. These groups could benefit as well from an adapted, tailored therapist-aided, internet-based treatment programme.

Furthermore, a FITNET variant without the feedback of a therapist could assess the additional value of involving a therapist. Qualitative research on the user experiences with digital communication, with its high number of log-ins and e-mails, would provide data on the uptake of web-based CBT. A cost-effectiveness study on web-based vs. face-to-face CBT would supply interesting data for health care suppliers, legislators and healthcare insurance companies.

Finally, FITNET should become available in different language regions, with parallel studies of its effectiveness.

REFERENCES

1. Myalgic encephalomyelitis by proxy. BMJ 1989; 299(6706): 1030-1.

2. Chalder T, Goodman R, Wessely S, Hotopf M, Meltzer H. Epidemiology of chronic fatigue syndrome and self reported myalgic encephalomyelitis in 5-15 year olds: cross sectional study. BMJ 2003; 327(7416): 654-5.

3. Farmer A, Fowler T, Scourfield J, Thapar A. Prevalence of chronic disabling fatigue in children and adolescents. Br J Psychiatry 2004; 184: 477-81.

4. Jones JF, Nisenbaum R, Solomon L, Reyes M, Reeves WC. Chronic fatigue syndrome and other fatiguing illnesses in adolescents: a population-based study. J Adolesc Health 2004; 35(1): 34-40.

5. Rimes KA, Goodman R, Hotopf M, Wessely S, Meltzer H, Chalder T. Incidence, prognosis, and risk factors for fatigue and chronic fatigue syndrome in adolescents: a prospective community study. Pediatrics 2007; 119(3): e603-9.

6. Lloyd AR, Hickie I, Boughton CR, Spencer O, Wakefield D. Prevalence of chronic fatigue syndrome in an Australian population. Med J Aust 1990; 153(9): 522-8.

7. Krilov LR, Fisher M, Friedman SB, Reitman D, Mandel FS. Course and outcome of chronic fatigue in children and adolescents. Pediatrics 1998; 102(2 Pt 1): 360-6.

8. Bell DS, Jordan K, Robinson M. Thirteen-year follow-up of children and adolescents with chronic fatigue syndrome. Pediatrics 2001; 107(5): 994-8.

9. van Geelen SM, Bakker RJ, Kuis W, van de Putte EM. Adolescent chronic fatigue syndrome: a follow-up study. Arch Pediatr Adolesc Med 2010; 164(9): 810-4.

10. Knoop H, Stulemeijer M, de Jong LW, Fiselier TJ, Bleijenberg G. Efficacy of cognitive behavioral therapy for adolescents with chronic fatigue syndrome: long-term follow-up of a randomized, controlled trial. Pediatrics 2008; 121(3): e619-25.

11. Nijhof SL, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue

syndrome (FITNET): a randomised controlled trial. Lancet 2012; 379(9824): 1412-8.

12. Stulemeijer M, de Jong LW, Fiselier TJ, Hoogveld SW, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. BMJ 2005; 330(7481): 14.

13. Chalder T, Deary V, Husain K, Walwyn R. Family-focused cognitive behaviour therapy versus psycho-education for chronic fatigue syndrome in 11- to 18-year-olds: a randomized controlled treatment trial. Psychol Med 2010; 40(8): 1269-79.

14. Nijhof SL, Maijer K, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Adolescent Chronic Fatigue Syndrome: Prevalence, Incidence, and Morbidity. Pediatrics 2011; 127: e1169-75.

15. Knoop H, Bleijenberg G, Gielissen MF, van der Meer JW, White PD. Is a full recovery possible after cognitive behavioural therapy for chronic fatigue syndrome? Psychother Psychosom 2007; 76(3): 171-6.

16. Castell BD, Kazantzis N, Moss-Morris RE. Cognitive Behavioral Therapy and Graded Exercise for Chronic Fatigue Syndrome: A Meta-Analysis. Clinical Psychology: Science and Practice 2011; 18(4): 311-24.

17. van de Putte EM, van Doornen LJ, Engelbert RH, Kuis W, Kimpen JL, Uiterwaal CS. Mirrored symptoms in mother and child with chronic fatigue syndrome. Pediatrics 2006; 117(6): 2074-9.

18. Knoop H, Prins JB, Moss-Morris R, Bleijenberg G. The central role of cognitive processes in the perpetuation of chronic fatigue syndrome 6. J Psychosom Res 2010; 68(5): 489-94.

19. Vercoulen JH, Bazelmans E, Swanink CM, Galama JM, Fennis JF, van der Meer JW, Bleijenberg G. Evaluating neuropsychological impairment in chronic fatigue syndrome. J Clin Exp Neuropsychol 1998; 20(2): 144-56.

20. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994; 121(12): 953-9.

21. van de Putte EM, Uiterwaal CS, Bots ML, Kuis W, Kimpen JL, Engelbert RH. Is chronic fatigue syndrome

a connective tissue disorder? A cross-sectional study in adolescents. Pediatrics 2005; 115(4): e415-22.

22. Michiels V, Cluydts R. Neuropsychological functioning in chronic fatigue syndrome: a review. Acta Psychiatr Scand 2001; 103(2): 84-93.

23. Davies S, Crawley E. Chronic fatigue syndrome in children aged 11 years old and younger. Arch Dis Child 2008; 93(5): 419-21.

24. Cockshell SJ, Mathias JL. Cognitive functioning in chronic fatigue syndrome: a meta-analysis. Psychol Med 2010; : 1-15.

25. Godfrey E, Cleare A, Coddington A, Roberts A, Weinman J, Chalder T. Chronic fatigue syndrome in adolescents: do parental expectations of their child's intellectual ability match the child's ability? J Psychosom Res 2009; 67(2): 165-8.

26. Kingma EM, Janssens KA, Venema M, Ormel J, de Jonge P, Rosmalen JG. Adolescents with low intelligence are at risk of functional somatic symptoms: the TRAILS study. J Adolesc Health 2011; 49(6): 621-6.

27. Bartels M, Rietveld MJ, Van Baal GC, Boomsma DI. Heritability of educational achievement in 12-year-olds and the overlap with cognitive ability. Twin Res 2002; 5(6): 544-53.

28. Tak LM, Cleare AJ, Ormel J, Manoharan A, Kok IC, Wessely S, Rosmalen JG. Meta-analysis and meta-regression of hypothalamic-pituitary-adrenal axis activity in functional somatic disorders. Biol Psychol 2011; 87(2): 183-94.

29. Roberts AD, Wessely S, Chalder T, Papadopoulos A, Cleare AJ. Salivary cortisol response to awakening in chronic fatigue syndrome. Br J Psychiatry 2004; 184: 136-41.

30. Heim C, Ehlert U, Hellhammer DH. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. Psychoneuroendocrinology 2000; 25(1): 1-35.

31. Cleare AJ. The neuroendocrinology of chronic fatigue syndrome. Endocr Rev 2003; 24(2): 236-52.

32. Bicanic IA, Postma RM, Sinnema G, De Roos C, Olff M, Van Wesel F, Van de Putte EM. Salivary cortisol and dehydroepiandrosterone sulfate in adolescent rape victims with post traumatic stress disorder. Psychoneuroendocrinology 2013;

38(3): 408-15.
33. Cuijpers P, van SA, Andersson G. Internet-administered cognitive behavior therapy for health problems: a systematic review. J Behav Med 2008; 31(2): 169-77.

NEDERLANDSE SAMENVATTING

Sinds de eerste publicatie over het chronisch vermoeidheidssyndroom (CVS) bij adolescenten in het tijdschrift 'British Medical Journal' in 1989 zijn er vele artikelen gepubliceerd over deze invaliderende aandoening bij jongeren. Onderzoek naar CVS bij adolescenten heeft de afgelopen decennia zeker evenveel nieuwe vragen gegenereerd als beantwoord. De weg naar herstel blijft een uitdaging voor zowel patiënten en behandelaren, als voor onderzoekers.

CVS in adolescenten wordt gekenmerkt door ernstige, medisch onverklaarde, langdurige vermoeidheid, die tot grote beperkingen leidt in het dagelijks functioneren. Dit kan vervolgens leiden tot fors schoolverzuim. Deze beperkingen kunnen de normale ontwikkeling op sociaal, emotioneel en educatief gebied verstoren. Deze ernstige gevolgen voor de patiënt onderstrepen de noodzaak tot onderzoek naar dit syndroom. Maar tevens is er de noodzaak tot het ontwikkelen van effectieve, toegankelijke behandelprogramma's, want het tijdig stellen van de diagnose en het vlot starten van behandeling verbetert de kans op herstel.

In dit proefschrift worden studies beschreven gericht op verschillende aspecten van CVS bij adolescenten: epidemiologie, behandeling, en de klinische en biologische kenmerken die geassocieerd zijn met (herstel van) CVS. De hoeksteen van dit proefschrift is de FITNET-trial, waarin wij de effectiviteit van internettherapie voor CVS bij adolescenten hebben onderzocht.

Epidemiologie

Kennis van de incidentie en prevalentie van CVS bij adolescenten is van belang omdat het inzicht geeft in wat de impact van deze ziekte op de samenleving is en hoe daar het behandelaanbod op af te stemmen.

In eerdere populatieonderzoeken naar het vóórkomen van CVS onder adolescenten, met name in Groot-Brittannië en de Verenigde Staten, werd veelal gebruik van gemaakt van steekproeven onder de bevolking middels telefonisch interviews en zelfrapportage van CVS. De uitkomsten van deze onderzoeken variëren: een prevalentie van 0.19% tot 1.29% wordt beschreven. Het juist stellen van de diagnose CVS vereist ervaring, evenals het uitsluiten van andere aandoeningen die zelfde klachten kunnen veroorzaken, maar een andere behandeling nodig hebben. Daarom wilden wij een klinische inschatting maken van de incidentie en prevalentie van CVS onder adolescenten in Nederland, waarbij de diagnose primair door de huisarts of kinderarts werd gesteld. Hiertoe

werden een cross-sectionele prevalentiestudie in een steekproef onder 10% van de Nederlandse huisartsen en een prospectieve incidentiestudie onder alle Nederlandse kinderartsen uitgevoerd. In *hoofdstuk 2* worden de resultaten van deze onderzoeken beschreven.

In ons onderzoek schatten wij de prevalentie van CVS onder Nederlandse adolescenten op 0.11% en de diagnose wordt jaarlijks bij 1 op de 10.000 adolescenten gesteld. Dit zijn lagere cijfers dan die in eerdergenoemde populatiestudies. Mogelijk onderschatten wij het vóórkomen van CVS, omdat niet alle patiënten met CVS zich presenteren bij de huisarts of (door)verwezen worden naar de kinderarts. Een andere reden voor een onderschatting zou kunnen zijn dat de diagnose CVS bij adolescenten niet altijd wordt erkend door de huisarts of kinderarts, wat leidt tot misclassificatie.

In onze studie hebben we ook de attitude van artsen ten aanzien van de diagnose CVS bij adolescenten onderzocht. Een belangrijk verschil werd gevonden tussen kinderartsen en huisartsen. De kennis van CVS bleek groter bij kinderartsen, ook verwezen zij vaker door voor behandeling. Huisartsen waren vaker terughoudend om een adolescent het label CVS 'op te plakken'. Dit is deels terecht: gewone vermoeidheid herstelt zonder behandeling en zou zelfs erger kunnen worden door (over)behandeling. Maar wanneer vermoeidheid lang aanhoudt en leidt tot uitval op school of beperkingen in het fysiek en/of sociaal functioneren, dan adviseren wij te verwijzen naar een kinderarts. Een juiste diagnose CVS blijft echter moeilijk; 39% van de verwezen adolescenten met chronische vermoeidheid in onze FITNET-studie voldeed niet aan de CDC-criteria voor CVS. Dit roept de vraag op wie CVS zou moeten diagnosticeren bij adolescenten: de huisarts die het dichtste bij de patiënt staat, de kinderarts of een team gespecialiseerd in de diagnose en behandeling van CVS?

De gemiddelde ziekteduur in onze epidemiologische studie was 17 maanden. Dit komt waarschijnlijk deels door uitstel in diagnosticeren of verwijzing, gecombineerd met wachtlijsten voor adequate behandeling. Een snelle diagnose en tijdige behandeling geeft meer kans op herstel van CVS, zoals we in *hoofdstuk 5* aantonen. Dit onderstreept het belang van een juiste en vlotte diagnose. Het onderstreept tevens het belang dat zorgverleners op de hoogte zijn van het bestaan van CVS bij adolescenten en van de mogelijke behandelopties.

Behandeling

Het FITNET-onderzoek is het eerste in zijn soort dat de effectiviteit van internet-therapie voor CVS heeft onderzocht. In dit onderzoek werd internettherapie vergeleken met 'usual care': de aanwezige zorg in de regio van de patiënt. *Hoofdstuk 3* beschrijft

de opzet van dit onderzoek. In *hoofdstuk 4* worden de uitkomsten van dit onderzoek beschreven. *Hoofdstuk 5* beschrijft de lange termijn resultaten van FITNET.

Internettherapie bleek effectief na 6 maanden behandeling, met een 63% herstelpercentage vs. 8% herstelpercentage in de 'usual care'-groep. Dit herstel bleef na 12 maanden follow-up bestaan. De adolescenten die FITNET volgden nadat ze aanvankelijk gerandomiseerd waren voor behandeling middels 'usual care' en hiermee niet hersteld waren na 6 maanden lieten een vergelijkbaar herstelpercentage zien na 6 maanden FITNET-behandeling.

Het definiëren van herstel van CVS bij adolescenten is complex en er is geen internationale overeenstemming over herstelcriteria. Wij definieerden volledig herstel in onze studie als een combinatie van vier uitkomstmaten. Om volledig hersteld te zijn moest de patiënt niet meer ernstig moe zijn, niet meer lichamelijk beperkt zijn, een normale schoolparticipatie hebben en zelf ook vinden hersteld te zijn (zie *hoofdstuk 4*). Voor het definiëren van normaalwaarden vergeleken wij de scores op de uitkomstmaten met een gezonde controle groep. Per onderdeel moest gescoord worden binnen twee standaarddeviaties van deze normaalgroep.

Onlangs pleitten andere onderzoekers ervoor om afkappunten voor herstelcriteria te hanteren binnen 1 SD van de gezonde (volwassen) populatie, echter zij kozen voor een combinatie van 2 herstelcriteria (vermoeidheid en lichamelijke beperkingen). Bij adolescenten is schoolparticipatie echter een belangrijke en de meest objectieve uitkomstmaat.

De keuze van de uitkomstmaat heeft natuurlijk effect op het herstelpercentage; een strengere norm voor zowel het aantal criteria als voor afkappunten betekent minder herstel. Dit impliceert ook dat bij een combinatie van meer criteria én strengere afkappunten een groter deel van de gezonde adolescenten tot de afwijkende groep zal behoren. Internationale afspraken hierover zouden de vergelijkbaarheid van studieresultaten vergemakkelijken.

Wij hebben de FITNET-behandeling vergeleken met 'usual care', bestaande uit verschillende soorten behandelingen. Van de 'usual care'-behandelingen hadden wij minder gedetailleerde informatie betreffende het aantal behandelsessies, of de duur van de behandeling. Het type behandeling werd wel geregistreerd. Voor een CVS patiënt sluit dit aan bij de werkelijkheid; er is vaak keuze uit verschillende behandelingen. Wij hebben FITNET bewust niet vergeleken met een inactieve controle groep, zoals bijvoorbeeld een wachtlijstconditie. Dit zou in de controlegroep het natuurlijk herstel van CVS weergeven, maar in eerder onderzoek werd reeds aangetoond dat de prognose van onbehandelde CVS ongunstig is. Om deze reden achtten wij het onthouden van

behandeling niet ethisch.

We hadden kunnen kiezen voor een 'non-inferiority clinical trial' met een vergelijking tussen 'face-to-face' cognitieve gedragstherapie vs. cognitieve gedragstherapie via het internet. Echter, één van de belangrijkste redenen om een internettherapie te ontwikkelen was de beperkte beschikbaarheid van gespecialiseerde 'face-to-face' cognitieve gedragstherapie (CGT); de enige evidence-based behandeling voor jongeren met CVS. We hebben dus gekozen voor een pragmatisch studieontwerp dat ons in staat stelt om de waarde van de FITNET-behandeling te beoordelen ten opzichte van het huidige behandelaanbod voor adolescenten met CVS in Nederland.

Het innovatieve aan FITNET is het gebruik van internet om therapie aan te bieden. Internettherapie is altijd toegankelijk, makkelijk aan te bieden en flexibel voor zowel de patiënten, hun ouders, als voor de therapeuten. Een groot verschil met 'face-to-face' therapie is dat het op elk moment beschikbaar is.

FITNET werd intensief gebruikt. Dit zagen wij terug in de inloggegevens: gemiddeld logden de patiënten 255x in, stuurden ze 90 e-consulten en kregen ze 49 reacties van de therapeut. Dit is veel vaker dan mogelijk is met reguliere CGT. Uit eerder onderzoek bleek dat de intensiviteit van therapie, bijvoorbeeld het aantal sessies, positief geassocieerd is met herstel. Deze intensiviteit zou kunnen hebben bijgedragen aan de effectiviteit van FITNET. Uiteindelijk is het ook van belang om te weten of de FITNET-behandeling ook met minder intensieve begeleiding van een therapeut toe zou kunnen.

Een groot verschil met de controlegroep is dat er werkelijk geen enkel 'face-to-face' contact heeft plaatsgevonden tussen de patiënt en de therapeut. Anders dan de adolescenten, gaven ouders en therapeuten aan dit een gemis te vinden. Hier zou mogelijk een 'generatieverschil' aan ten grondslag kunnen liggen: jonge mensen zijn waarschijnlijk meer gewend aan digitale communicatie en sociale media (ze zijn hier immers mee opgegroeid). Patiënten en hun ouders werden na het doorlopen van de FITNET-behandeling geïnterviewd aan de hand van een semi-gestructureerd interview over hun ervaringen en tevredenheid. Zowel de patiënten als hun ouders waren tevreden over FITNET: gemiddeld gaven ze FITNET respectievelijk een 7.1 en 7.3. De meeste jongeren gaven aan dat ze de FITNET-therapeut niet per sé persoonlijk hoefden te ontmoeten. Opvallend was dat ze de band die ze opgebouwd hadden met de FITNET-therapeut gemiddeld slechts een 4.6 gaven. Niet geheel onverwacht waren de herstelde patiënten meer tevreden en scoorden ze een betere band met hun therapeut. Zie hiervoor figuur 1 in de Engelstalige 'Summary and Discussion'. Wij hebben niet onderzocht of een positiever idee van de behandeling ook meer kans op herstel geeft, maar dit klinkt aannemelijk.

De therapeuten bemerkten ook het voordeel van geschreven communicatie. Ze

konden terugvallen op eerdere opmerkingen en e-consulten.

Het lijkt aannemelijk dat de effectiviteit van CGT mede afhankelijk is van de ervaring van een therapeut. Hoewel er grote verschillen waren in ervaringsjaren tussen de verschillende FITNET-therapeuten, vonden wij geen significante verschillen in behandelresultaat tussen de therapeuten. Het feit dat alle therapeuten in hetzelfde gespecialiseerde behandelcentrum werken onder supervisie van dezelfde persoon, verklaart wellicht dat er geen verschillen werden gevonden.

De lange termijn uitkomsten van CVS in onze studie waren doorgaans gunstig (*hoofdstuk 5*). Gemiddeld bleef 60% van de patiënten hersteld, 2.7 jaar na het starten van de behandeling en 4.5 jaar na het ontstaan van de aandoening. De eerder aangetoonde behandeleffecten van FITNET bleven behouden op de lange termijn. Ook van de adolescenten die in de 'usual care' groep waren gebleven bleek 60% hersteld op de lange termijn. Ondanks grote methodologische verschillen in studieopzet en definities van herstel, komen deze uitkomsten overeen met eerdere studies. Het feit dat de adolescenten in de 'usual care' groep eenzelfde herstelpercentage bereiken, maar veel trager dan de adolescenten behandeld middels FITNET, geeft eens te meer het belang aan van toegankelijke en flexibele behandelingsopties voor deze kwetsbare groep jongeren.

In *hoofdstuk 5* beschrijven wij ook met welke factoren herstel op de lange termijn in onze studie is geassocieerd. Omdat toch ook een substantieel deel van de patiënten niet herstelt, is het van belang zo vroeg mogelijk te differentiëren tussen 'responders' en 'non-responders', opdat de inhoud, duur of keuze van behandeling aangepast kan worden. De belangrijkste factor geassocieerd met herstel was de ziekteduur voorafgaand aan de diagnose. Hoe langer patiënten gediagnosticeerd waren met CVS, hoe kleiner de kans op herstel. Een andere factor geassocieerd met herstel was de 'focus van de moeder op lichamelijke symptomen'. Wanneer de moeder meer gericht was op (haar eigen) lichamelijke symptomen, was de kans op herstel van de adolescent met CVS kleiner. In eerdere onderzoeken kwamen ook maternale factoren, zoals de ernst van moeheid bij de moeder, naar voren als negatief voorspellende factoren voor de kans op herstel. De rol van de vader werd onderzocht in onze studie, maar hierbij werd geen associatie met herstel aangetoond.

Zowel de adolescenten als de ouders werden gelijktijdig behandeld in de FITNET-behandeling, in een bilateraal contact met de therapeut. Onze bevinding dat lange termijn herstel negatief beïnvloed wordt door de focus van de moeder op (haar eigen)

lichamelijk symptomen suggereert dat er een interactie tussen moeder en kind bestaat op dit gebied en mogelijk ook dat er een intergenerationele kwetsbaarheid voor deze klacht bestaat. De mogelijke implicatie van deze bevinding is een intensievere behandeling gericht op 'het systeem' rondom het kind, dan wel een intensievere begeleiding van de moeder bij een subgroep van de adolescenten met CVS. Het feit dat een langere ziekteduur de kans op herstel vermindert geeft wederom het belang aan van het stellen van een tijdige diagnose en vlot starten met de behandeling. Niet alleen vermindert dit de belasting van de aandoening op het kind (met zijn nadelige effecten op de sociale en academische ontwikkeling), het verbetert ook de kans op herstel.

FITNET is momenteel beschikbaar in Nederland voor adolescenten met CVS (www.umcutrecht.nl/cvs en https://mijn.nkcv.nl). Onze intentie is om het programma internationaal beschikbaar te maken. Waarschijnlijk wordt FITNET binnenkort vertaald in het Engels in samenwerking met collega's uit Groot-Brittannië.

Klinische kenmerken

Simultaan aan het FITNET onderzoek hebben wij studies verricht naar verschillende klinische kenmerken van CVS in adolescenten. We hebben onderzocht wat de rol is van pijn (*hoofdstuk 6*), intelligentie (*hoofdstuk 7*) en het hormoon cortisol (*hoofdstuk 8*). Een van de doelen van dit proefschrift was om meer zicht te krijgen op de complexe interactie tussen deze klinische kenmerken en het symptoomcomplex van CVS zoals deze is beschreven in de CDC-criteria. In het bijzonder wilden wij onderzoeken of eventuele afwijkingen/verstoringen van deze factoren ten tijde van CVS reversibel zijn na succesvolle behandeling.

De oorzaak van CVS is nog steeds onbekend. CVS wordt uitgelegd als een verstoring van een centraal neurobiologisch systeem met direct uitlokkende, predisponerende en instandhoudende factoren op zowel biologisch als psychosociaal vlak. Het bio-psychosociale model levert een verklaringsmodel voor de adolescenten en hun ouders en kan bovendien een basis bieden voor behandeling. Dit is uitgebreider beschreven in *hoofdstuk 1*. Predisponerende en direct uitlokkende factoren gaan vooraf aan het ontstaan van CVS, instandhoudende factoren hinderen het herstel. CGT is gericht op de attributies en instandhoudende cognities ten aanzien van de klachten. Echter, niet alle patiënten herstellen middels CGT. Het op tijd identificeren van de patiënten met een lagere kans op succes van de behandeling is belangrijk, zodat voor diegenen de behandeling kan worden aangepast, gezien vertraging in het herstel een forse impact kan hebben op de sociale en educatieve ontwikkeling.

Het is onbekend of verstoringen in pijn(beleving), intelligentie of cortisol primair voorafgaan aan CVS (en dus predisponerende of direct uitlokkende factoren zouden kunnen zijn in het ontstaan van CVS), dan wel secundair ontstaan als gevolg van CVS (en misschien bijdragen aan het instandhouden van CVS). Hoe de verhoudingen tussen al deze factoren ook moge zijn, een beter begrip van de mate van verstoring van deze (klinische) kenmerken en hun reversibiliteit na succesvolle behandeling draagt bij aan het begrip van de aandoening. Kennis hierover kan mogelijk de huidige behandelingen verbeteren, dan wel subgroepen van patiënten identificeren die een op maat gemaakte behandeling nodig hebben.

Onze longitudinale studieopzet heeft het mogelijk gemaakt bovengenoemde factoren op meerdere tijdsmomenten te meten, namelijk voor en na behandeling. Hierdoor konden wij uitspraken doen over de reversibiliteit van de verstoring van deze factoren bij diagnose. Bovendien konden we afwijkingen in deze factoren interpreteren in relatie tot bijvoorbeeld fysieke activiteit, slaap-waakritme, en psychosociale factoren zoals de mate van aanwezigheid van angst en depressie. Al deze parameters werden in het kader van het FITNET-onderzoek gemeten. Daarnaast hebben wij een relatief grote groep patiënten kunnen onderzoeken met een relatief grote gezonde controlegroep van adolescenten die op precies dezelfde wijze als de FITNET-deelnemers hun data hebben verzameld. Wel is het belangrijk om te realiseren dat het primaire doel van de FITNET-trial was om een behandeleffect aan te tonen. De studies naar bovengenoemde klinische kenmerken zijn dan ook meer exploratief van aard. Onze studieopzet leende zich niet primair voor het beantwoorden van etiologische vraagstellingen, aangezien we geen kennis hebben van de factoren vóórdat de diagnose CVS gesteld was. Onderzoeken of er een primaire oorzakelijke rol bestaat voor bijvoorbeeld hypothalamus-hypofyse-bijnier (HPA)-as dysfunctie in de etiologie van CVS is alleen mogelijk in zeer grote cohort studies waarin gezonde adolescenten worden vervolgd. Gezien de lage incidentie van CVS bij adolescenten zou dit zeer grote populaties vereisen om voldoende power te verkrijgen om juiste uitspraken te kunnen doen.

Pijn

CVS gaat vaak gepaard met ernstige pijnklachten en pijn wordt gezien als een integraal onderdeel van het symptomencomplex van CVS. Vijf van de acht nevenkenmerken van de CDC-criteria voor CVS zijn gerelateerd aan pijn: een zere keel, gevoelige cervicale of axillaire lymfeklieren, spierpijn, gewrichtspijnen en hoofdpijn. De aanhoudende pijn is invaliderend en beperkend met betrekking tot het fysiek en

sociaal functioneren. Eerder onderzoek toonde behalve meer pijnklachten ook een lagere pijndrempel aan bij adolescenten met CVS ten opzichte van gezonde jongeren. Wij vroegen ons af of een succesvolle behandeling zou leiden tot 'normaliseren' van pijnklachten en de pijndrempel.

In *hoofdstuk 6* hebben wij beschreven hoe pijndrempels en pijnbeleving veranderden voor en na behandeling van CVS. We concluderen dat pijn een intrinsiek onderdeel is van het symptomencomplex van CVS, waarbij er een duidelijke associatie bestaat tussen pijnklachten en vermoeidheid (hoe meer moe, hoe meer pijn). Zowel de pijnklachten als de pijndrempel 'normaliseren' na herstel van CVS. De mate van pijn bij aanvang van behandeling of de hoogte van de pijngrens waren niet voorspellend voor de kans op herstel.

Hieruit concluderen wij dat er geen specifieke module voor pijnklachten opgenomen hoeft te worden in de behandeling van adolescenten met CVS, omdat de behandelingen aangeboden in de FITNET-studie zich primair hebben gericht op de vermoeidheid en niet specifiek op (het beheersen van) pijnklachten. Dit is waardevolle informatie voor CVS-patiënten met pijnklachten als ze worden geïnformeerd over de behandeling en de prognose van hun ziekte.

Intelligentie

De meeste adolescenten met CVS rapporteren aandachts- en concentratieproblemen, met daaropvolgend verslechterende schoolprestaties. Verschillende studies, voornamelijk gericht op volwassenen met CVS, hebben een verminderd cognitief presteren beschreven op neuropsychologische taken. Met name een tragere verwerkingssnelheid bij complexe informatietaken wordt gerapporteerd. De intellectuele capaciteit van jongeren met CVS is, in tegenstelling tot onderzoek naar geheugen- en concentratieproblemen, echter zelden onderzocht. Slechts één eerdere studie heeft de discrepantie tussen het werkelijk gemeten en het verwachte IQ onderzocht voor adolescenten met CVS in vergelijking met gezonde leeftijdsgenoten in een cross-sectioneel studiedesign. Hierin werd aangetoond dat de verwachtingen van de ouders ten aanzien van het IQ van adolescenten met CVS significant hoger waren dan die van gezonde leeftijdsgenoten. De auteurs concludeerden vervolgens dat hoge verwachtingen van ouders zouden kunnen bijdragen aan de ontwikkeling van CVS. Echter, deze discrepantie tussen het werkelijk gemeten en het verwachte IQ zou zowel een risicofactor kunnen zijn voor het ontstaan van CVS, als een gevolg van de aandoening. Door de cross-sectionele opzet van de studie kan hier niet met zekerheid

een uitspraak over worden gedaan.

Een recente grote cohortstudie toonde aan dat een lagere intelligentie gemeten op de leeftijd van 11 jaar was geassocieerd met functionele somatische symptomen tijdens de adolescentie (niet specifiek CVS). Dit was met name het geval bij de adolescenten die hoge verwachtingen van hun ouders ervaarden.

Hoofdstuk 7 geeft de verschillen weer in intelligentieonderzoek voor en na het ontstaan van CVS. In Nederland wordt middels de zogenaamde CITO-test het intellectueel presteren van alle kinderen gemeten op de leeftijd van 12 jaar. Deze unieke setting, met een algemene beschikbaarheid van de CITO-testscores, maakt het mogelijk om huidige cross-sectionele intelligentie-data ten tijde van CVS te vergelijken met retrospectieve (pre-CVS) intelligentie-data. Van alle deelnemers werden om deze reden CITO-scores opgevraagd. Wij hebben deze uitkomsten vergeleken met een gezonde controle groep.

Uit dit onderzoek bleek dat de huidige IQ-scores van jongeren met CVS lager waren dan verwacht zou mogen worden op basis van hun schoolniveau. Daarbij werd een achteruitgang van intelligentie in het verloop van de tijd waargenomen, als vergeleken werd met de CITO-scores op de leeftijd van 12 jaar. Overigens komen de CITO-scores wél overeen met het schoolniveau waar de adolescenten met CVS in de brugklas mee gestart zijn. Bij de controlegroep bleek het IQ zowel in overeenstemming met het huidige schoolniveau, als met de CITO-score jaren eerder. Deze uitkomsten wijzen er op dat het meten van een verminderd IQ ten tijde van CVS een gevolg zou kunnen zijn van het hebben van CVS. *Hoofdstuk 7* gaat verder in op mogelijke verklaringen voor de gemeten discrepantie.

Een andere mogelijke verklaring is dat de CVS jongeren ‘in hun afwijking groeien’. Want hoewel de CITO-test een hoge correlatie vertoont met IQ-testuitslagen, is het geen formele IQ-test. De adolescenten met CVS presteerden in onze studie met name slecht op performale taken, terwijl geen significante verschillen gevonden werden bij de uitvoering van verbale taken. Komt dit mogelijk door de verminderde verwerkingssnelheid waarmee zij complexe informatie kunnen verwerken? Komt het daardoor dat ze op de (vaak tijdsgebonden) performale taken slechter scoren? Of komt het doordat de CITO-test niet genoeg onderscheid maakt tussen deze twee vormen van intelligentie?

De conclusie van *hoofdstuk 7* is dat CVS kan samengaan met een (mogelijk tijdelijke) achteruitgang van cognitief functioneren. Gebaseerd op de CITO-scores zijn de CVS jongeren naar het voor hen aangewezen middelbare schoolniveau gegaan. Op basis van de CITO-score lijkt de afname in IQ dus eerder een gevolg dan een oorzaak voor het

ontstaan van CVS te zijn. Maar we kunnen niet uitsluiten dat een eerder al aanwezige afwijking in het intellectueel functioneren, niet opgepikt door de CITO-test, iemand kwetsbaar maakt voor het krijgen van CVS. Ongeacht of intelligentie een rol speelt in het ontstaan van CVS of dat deze daling van het IQ wellicht het gevolg is van het ontstaan van CVS, adviseren wij om IQ uitslagen voorzichtig te interpreteren wanneer iemand CVS heeft. We weten namelijk niet of een lagere IQ score komt door concentratieproblemen, een tijdelijk verlaagde verwerkingssnelheid ten gevolge van CVS of een pre-existent lager performaal IQ. Gezien de kritieke leeftijd voor intellectuele ontwikkeling benadrukt dit wederom het belang van een snelle diagnose en van het vlot starten van een behandeling.

Op dit moment voeren wij vervolgonderzoek uit waarin de jongeren opnieuw worden opgeroepen voor een intelligentietest. In dit onderzoek willen wij meten hoe het IQ zich ontwikkelt na het al of niet herstellen van CVS. We zijn met name benieuwd of een verminderd intellectueel presteren ten tijde van CVS (gerelateerd aan het schoolniveau van de CVS-patiënt en de CITO-scores) reversibel is na succesvolle behandeling van CVS. Als de waargenomen 'afname' in IQ blijft bestaan na herstel pleit dit voor de hypothese van 'growing-into-the-deficit' met een te laag IQ voor het schoolniveau als een predisponerende factor voor het ontwikkelen van CVS. Als, daarentegen de IQ-score na herstel van CVS weer 'toeneemt', mogen we concluderen dat de 'verslechtering' in IQ onderdeel is van het symptoomcomplex van CVS.

Cortisol

Eerder onderzoek bij volwassenen met CVS heeft uitgebreid aangetoond dat de HPA-as verminderd actief is, wat zich uit in een verlaagde cortisol piek bij het opstaan ('Cortisol Awakening Response'; CAR). De rol van deze hypofunctie is nog niet geheel duidelijk. Zo is het bijvoorbeeld niet bekend of hypocortisolisme een relevante biologische factor is die van invloed is op het ontstaan van CVS, of dat het een gevolg is van het ontstaan van CVS. Het is mogelijk dat hypocortisolisme ten tijde van CVS (deels) verklaard wordt door de klinische of gedragsmatige symptomen die samengaan met CVS: een verstoord slaap-waakritme, inactiviteit en/of stress. Tot op heden heeft er geen longitudinaal onderzoek plaatsgevonden naar (reversibele) afwijkingen van cortisol in adolescenten met CVS.

In *hoofdstuk 8* hebben we het functioneren van de HPA-as, gemeten middels de CAR, onderzocht bij zowel gezonde jongeren als bij adolescenten met CVS voor en na behandeling. Jongeren met CVS hadden een mild, maar significant, lager cortisol

dan gezonde jongeren, wat normaliseerde na succesvolle behandeling. De absolute toename in cortisol was voorspellend voor behandelsucces; patiënten met een grotere toename in cortisol hadden meer kans op herstel en vice versa.

Deze associatie tussen de CAR en (herstel van) CVS zou kunnen worden gemedieerd door een verandering in klinische of gedragsmatige symptomen die ook samengaan met herstel van CVS, zoals een verbeterd slaap-waakritme of toegenomen fysieke activiteit. Al deze mogelijke 'confounding factoren' zijn gelijktijdig met het bepalen van de CAR gemeten. Een multipele regressieanalyse waarin gecorrigeerd werd voor al deze mogelijke 'confounders' veranderde niet wezenlijk de bevindingen. Hieruit concluderen wij dat een reversibel (mild) hypocortisolisme onderdeel is van het symptomencomplex van CVS. Dit wordt ondersteund door het feit dat de mate van klinische symptomen van CVS, zoals de mate van vermoeidheid en beperkingen, significant correleren met de mate van hypocortisolisme.

Desalniettemin blijft het moeilijk om aan te geven of een mild hypocortisolisme simpelweg samengaat met CVS als onderdeel van het symptomencomplex, of het secundair ontstaat aan verlaagde activiteit en een verstoord slaap-waakritme, of dat het een losstaande factor is van (biologisch) belang in het ontstaan/onderhouden van CVS. Onze data pleiten meer in de richting van het ontstaan van een hypocortisolisme als gevolg van de aandoening, welke herstelt na herstel van de aandoening. De opzet van ons onderzoek is echter niet geschikt om een uitspraak te doen of het milde hypocortisolisme al pre-existent aanwezig is en zo een mogelijke etiologische factor is voor het ontstaan van CVS.

Hoewel een verandering in de CAR iets lijkt te zeggen over de status van CVS, is het niet geschikt om op deze manier de diagnose CVS of herstel ervan vast te stellen. Het hypocortisolisme dat wij vonden is slechts mild en zou niet voldoende onderscheid maken tussen adolescenten met CVS en gezonde adolescenten. Wel veronderstellen wij dat het meten van de CAR gedurende de behandeling eerder zou kunnen aanwijzen welke adolescenten mogelijk herstellen na volledige behandeling en welke niet. De verandering in CAR tijdens de behandeling zou dan kunnen dienen als een 'biomarker' voor behandelsucces. Dit kan gevolgen hebben voor toekomstige behandelstrategieën. Toekomstig vervolgonderzoek zou kunnen worden gericht op veranderingen in de HPA-as tíjdens de behandeling.

Concluderend kunnen we stellen dat de 3 klinische kenmerken hierboven uiteengezet gemeenschappelijk hebben dat ze afwijkend zijn bij adolescenten met CVS (ten opzichte van hun gezonde controlegroep), en zo kenmerkend zijn voor de aanwezigheid van de aandoening. Zowel de mate van pijn als van het hypocortisolisme voorspelt niet

de kans op herstel, maar beide factoren zijn gerelateerd aan ziekte-ernst (gemeten aan de mate van klachten en beperkingen) en beide 'normaliseren' na herstel van CVS. Deze bevindingen suggereren dat pijn en hypocortisolisme intrinsiek onderdeel van het symptomencomplex CVS zijn. Het feit dat beide klinische kenmerken niet worden verklaard door gedragssymptomen, zoals een verstoord slaap-waakpatroon of verminderde fysieke activiteit, maken het onwaarschijnlijk dat deze factoren uitsluitend een 'bijverschijnsel' van de ziekte zijn.

Uiteraard zijn de beschreven (klinische) kenmerken niet uniek voor CVS. Zo is een post-traumatische stress-stoornis als gevolg van een trauma door seksueel geweld ook geassocieerd met een ontregeling van de HPA-as, met als gevolg een hypocortisolisme. Noch zijn pijn en/of hypocortisolisme in elke individuele patiënt in dezelfde mate aanwezig, of zodanig afwijkend ten opzichte van een gezond persoon dat zij als een diagnostische test gebruikt kunnen worden voor het stellen van de diagnose. Ze zijn echter wel nuttig in de beschrijving van 'de toestand' CVS, en zouden mogelijk kunnen bijdragen in de toekomst als een 'biomarker' voor het succes van de behandeling, indien gemeten gedurende de behandeling.

De discrepantie tussen de gemeten intelligentie ten tijde van CVS en voorafgaande aan het ontstaan van CVS (zoals afgeleid uit de CITO-testscore) zou een factor kunnen zijn die de adolescent kwetsbaarder maakt voor het ontwikkelen van CVS. Vervolg-onderzoek zou moeten uitwijzen of het IQ 'verbetert' na herstel van CVS.

Toekomstig onderzoek

Om de behandeling en prognose van adolescenten met CVS verder te verbeteren is het belangrijk om de factoren te identificeren die bijdragen aan de effectiviteit van behandeling en te beoordelen welke factoren zijn geassocieerd met 'non-recovery'. Want hoewel de FITNET-behandeling als effectief wordt gezien, herstelt een derde van de deelnemers niet. Het feit dat de kans op herstel op de lange termijn negatief geassocieerd is met de maternale focus op lichamelijke symptomen, kan een aanwijzing zijn dat deze specifieke predictor onvoldoende belicht wordt in de behandeling. De mogelijke implicatie van deze bevinding is dat voor een subgroep van de adolescenten met CVS een meer intensieve 'systeem-behandeling' nodig is, of een afzonderlijke behandelprogramma voor de moeder. Vervolgonderzoek zou zich op deze vraag kunnen richten.

Ook zou het in de toekomst nodig kunnen zijn om verschillende subgroepen van CVS te onderscheiden op basis van de beoordeling van de HPA-as functie tijdens de behandeling. Wellicht zouden diegenen die waarschijnlijk niet herstellen dan eerder geïdentificeerd worden. Als deze veronderstelling in toekomstig onderzoek zou worden

bevestigd, zou het uitvoeren van een 'randomised controlled trial' die de effectiviteit van een lage dosis hydrocortisonsuppletie onderzoekt om de effectiviteit van CGT te vergroten bij een subgroep van patiënten interessant zijn.

De rol van intelligentie in de ontwikkeling van CVS verdient ook verder onderzoek. Vooral met betrekking tot de mogelijke mechanismen die verantwoordelijk zijn voor de gemeten 'afname' in intelligentie in onze studie en op de mogelijke reversibiliteit hiervan. Halen de voormalig CVS patiënten hun gezonde klasgenoten weer bij of is er een blijvende 'achterstand' in hun intellectuele ontwikkeling?

Betreffende internettherapie zou een FITNET behandelvariant ontwikkeld kunnen worden zonder de feedback van een cognitief gedragstherapeut, om de toegevoegde waarde van de therapeut te onderzoeken. Kwalitatief onderzoek naar de gebruikers-ervaringen met digitale communicatie zou meer informatie kunnen verschaffen over de (meest) effectieve onderdelen van de therapie. Een kosten-effectiviteitsstudie waarin internettherapie vergelijken wordt met reguliere therapie zou interessante informatie opleveren voor aanbieders van zorg en zorgverzekeraars. Tot slot zou de FITNET-behandeling internationaal beschikbaar moeten worden gemaakt, met parallelle studies naar de effectiviteit van de FITNET-behandeling aldaar.

Onze bevindingen ondersteunen het idee dat internettherapie ook effectief zou kunnen zijn voor adolescenten met een chronische aandoening waar vermoeidheid mede op de voorgrond staat. Vermoeidheid en een verstoord slaap-waakritme wordt bijvoorbeeld ook gezien bij adolescenten met een auto-immuunziekte, zoals juveniele idiopathische artritis, of bij adolescenten die op de kinderleeftijd zijn behandeld voor kanker. Deze groepen zouden ook kunnen profiteren van een internettherapie gericht op de vermoeidheidsklachten, aangepast aan hun behoeftes.

CONTRIBUTORS

Prof.dr. Gijs Bleijenberg
Expert Centre for Chronic Fatigue, University Medical Centre St. Radboud, Nijmegen, The Netherlands

Prof.dr. Raoul H. Engelbert
Amsterdam School of Health Professions, University of Applied Sciences Amsterdam
Department of Rehabilitation, Academic Medical Centre, University of Amsterdam, The Netherlands

Prof.dr. Hilleke E. Hulshoff Pol
Rudolf Magnus Institute of Neuroscience, Department of Psychiatry, University Medical Centre Utrecht, The Netherlands

Prof.dr. Jan L.L. Kimpen
Department of Paediatrics, Wilhelmina Children's Hospital, University Medical Centre Utrecht, The Netherlands

Drs. Kimberley Maijer
Department of Paediatrics, Wilhelmina Children's Hospital, University Medical Centre Utrecht, The Netherlands

Linde N. Nijhof, MSc.
Department of Paediatrics, Wilhelmina Children's Hospital, University Medical Centre Utrecht, The Netherlands

Drs. Loudy P. Priesterbach
Department of Paediatrics, Wilhelmina Children's Hospital, University Medical Centre Utrecht, The Netherlands

Dr. Elise M. van de Putte
Department of Paediatrics, Wilhelmina Children's Hospital, University Medical Centre Utrecht, The Netherlands

Drs. Juliette M.T.M. Rutten
Department of Paediatrics, Emma Children's Hospital, Academic Medical Centre Amsterdam, The Netherlands

Rebecca K. Stellato, MSc.
Biostatistics, Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, The Netherlands

Dr. Cuno S.P.M. Uiterwaal
Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, The Netherlands

Charlotte L. Werker, BSc.
Department of Paediatrics, Wilhelmina Children's Hospital, University Medical Centre Utrecht, The Netherlands

DANKWOORD

Vanaf een zonnig terras, hoog boven de rotsen aan de kust van Portofino, kijk ik uit over de Middellandse zee. Werkend aan de laatste fase van dit proefschrift gaan de gedachten automatisch terug naar de start van het onderzoek en de afgelopen jaren die doorvlochten zijn geweest van kliniek en wetenschap. Het werk geleverd voor dit boekje werd mogelijk dankzij de hulp en steun van vele anderen. Een aantal mensen wil ik hiervoor in het bijzonder bedanken.

Allereerst wil ik alle patiënten en hun ouders bedanken die deel hebben genomen aan de verschillende onderzoeken van de FITNET-studie voor hun inzet, tijd en openhartigheid. Ook de jongeren en ouders van scholengemeenschap De Breul uit Zeist die belangeloos deel hebben genomen aan de FITNET studie als gezonde controlegroep wil ik heel hartelijk bedanken.

Eén van de belangrijkst redenen om te gaan promoveren was het idee dat ik veel zou kunnen leren van mijn co-promotor, dr. E.M. Van de Putte. Dit was inderdaad het geval, zowel klinisch als in het onderzoek. Lieve Elise, ik bewonder je aanstekelijke enthousiasme, integriteit en positieve kijk op het leven, niet in staat om de moed ooit te laten varen. Ik ben je ongelooflijk dankbaar voor alle kansen en de vrijheid die je me gaf, ik vond het geweldig om dit project onder jouw leiding vorm te geven.

Professor dr. J.L.L Kimpen, beste Jan, zowel als opleider en als promotor heb ik veel vertrouwen geput uit jouw begeleiding, wat mij telkens weer nieuwe energie gaf. Op afstand en toch heel dichtbij. Altijd maakte je ruimte in je agenda en gaf je advies als ik dat nodig had. Je commentaren op de artikelen waren ondanks je drukke agenda razendsnel en waardevol. Bedankt voor alles wat je me geleerd hebt.

Professor dr. G. Bleijenberg, beste Gijs, mijn eerste ontmoeting met jou was in het najaar van 2006 bij een ontwerpbureau toen we aan de start stonden van FITNET. Het eindigde in de overeenkomst dat ik ‘de FITNET-teksten’ zou gaan schrijven. Een dag later zat ik bij jou in Nijmegen in het NKCV als laatstejaars geneeskunde student. Je vertelde me per uur of ik verder mocht schrijven en die tijd die je ertussen liet voordat je de tekst weer controleerde werd steeds wat langer. Wat vond ik dat spannend, maar ook leerzaam! Jij bent voor mij een voorbeeld in de wetenschap. Jouw kennis, kritische blik, inzicht en enthousiasme voor het onderzoek zijn indrukwekkend. Dank je wel dat je er altijd voor me was, zelfs na je emeritaat.

Dr. C.S.P.M. Uiterwaal, beste Cuno, Jij hebt de gave om dingen die in mijn hoofd heel ingewikkeld leken te vereenvoudigen. Je destilleerde de essentie van de vraag en formuleerde daarna je antwoorden zo helder, dat zelfs ingewikkelde analyses voor mij begrijpelijk werden. Heel veel dank voor de tijd die je elke keer vrijmaakte, maar ook voor de persoonlijke interesse die je toonde.

Ook mijn opleider Kindergeneeskunde Joost Frenkel wil ik bedanken voor de steun en het meedenken in mijn wens kliniek en wetenschap te combineren. Je hebt het altijd weer mogelijk gemaakt dat er tijd was voor onderzoek binnen de opleiding en me gestimuleerd het beste uit mezelf naar boven te halen. Je enthousiasme, kennis en betrokkenheid zijn voor mij een voorbeeld!

De leden van de leescommissie: Prof. Dr. E.E.S Nieuwenhuis, Prof. Dr. A.B.J. Prakken, Prof. Dr. H.E. Hulshoff Pol, Prof. dr. J.G.M. Rosmalen en dr. H. Knoop. Dank voor jullie bereidheid om mijn manuscript te beoordelen en voor de bereidheid om zitting te nemen in de promotiecommissie. Prof. Hulshoff Pol wil ik graag ook bedanken voor het kritisch meedenken betreffende het intelligentie-artikel, dat was ontzettend waardevol. Edward Nieuwenhuis wil ik bovendien bedanken voor zijn stimulerende houding en persoonlijke interesse. Ik heb bewondering voor de manier waarop jij mensen coacht en ruimte geeft.

Veel dank gaat uit naar de (oud)-FITNET-therapeuten van het NKCV. Lieve Thea, Annemarie, Dennis, Jan, Pauline en Henriette, wat heb ik veel respect voor jullie. Dank dat jullie zo vol enthousiasme steeds weer beschikbaar waren voor een nieuwe 'FITNET-ter', ondanks overvolle agenda's. Jullie zijn de pioniers van het NKCV geweest in het web-based communiceren met adolescenten. Lieve Annemarie, dank dat ik een aantal 'face-to-face' sessies hebben mogen bijwonen tijdens de ontwikkelingsfase van het FITNET-portaal. De wijze waarop jij uitleg gaf aan CVS, gebruik ik nu nog steeds in de spreekkamer. Lieve Thea, wat vind ik het altijd gezellig om met jou workshops te geven op congressen en cursussen over de FITNET-behandeling. Je bent een fantastisch mens!

Vele studenten hebben in de loop der tijd onderzoeksstages gedaan. Beste Kim, Merel, Melanie, Sandra, Lien, Loudy, Juliette, Nikita, Charlotte en lieve Linde, ik vond het erg leuk om met jullie samen te werken. Dank voor jullie geduld als ik weer eens langer in de kliniek werd gehouden dan afgesproken. En dank voor jullie interesse en vragen, dat heeft me erg gestimuleerd. Ik wens jullie veel succes in jullie vervolgoplei-

dingen. Lieve Loudy, ook als onderzoeksassistent voor het invoeren van data was je van onschatbare waarde. Heel erg bedankt!

De arts-assistenten en kinderartsen van het Wilhemina Kinderziekenhuis wil ik graag als groep bedanken voor de fijne samenwerking. De combinatie onderzoek, kliniek en een druk sociaal leven (met een jong gezinnetje) blijft uitdagend en het is altijd fijn om hierover van gedachten te wisselen! Ook de kinderartsen en collegae uit het Gelre Ziekenhuis Apeldoorn wil ik bedanken. Ik heb de anderhalf jaar dat ik bij jullie mijn opleiding mocht volgen heel veel geleerd en het ontzettend naar mijn zin gehad. Bedankt voor het meedenken en de interesse in mij en in mijn onderzoek. Beste Pieter, heel wat uren hebben we naast elkaar in de auto gezeten. Dank je wel voor de gezelligheid, ik vond het heel fijn om samen met jou de tijd in Apeldoorn te delen. Lieve Saskia, dank je wel voor je interesse in mij, ik vind het heel bijzonder om zo nu en dan nog eens een mailtje te ontvangen. Beste DJ, samen hebben we vele Brede Blik poli's gedaan, ik vond dat ontzettend leuk en leerzaam. Je bent een bijzonder en eigenzinnig persoon.

Annick, Arjan, Coralie, Evelien, Gerwin, Judith, Lieke, Sanne, Sabine en menig andere bewoner van de flexkamer: Bedankt dat ik hier met veel plezier kon 'wonen' en mijzelf kon zijn. Of het onderzoek nu één dag per week of fulltime was, ik heb me altijd thuis gevoeld op onze onderzoekskamer. Samen met de bewoners van de andere onderzoekskamer, zoals Hubert en Wendy, heb ik heel wat kopjes koffie gedronken, lief en leed gedeeld wat betreft de onderzoeksperikelen en wat ons al zo nog meer bezig hield. Ik zou dat graag blijven doen.

Lieve paranimfen, lieve Judith en Linde, wat ben ik blij dat jullie mij ter zijde willen staan. Judith, zowel letterlijk als figuurlijk zij aan zij deden we allebei onderzoek onder Elise's vleugels. Direct vanaf de start hadden we een fijne band die veel vertrouwen gaf. We waren tegelijkertijd zwanger en hebben allebei een prachtige dochter. Ik bewonder je onuitputtelijke energie en belangstelling voor iedereen. Heel veel succes met de laatste loodjes van jouw proefschrift! Ik ben heel blij dat je naast me staat. Lief Vlindertje; Kleine zusjes worden groot. Wat ben je toch een evenwichtig, intelligente en zorgzame dame. Jouw nuchtere en eerlijke kijk op de wereld brengt mij weer met beiden benen op de grond. Je hebt heel zelfstandig de neuro-psychologische testen uitgevoerd binnen het FITNET onderzoek met een natuurlijk houding die erg gewaardeerd werd door de jongeren. Ik bewonder je enthousiasme waarmee je werkt. Wat ben ik trots op jou en alles wat je doet.

Lieve Montessori-vriendinnetjes, oud huisgenootjes, jaarclub en studievrienden, dank voor jullie interesse in de voortgang van dit onderzoek. Maar vooral ook voor de trouwe vriendschap tijdens mijn afgelopen drukke jaren, dat betekent heel veel!

Beste Peter, dank voor het prachtige schilderij wat je gemaakt hebt en wat de omslag van mijn proefschrift siert. Ik was geraakt toen ik het voor de eerste keer zag. Een kleurrijke vertolking van het origineel.

Lieve Elly en Elibart, Annelies en Wytse, Saskia en Jasper, Marieke en Niels: het is heerlijk om je zo thuis te voelen bij je schoonfamilie. Veel dank voor jullie warmte en gezelligheid, en natuurlijk het vele oppassen. Ik vind het prettig dat ik bij jullie altijd mijzelf mag zijn. Lieve Marieke, altijd een verrassing welke teksten je Julia weer geleerd heb als je hebt opgepast ("Mama, ik heb bloedgroep O positief"). Dank je wel dat ik jou tot 'lijdend voorwerp' mocht maken als er weer eens iets moest gebeuren voor FITNET, zoals model staan voor de foto's van de informatieve website. Lieve Annelies, ik ben er trots op dat jij de vormgeving van dit proefschrift heb gedaan. Je bent ongelofelijk creatief en snapt zonder uitleg wat ik mooi vind. Wat kun jij toch veel! Heel veel dank!

Lieve Maurick, wat zijn Linde en jij toch leuk samen. Dank voor je open interesse en speelse omgang met Julia.

Lieve Inger, lief tweelingzusje, wat zou ik graag, net als vroeger, jouw hand vasthouden en samen, tegelijk of om de beurt, de verdediging uitvoeren. Onze levens zijn altijd verbonden gebleven. Voor de collega's in het UMC is het soms lastig welke Nijhof ze nu weer op de SEH tegenkomen… Je bent heel belangrijk voor me, maar dat weet je. Ik vind het ontzettend fijn dat ik altijd op je terug kan vallen, voor alles. Julia kon eerder Inger zeggen dan mama, dat zegt genoeg… Samen, met Ron en Thijs, zijn jullie echt onderdeel van ons dagelijks leven en ik hoop dat dat altijd zo zal blijven.

Lieve papa en mama. Ik kan me geen betere ouders voorstellen. Jullie hebben ons een heerlijke warme thuisbasis gegeven met alle ruimte, steun en vertrouwen. Buiten dat zijn jullie voor mij een groot voorbeeld in hoe jullie een drukke huisartsenpraktijk hebben gecombineerd met ons als gezin en daarnaast een rijk sociaal leven kunnen combineren. Ontzettend bedankt dat jullie altijd voor me klaar staan! Dit proefschrift is aan jullie opgedragen.

Lieve Julia, wat is mama blij met jou. Trots op elke kleine stap die je maakt. Samen met jou heb ik in mijn verlof de rebuttal van ons Lancet-artikel geschreven. Je was 4 weken oud. In de acht weken die volgde heb ik elke week een reviewer beantwoord. Met jou op mijn arm als mijn inspiratiebron achter de laptop als afwisseling tussen het wennen aan elkaar en tussen het bezoek door. Zo vaak zou ik de tijd stil willen zetten om te genieten van je zoals je nu bent, maar ik ben ook zo nieuwsgierig naar hoe je je ontwikkelen zal.

Lieve Rob, wat ben ik blij dat ik jou ben tegengekomen tijdens de studie. Ik ben intens gelukkig met jou en ons leventje samen, bedankt voor het feit dat je er altijd voor me bent en zoveel moois toevoegt aan mijn leven. Zonder jou was me dit nooit gelukt. Duizend maal dank, ik hou van je.

Ook ben ik enige dank verschuldigd aan de Italiaanse ober die met gevaar voor eigen leven mijn memorystick (vol met data van mijn proefschrift en laatste versies artikelen) heeft gered uit de afgrond grenzend aan datzelfde zonnige terras aan de Middellandse zee…

LIST OF PUBLICATIONS

Nijhof SL, Priesterbach LP, Bleijenberg G, Engelbert RH, van de Putte EM. Functional improvement is accompanied by reduced pain in adolescent chronic fatigue syndrome. *Pain Med.* 2013 Sep;14(9):1435-8.

Werker CL, **Nijhof SL**, van de Putte EM. Clinical Practice: Chronic fatigue syndrome. *Eur J Pediatr*. 2013 Oct;172(10):1293-8.

Nijhof SL*, Priesterbach LP*, Uiterwaal CS, Bleijenberg G, Kimpen JL, van de Putte EM. Internet-based therapy for adolescents with chronic fatigue syndrome: long-term follow-up. *Pediatrics*. 2013 Jun;131(6):e1788-95.

Nijhof SL. Nederlands-Vlaams toponderzoek. Cognitieve gedrags-therapie via internet helpt tegen chronische vermoeidheidssyndroom. *Tijdschrift voor Psychiatrie* 2012 54;10:899-900. Dutch.

Nijhof SL, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. *Lancet*. 2012 Apr 14;379(9824):1412-8.

Author replies to Kindlon T and Crawford J. *Lancet*. 2012 Aug 11;380(9841):562

Nijhof SL, Maijer K, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Adolescent chronic fatigue syndrome: prevalence, incidence, and morbidity. *Pediatrics*. 2011 May;127(5):e1169-75.

Nijhof SL, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Fatigue In Teenagers on the interNET--the FITNET Trial. A randomized clinical trial of web-based cognitive behavioural therapy for adolescents with chronic fatigue syndrome: study protocol. [ISRCTN59878666]. *BMC Neurol*. 2011 Feb 19;11:23.

Nijhof SL, Bakker AL, Van Nieuwenhuizen O, Oostrom K, van Huffelen AC. Is the sleep-deprivation EEG a burden for both child and parent? *Epilepsia*. 2005 Aug;46(8):1328-9.

SUBMITTED

Nijhof SL*, Nijhof LN*, Bleijenberg G, Stellato RK, Kimpen JL, Hulshoff Pol HE, van de Putte EM. The role of intelligence in chronic fatigue syndrome. *Submitted*

Nijhof SL, Rutten JM, Uiterwaal CS, Bleijenberg G, Kimpen JL, van de Putte EM. The role of hypocortisolism in chronic fatigue syndrome. *Under review after revisions*

LIST OF ABBREVIATIONS

AUC_G;	Integrated Area Under the Curve with respect to the ground
BCS:	Body Consciousness Scale
BMI:	Body Mass Index
BSI SCL-90:	Brief Symptom Inventory, short version of the Symptom Check List (90 items)
CAL:	Causal Attribution List
CAR:	Cortisol Awakening Response
CBS:	Dutch Buraeu of Statistics
CBT:	Cognitive Behavioural Therapy
CDC:	Centers for Disease Control and Prevention
CDI:	Children's Depression Inventory
CFS:	Chronic Fatigue Syndrome
CHQ-CF87:	Child Health Questionnaire
CI:	Confidence Interval
CIS-20:	Checklist Individual Strength (20 items)
CITO:	Centraal Instituut Toets Ontwikkeling
CSI:	Children's Somatization Inventory
CVS:	Chronisch Vermoeidheidssyndroom
DOP:	Mean Daily Observed Pain
DPSU:	Dutch Pediatric Surveillance Unit
ECCF:	Expert Centre Chronic Fatigue
EMBU-P/A:	Egna Minnen Betraffende Uppfostran - parental/adolescent version
FITNET:	Fatigue In Teenagers on the interNET
FU:	Follow-up
GET:	Graded Exercise Therapy
GP:	General Practitioner
HPA:	Hypothalamic Pituitary Adrenal
ICPC:	International Classification of Primary Care
IQ:	Intelligence Quotient
IQR:	Inter Quartile Range
LTFU:	Long Term Follow Up
ME:	Myalgic Encephalomyelitis
NA:	Not applicable
NIVEL:	Dutch Institute for Research of Health Services

NNT:	Number needed to treat
OR:	Odds Ratio
PD:	Pediatric Department
PMTK:	Achievement Motivation Test for Children
RCT:	Randomised Controlled Trial
RR:	Relative Risk
SES-28:	Self Efficacy Scale
SPSS:	Statistical Package for the Social Sciences
SRI:	Self Rated Improvement
STAIC:	State-Trait Anxiety Inventory for Children
UC:	Usual Care
UK NICE:	United Kingdom National Institute of Health and Clinical Excellence
UMCU:	University Medical Center Utrecht
Z-score:	Normal score: number of standard deviations below or above the mean

CURRICULUM VITAE

Sanne Nijhof was born, together with her twin sister Inger, on the 21st of June 1982 in Hoorn. Together with their younger sister Linde they grew up in Ooltgensplaat. After secondary education at the Montessori Lyceum Rotterdam she entered medical school at Utrecht University in 2000.

During her medical study she did a clinical rotation Obstetrics & Gynaecology at the University of Sydney, and travelled through Australia for three months. As part of her medical training she performed research at the department of paediatric neurology on the burden of the sleep-deprivation EEG under supervision of prof dr. O. van Nieuwenhuizen. In the final stage of her medical study she did an research elective in social paediatrics under supervision of dr. E. van de Putte. Supervised by her and prof. dr. G. Bleijenberg she adapted the existing cognitive behavioural therapy, which led to the FITNET treatment discussed in this thesis. She graduated in October 2006 and started her residencies in paediatrics at the Wilhelmina Children's Hospital in Utrecht, under supervision of dr. J. Frenkel and prof. dr. J.L.L. Kimpen, and currently dr. J. Frenkel and prof. dr. E.E.S. Nieuwenhuis. At the same time, funding was approved for this thesis on chronic fatigue syndrome in adolescents. Clinical work and research where intertwined ever since. From July 2009 till December 2010 she worked at the department of Child and Youth at the Gelre Hospital Apeldoorn, under supervision of prof. dr. C. Schröder†. In 2012 she won the Maarten Kappelle Tweelingprijs for clinical research. In 2013 she was granted a fellowship for clinical research from the UMC Utrecht to explore the benefits of web-based fatigue treatment in paediatric auto-immune diseases and cancer survivors. She will finish her paediatric training in 2015, after which she hopes to be able to continue combining clinical work with research.

Sanne lives together with her partner Robert Wisse and daughter Julia (2011) in Utrecht.

FITNET SCREENSHOTS

FIGURE 1. FITNET introduction screen / Welkomstscherm FITNET met berichten en mededelingen

FITNET screenshots

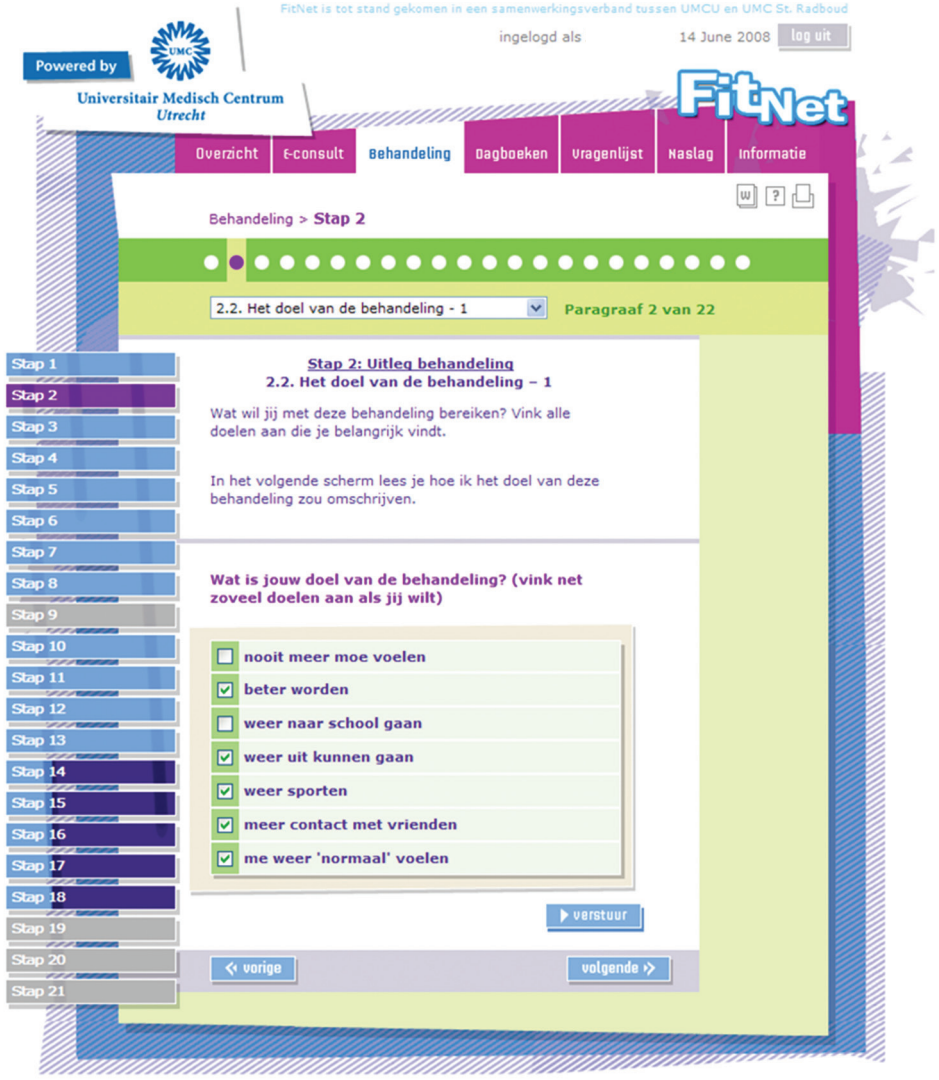


FIGURE 2. Screenshot of treatment module / Voorbeeldpagina van een behandelingmodule

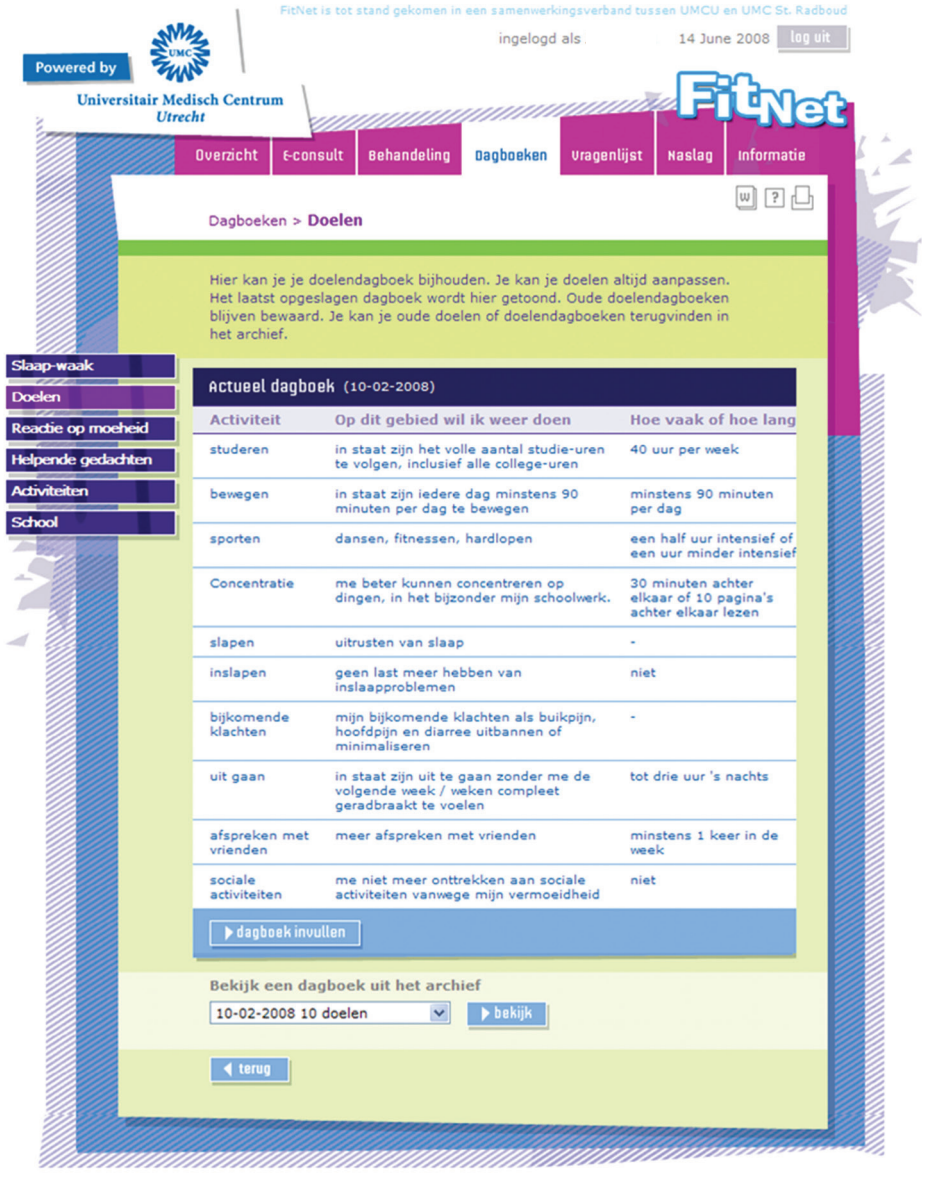


FIGURE 3. Diary with formulated personal treatment goals / Dagboek met persoonlijke behandeldoelen

FIGURE 4. The E-consult screen / Het scherm met E-consulten

FIGURE 5. Filling out the sleeproutine diary / Het slaap-waak dagboek invullen

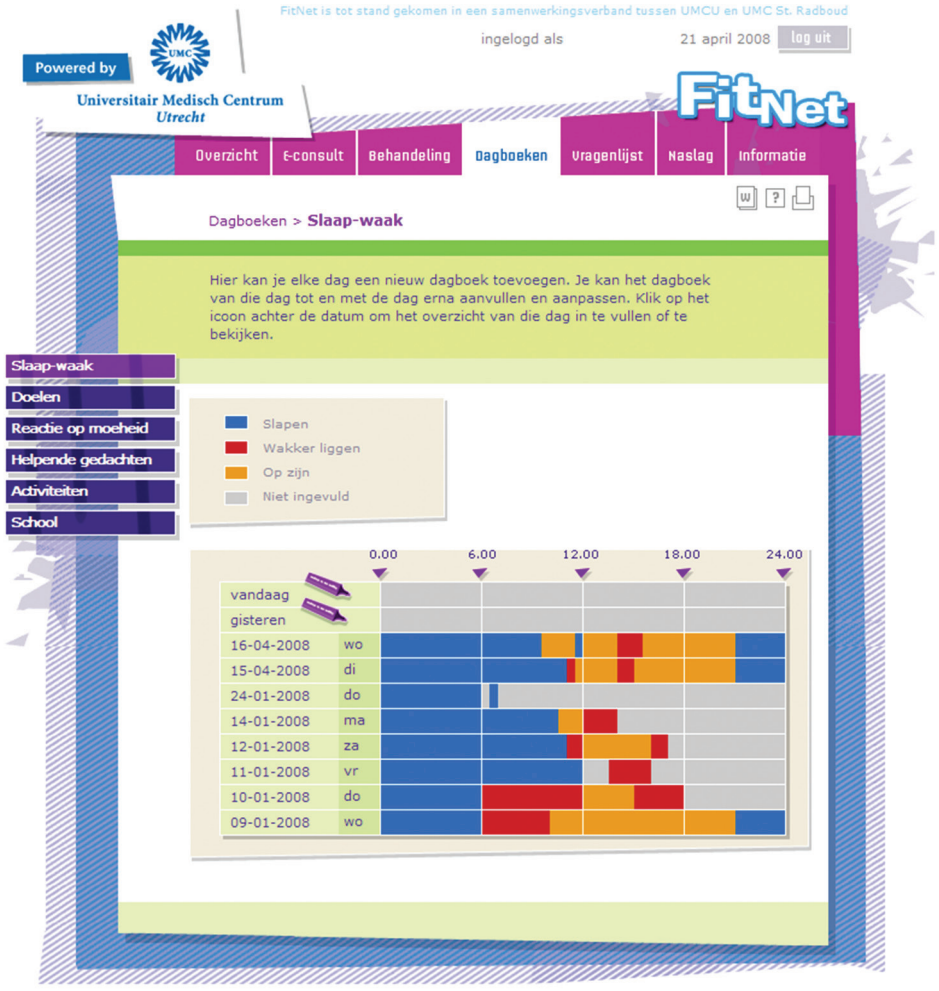


FIGURE 6. A filled out sleeproutine diary / Overzichtspagina van een ingevuld slaap-waakdagboek

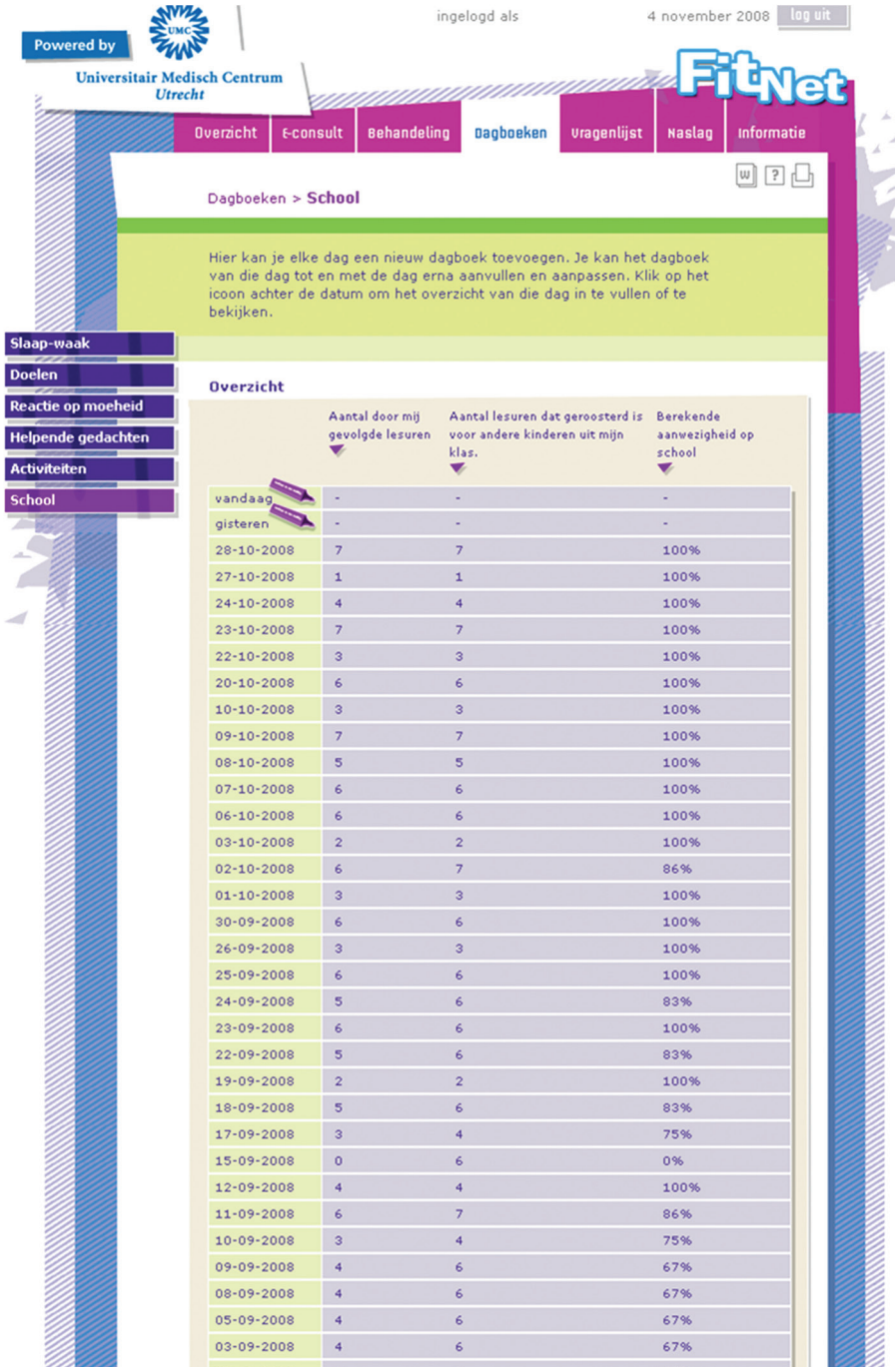


FIGURE 7. Scoring school attendance / Het bijhouden van schoolpresentie