The Application of the International Consensus Criteria to Assess Prevalence of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis in Australia

The application of the International Consensus Criteria to assess prevalence of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis in Australia

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Abstract

Chronic Fatigue Syndrome, also referred to as Myalgic Encephalomyelitis (CFS/ME) is receiving greater public health attention as a complex condition that results in substantial functional impairment. It is largely characterised by severe, medically unexplained fatigue and is associated with a broad range of further symptoms. Diagnosis remains a particular challenge and case definitions remain the primary tool in the absence of reliable and consistent clinical and biological markers. Several case definitions have been proposed and these differ significantly in symptom criteria, comorbid considerations and exclusion of other conditions, thus representing contrasting clinical profiles. This contributes to large differences in reported population, clinical, and laboratory findings reported for CFS/ME.

A systematic review of worldwide prevalence studies was performed and demonstrated that the Fukuda et al. definition has been adopted as a standard. Furthermore, no studies had adopted the more recently proposed International definition. Despite the numerous studies demonstrating the public health impact of CFS/ME abroad, only one report was found estimating CFS/ME prevalence in the Australian population but this report predated the Fukuda and more recent case definitions. In the absence of a prevalence estimate for Australia, a meta-analysis was performed to pool worldwide prevalence figures of Fukuda defined cases. The pooled prevalence for self-reporting assessment was 3.28% (95% CI: 2.24–4.33) and 0.76% (95% CI: 0.23–1.29) for clinical assessment.

The aim of this research was to summarise socio-demographic and illness characteristics of Australians with reported CFS/ME symptoms. To do so, this project established an Australian research registry hosted by the National Centre for Neuroimmunology and Emerging Diseases (NCNED), within Griffith University. This registry consists of enrolled CFS/ME patient information and the results from a cross-sectional survey of patients between April 2013 and April 2015.

Participants were further classified according to Fukuda and International consensus criteria to examine potential differences between these patient sets. A particular concern is that the Fukuda definition may be too broad and select widely heterogeneous patient sets that contribute to inconsistent biological findings in the literature as research continues to test potential aetiology and pathophysiologies for this illness. This research was particularly interested in whether the International definition may identify more specific characteristics as it requires a greater number of symptoms.

The majority of participants were between 40 and 50 years of age, largely female, Caucasian and highly educated. It was found that a subset of patients reporting Fukuda symptoms further fulfilled the International definition. The most common triggers of the onset of CFS/ME symptoms included cold or flu, gastrointestinal illness, and periods of undue stress. Of 54 symptoms surveyed, fatigue, cognitive and short term memory symptoms, headaches, muscle and joint pain, unrefreshed sleep, sensory disturbances, muscle weakness, and intolerance to extremes of temperature were the most commonly occurring symptoms. Significant differences in symptom occurrence between Fukuda and International defined cases were also identified. Further, International defined cases were found to report significantly greater functional impairment.

The findings presented in this thesis represent the first screening of patients reporting CFS/ME symptoms across Australia. This is vital for identifying potential risk factors associated with CFS/ME, and for guiding decisions regarding health care provision, diagnosis and management. In addition to the outcomes reported in this thesis, the database established for this thesis further serves as a sampling pool for further clinical and biological investigations led by NCNED.

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Statement of originality

This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

Samantha Claire Johnston

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Publications arising from this thesis

Journal articles

Included in this thesis are papers in Chapters 2, 3, 4, 5 and 6 which are co-authored with other researchers. My contribution to each co-authored paper is outlined at the front of the relevant chapter. The bibliographic details for these papers including all authors are:

Chapter 2:

Johnston, S., Brenu, E. W., Staines, D., & Marshall-Gradisnik, S. (2014). The role of clinical guidelines for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis in research settings. *Fatigue: Biomedicine, Health & Behaviour, 2*(1), 28-39.

Chapter 3:

Johnston, S., Brenu, E. W., Staines, D., & Marshall-Gradisnik, S. (2013). The adoption of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis case definitions to assess prevalence: a systemic review. *Annals of Epidemiology, 23*, 371-376.

Chapter 4:

Johnston, S., Brenu, E. W., Staines, D., & Marshall-Gradisnik, S. (2013). The prevalence of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: a meta-analysis. *Clinical Epidemiology, 5*, 105-110.

Chapter 5:

Johnston, S. C., Brenu, E. W., Hardcastle, S. L., Huth, T. K., Staines, D. R., & Marshall-Gradisnik, S. M. (2014). A comparison of health status in patients meeting alternative definitions for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. *Health Qual Life Outcomes, 12*, 64.

Chapter 6:

Johnston, S. C., Staines, D. R., & Marshall-Gradisnik, S. M. (2015). An evaluation of differential diagnosis in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An Australian registry for CFS/ME study. *BMC Public Health,* (In review).

Chapter 7:

Johnston, S. C., Staines, D. R., & Marshall-Gradisnik, S. M. (2015). Epidemiological characteristics of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis in Australian patients. *Journal of Clinical Epidemiology*, (In review).

Chapter 8:

Johnston, S., Staines, D., Brenu, E. W., & Marshall-Gradisnik, S. (2014). Management of Chronic Fatigue Syndrome: Current approaches and future directions. In C. Hudson (Ed.), *Chronic Fatigue Syndrome: Risk factors, management and impacts on daily life* (pp. 79-90). New York: Nova Science.

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Conference abstracts

Oral presentations:

Johnston, S., Staines, D. R., Marshall-Gradisnik, S. M. (2015). Epidemiological characteristics of Chronic Fatigue Syndrome in an Australian cohort. *European Congress of Epidemiology*, Maastricht, Netherlands.

Johnston, S., Staines, D. R., Marshall-Gradisnik, S. M. (2015). Development of the Australian registry for Chronic Fatigue Syndrome: Applying new methods of e-research and mixed design in epidemiology. *European Congress of Epidemiology*, Maastricht, Netherlands.

Johnston, S., Staines, D. R., Brenu, E.W., Marshall-Gradisnik, S. M. (2015). Immunological abnormalities in patients fulfilling new diagnostic criteria for Chronic Fatigue Syndrome. *International Student Research Forum,* Aberdeen, Scotland.

Johnston, S., Brenu, E. W., Hardcastle, S. L., Huth, T. K., Ramos, S. B., Staines, D. R., Marshall-Gradisnik, S. M., (2014). Immunological, physical and social functioning in varying cases of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis, *11th International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis Biennial International Research and Clinical Conference*, San Francisco, United States of America.

Johnston, S., Brenu, E.W., Staines, D. R., Marshall-Gradisnik, S. M. (2013). The application of case definitions in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis research. *2nd International Symposium for Chronic Fatigue Syndrome,* Gold Coast, Australia.

Poster presentations:

Johnston, S., Staines, D. R., Brenu, E.W., Marshall-Gradisnik, S. M. (2014). Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: An update for mental health professionals. *14th International Mental Health Conference,* Gold Coast, Australia.

Johnston, S., Brenu, E.W., Staines, D. R., Marshall-Gradisnik, S. M. (2013). A meta-analysis of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis prevalence. *European Congress of Epidemiology*, Aarhus, Denmark.

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Brenu, E., **Johnston, S.,** Hardcastle, S., Huth, T., Fuller, K., Ramos, S., Staines, D., & Marshall-Gradisnik, S. (2013). Immune abnormalities in patients meeting new diagnostic criteria for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. *J Mol Biomark Diagn,* 4(3), 152.

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Additional conference abstracts

Collatz, A., **Johnston, S.,** Staines, D. R., Marshall-Gradisnik, S. M. (2015). Review of drug therapies in the treatment and management of Chronic Fatigue Syndrome. *Population Health Congress*, Hobart, Australia.

Collatz, A., **Johnston, S.,** Staines, D. R., Marshall-Gradisnik, S. M. (2015). Drug Therapy in an Australian Chronic Fatigue Syndrome cohort. *Population Health Congress*, Hobart, Australia.

Fuller, K., Brenu, E. W., Huth, T. K., Hardcastle, S. L., **Johnston, S.**, Nguyen, T., Staines, D. R. & Marshall-Gradisnik, S. M. (2014). Comprehensive analysis of peripheral B cell phenotypes in Chronic Fatigue Syndrome. *9th International Congress on Autoimmunity,* Nice, France.

Fuller, K., Brenu, E. W., Huth, T. K., Hardcastle, S. L., **Johnston, S.,** Staines, D. R. & Marshall-Gradisnik, S. M. (2013). B-lymphocyte subsets in Chronic Fatigue Syndrome, *Autoimmunity Congress Asia*, Hong Kong.

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Hardcastle, S. L., Brenu, E. W., **Johnston, S.,** Nguyen, T., Huth, T. K., Ramos, S., Salajegheh, A., Staines, D. R. & Marshall-Gradisnik, S. M., Alterations in innate and adaptive immune cells in moderate versus severely affected Chronic Fatigue Syndrome/Myalgic Encephalomyelitis, *International Student Research Forum,* Odense, Denmark.

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Huth, T. K, Brenu, E. W., Fuller, K., Hardcastle, S. L., **Johnston, S.,** Staines, D. R. & Marshall-Gradisnik, S. M., Natural killer cell degranulation and lytic proteins in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis, *11th International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis Biennial International Research and Clinical Conference,* San Francisco, United States of America.

Marshall-Gradisnik, S. M., Brenu, E. W., Huth, T. K., Hardcastle, S. L., Kapur, M., **Johnston, S.,** Nguyen, T., Ramos, S., & Staines, D. R. (2014). Chronic fatigue Syndrome/Myalgic

Encephalomyelitis (CFS/ME): Immunological features and possible pathomechanisms, *2nd Asian Clinical Congress, Kyoto, Japan*.

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List of abbreviations

ABS	Australian Bureau of Statistics
AUD	Australian Dollar
BMI	Body Mass Index
CCC	Canadian Consensus Criteria
CDC	Centres for Disease Control and Prevention
CF	Chronic Fatigue
CFS	Chronic Fatigue Syndrome
HREC	Human Research Ethics Committee
HRQoL	Health Related Quality of Life
ICC	International Consensus Criteria
KIR	Killer Immunoglobulin-Like Receptor
ME	Myalgic Encephalomyelitis
NCNED	National Centre for Neuroimmunology and Emerging Diseases
NK	Natural Killer Cell
PENE	Post-exertional Neuroimmune Exhaustion
SEID	Systemic Exertion Intolerance Disease
SF-36	Short Form 36 Item Survey
SPSS	Statistical Package for the Social Sciences
Tregs	T Regulatory Cells
UK	United Kingdom
US	United States
WHO	World Health Organisation
WHO DAS II	World Health Organisation Disability Adjustment Schedule

Chapter 1 Introduction and overview

1.1 Background

Chronic Fatigue Syndrome, also referred to as Myalgic Encephalomyelitis (CFS/ME) is a debilitating illness though the aetiology or pathomechanism remains unknown. The nomenclature surrounding this illness itself, has been a source of debate as multiple terms have been proposed to describe an illness surrounding debilitating fatigue and accompanying symptoms. For the purpose of this thesis, the hybrid term CFS/ME has been adopted as the investigation has been based on formal definitions and review of literature that have used either or both of these terms.

CFS/ME can represent a broad range of contrasting conditions that has been a source of confusion among researchers, clinicians, and the patient community. A significant reason for this is that several case definitions have been proposed for CFS/ME that differ significantly in their symptom criteria. The Fukuda et al., (1994) definition for example, describes persistent fatigue for 6 months, accompanied by muscle and joint pain, sore throat, swollen lymph nodes, headaches, post-exertional malaise, and problems with short term memory and concentration. The recent International definition (Carruthers et al., 2011) has proposed further symptoms pertaining to neurological, cognitive, immunological, gastrointestinal, and autonomic dysfunction.

Case definitions remain the predominant diagnostic tool available for CFS/ME. Particular concerns for investigations on the potential aetiology or pathomechanism behind this illness is that a broad case definition maybe overly inclusive and fail to select homogenous sets of patients (Reeves et al. 2005; Jason et al., 2009; Reeves et al., 2003; Kennedy et al., 2004). Hence, there is a need to evaluate whether new definitions are suitable for research settings.

1.2 Aims and objectives

The primary aim of this thesis was to assess Fukuda and International defined cases in patients reporting CFS/ME in an Australian research database.

The project had the following objectives:

1. To establish a CFS/ME database that includes information on eligible patients across Australia
2. To engage with CFS/ME support networks to build the capacity for the database
3. Estimate the potential prevalence of CFS/ME in Australia
4. To examine differences in population health data including geographical distribution, age, sex, ethnicity, education, occupation, and health service use
5. To examine differences in medical history including comorbities, functional impairment, and reported symptoms
6. To identify a cohort available for long-term follow up and a sampling frame for future population, clinical and biological investigations for CFS/ME

It was hypothesised that substantial differences would be found between these patient sets, thus representing different subtypes of CFS/ME.

1.3 Structure of thesis

1.3.1 Setting

The body of work presented in this thesis was conducted within the National Centre for Neuroimmunology and Emerging Diseases (NCNED), a research centre within the Menzies Health Institute Queensland, Griffith University specialising in immunological, neurological, and clinical investigations into CFS/ME. Accordingly, the work was part of a population health component that accompanied these investigations on CFS/ME. This thesis encompasses a series of publications that aimed to address several public health questions regarding the characteristics of this illness in the Australian population.

This cross-sectional study utilised responses to a survey during a 2 year period from April 2013 and April 2015. The survey was delivered to volunteers during their enrolment into a research registry for CFS/ME managed by the National Centre for Neuroimmunology and Emerging Diseases (NCNED) within Griffith University. This registry serves as sampling pool for immunological and clinical research on CFS/ME, as well as provides a cohort available for longitudinal follow-up. It commenced following approval from Griffith University Human Research Ethics Committee (HREC reference number MSC0413).

1.3.2 Participants

Recruitment was based on self-identification in response to advertisement in CFS/ME community support networks across Australia, as well as general advertisement on local radio, and social media. Upon contacting the research centre, those interested in enrolling into the registry received an information pack and consent was obtained by agreeing to terms and conditions disclosed online or signing a hardcopy sent in the mail. To be eligible for the primary studies presented in this thesis participants were required to (i) report a diagnosis of CFS/ME by their primary physician (ii) be between 18 and 65 years of age and (iii) a resident of Australia.

As recruitment relied on self-identification, it is unknown whether there was a difference between responders and non-responders in this study. Rather than aim for comprehensive population based screening at this stage, the methods of this study enabled us to summarise potential cases of CFS/ME present in the Australian community.

1.3.3 Survey

Participants completed a self-report survey regarding their medical history. This was made available through an online link or by hardcopy in the mail. Items in the study questionnaire were developed by the authors and participants were asked to disclose sociodemographic details, medical history, and complete a 60 item checklist on their fatigue and concurrent symptoms. Responses were

collected using an online survey application known as LimeSurvey (Schmitz, 2012), and stored on a secure server hosted by Griffith University. Data from hardcopy versions of the study questionnaire returned to the research centre by mail were subsequently entered into the LimeSurvey application by a member of the research team to consolidate all responses. All personal data was encrypted to remove the identity of participants.

1.3.3 Case ascertainment

The disclosed medical history of participants were reviewed by the authors of the publications presented in this thesis to exclude any potential diagnoses or conditions that may be an alternative explanation for symptoms. This included, but was not limited to major heart disease, neurological disorders such as multiple sclerosis, autoimmune disease such as rheumatoid arthritis and diabetes, and thyroid disorders. These exclusionary conditions were reviewed by an author of the study who has extensive clinical experience with CFS/ME. If reported, these participants were classified as non-cases.

To be reported as a case of CFS/ME, reported symptoms had to comply with study criteria for fatigue and accompanying symptoms according to the Fukuda and/or International definitions that are outlined in Appendix 3. For this thesis, fatigue must have been present for at least 6 months. Patients accompanying symptoms should not have preceded the onset of fatigue and also be persistent or recurring for at least 6 months.

1.3.4 Chapter summary

The rationale of each publication presented in this thesis is summarised as follows:

Chapter 2: A review of clinical guidelines that have been published for CFS/ME was conducted to outline differences in symptom requirements, comorbid inclusions, and exclusionary criteria. The potential of the International definition in research is discussed.

Chapter 3: A systematic review was performed to assess which case definitions have been adopted to assess the prevalence of CFS/ME worldwide.

Chapter 4: In the absence of prevalence estimate for CFS/ME in Australia, a meta-analysis was performed to pool worldwide estimates of Fukuda defined cases of CFS/ME.

Chapter 5: A pilot study was performed to compare functional impairment between Fukuda and International defined patient sets

Chapter 6: Reported comorbidities were assessed to identify common illnesses that are concurrent in patients meeting Fukuda and International criteria that may aid in diagnosis. Common exclusionary conditions that present similar symptoms as CFS/ME were also reported to examine the role of differential diagnosis.

Chapter 7: Main outcomes of the database established for CFS/ME are reported, including key sociodemographic details and illness characteristics of Fukuda and International defined cases.

Chapter 8: Provides recommendations for management of CFS/ME based on the findings produced from this thesis regarding how patient groups are defined. Currently, the effectiveness of management strategies cannot be recommended universally and need to be confirmed in clearly-defined patient groups. Differences in case definitions, as identified throughout this thesis mean that positive outcomes reported in one study may not be applicable to patients that are defined differently. Hence, this chapter raises important considerations for future management of this illness in terms of how case definitions should be applied to identify good candidates for therapeutic interventions.

The relevant literature, specific aims, employed methodology, results and discussion are disclosed in each publication and further summarised in Chapter 9.

Chapter 2: The role of clinical guidelines for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis in research settings

Statement of Co-authorship

This chapter includes a co-authored paper. The bibliographic details of the co-authored paper, including all authors, are:

Johnston, S. C., Brenu, E. W., Staines, D. R., & Marshall-Gradisnik, S. M. (2014). *Fatigue: Biomedicine, Health & Behaviour, 2*, 28-39.

My contribution to the paper involved the design of the study, provision of data, analysis, and preparation of the resulting manuscript.

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Supervisor: Sonya Marshall-Gradisnik

2.1 Abstract

Background: Chronic Fatigue Syndrome, also known as Myalgic Encephalomyelitis (CFS/ME) is a particularly difficult illness to identify. Before cases can be classified for research, it is highly recommended that potential cases are evaluated according to clinical guidelines.

Purpose: The purpose of this paper is to provide an overview of three guidelines currently available: the Centres for Disease Control and Prevention (CDC) Toolkit (Centers for Disease Control and Prevention, 2006); the International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME) Primer (Friedberg et al., 2012a); and the International Consensus Primer (Carruthers et al., 2012b).

Methods: The guidelines were examined according to required symptoms, laboratory and investigative protocol, exclusionary and comorbid considerations. This comparison should clarify the developments that have been made in understanding the clinical presentation of CFS/ME and the important role they have in identifying patients for research.

Results: Guidelines vary significantly in their symptoms, and in their suggestion of comorbid disorders. There is also no specification on how symptoms should be measured, contributing to the significant variability found in CFS/ME.

Conclusions: Further revisions are required to ensure clinical guidelines are applied accurately and consistently in a research setting.

Keywords: Chronic Fatigue Syndrome; Myalgic Encephalomyelitis; Diagnosis; Case definition;

2.2 Introduction

Chronic fatigue syndrome, also referred to as Myalgic Encephalomyelitis (CFS/ME) is a complex and debilitating illness, of which the current aetiology and underlying physiology is unknown. In the absence of a biological marker, diagnosis is largely based on the presentation of symptoms and exclusion of other illness. A series of overlapping definitions have been proposed and continue to evolve as the clinical presentation and physiological evidence for

CFS/ME become better understood. The most common definition is the 1994 Centres for Disease Control and Prevention (1994 CDC) that describes a debilitating fatigue of more than 6 months, and at least four of eight core symptoms that include post-exertional malaise, unrefreshing sleep, memory and concentration difficulties, muscle pain, joint pain, sore throat, tender lymph nodes, and headaches (1994). Although the definition was originally intended for research purposes, it has also been used clinically.

More recent definitions feature more specific symptom criteria, and have been proposed primarily for use in clinical settings. Adoption of these definitions in a research setting however could potentially reduce the problem of clinical heterogeneity observed in CFS/ME patient sets based on broadly inclusive criteria. The 2003 Canadian Consensus Criteria (CCC) (Carruthers et al., 2003) includes the main symptoms found in the 1994 CDC, but added further symptoms relating to neurological, autonomic, endocrine and immune dysfunction. A revised version of the CCC was released in 2011, known as the International Consensus Criteria (ICC) (Carruthers et al., 2011). To clarify misperceptions about the role of fatigue in the illness, the definition no longer refers to chronic fatigue, but to 'post-exertional neuroimmune exhaustion' (PENE). This is characterized by a pathological low threshold for fatigue after minimal activity and typically long recovery periods of 24 hours or more. In addition to PENE, symptoms are classified under three pathologies: neurological; immune, gastrointestinal, and genitourinary; energy production and transportation.

All of the above definitions advise clinical and laboratory examination to be completed to fulfil their criteria. Accordingly, clinical guidelines have been developed to aid in their application and interpretation and therefore, have an important role in the accurate selection of cases. As researchers begin to adopt new definitions that are available, it is important to examine accompanying clinical guidelines. These are the CDC toolkit (Centers for Disease Control and Prevention, 2006), the International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME) primer (Friedberg et al.,

2012a), and the International Consensus primer (Carruthers et al., 2012b). The purpose of this review is to discuss the differences and similarities among criteria. Comparisons were drawn between diagnostic criteria, laboratory testing, exclusions, and comorbid conditions. Each section then discusses the most important differences and their implications in the diagnosis of CFS/ME. This is critical to understand in order to reduce a significant source of variability in how the illness is identified. The information provided in this review should assist clinicians in their understanding of the illness, as well as researchers in their classification of patient sets.

2.3 Criteria

The clinical guidelines examined are based on different symptom criteria: The CDC toolkit uses 1994 CDC for CFS; the IACFS/ME primer utilizes the CCC for ME/CFS; and the International Consensus primer is based on the ICC for ME. The first immediate difference between the three criteria is the adoption of different terminology. The CDC introduced the term CFS during the late 1980s following reports of a fatiguing illness of unknown cause (Holmes et al., 1988). The term however, may inadvertently emphasize the role of chronic fatigue in an illness accompanied by a range of other important symptoms. The CCC adopted the hybrid term ME/CFS (used interchangeably with CFS/ME) to integrate the use of both ME and CFS that has been used across the literature to describe the same or overlapping illnesses.

The ICC has suggested that those fulfilling its criteria be referred to exclusively as ME patients. While the term CFS may be considered too vague to capture the complexities of the illness, reference to ME alone remains controversial. Its use in this context implies that all cases are associated with inflammation of the central nervous system (CNS) in response to a bacterial, viral or parasitic infection. This finding has not been consistently demonstrated in the literature. This could lead to the assignation of the illness solely and directly to an infectious agent, which has been seen previously in the ill-fated XMRV proposition (Steffen et al., 2011, Cool et al., 2011, Shin et al., 2011, Erlwein et al., 2010, Lombardi et al., 2009, Simmons et al., 2011). This lack of

standard nomenclature can be a significant source of confusion; hence it is important to carefully examine what symptoms are being considered when either term is applied.

Table 2.1: Summary of symptom criteria

Guideline	**CDC Toolkit**	**IACFS/ME Primer**	**International Consensus Primer**
Terminology	CFS	ME/CFS	ME
Case Definition	1994 CDC	Canadian Consensus Criteria	International Consensus Criteria
Symptom criteria			
Chronic fatigue	x	x	
Post-exertional malaise	x	x	x
Impaired concentration and short term memory	x	x	x
Pain (including headaches)	x	x	x
Sleep disturbances	x	x	x
Neurosensory, perceptual and motor disturbances		x	x
Recurrent flu-like symptoms	x	x	x
Susceptibility to viral infections			x
Sensitivities to food, medications and odours		x	x
Cardiovascular		x	x
Respiratory			x
Gastrointestinal and genitourinary		x	x
Loss of thermostatic stability		x	x
Intolerance of extreme temperature			x
Paediatric considerations		x	x

Table 2.1 provides a summary of the type of symptoms found in each criterion. To be considered a patient by the 1994 CDC, patients must fulfil criteria for chronic fatigue of at least 6 months duration, and experience at least four of the following symptoms: post-exertional malaise of more than 24 hours, unrefreshing sleep, short-term memory or concentration problems, muscle pain, joint pain, headaches, tender lymph nodes, and sore throat. The CCC includes the same criteria as the 1994 CDC for chronic fatigue of at least 6 months, but made symptoms of post-exertional malaise, and pain, compulsory. Further symptoms were introduced and categorized according to neurocognitive, autonomic, neuroendocrine, and immune manifestations. Accordingly, a patient must exhibit at least two neurocognitive symptoms, and at least one symptom from two of the remaining categories. In effect, the CCC introduced the use of

symptom clusters where patients experience unique combinations of symptoms from several systems of the body.

The ICC is a revised version of the CCC, and significant changes were made to redefine the role of chronic fatigue in the illness. This included removing the 6 month requirement of chronic fatigue, and featuring post-exertional malaise, which the ICC refers to as PENE as the cardinal feature of CFS/ME. Lacking in the 1994 CDC is an explicit description of what constitutes post-exertional malaise. The CCC describes it as the loss of physical and mental stamina and/or worsening of other symptoms, with a delayed recovery period of more than 24 hours. The ICC expands on this further under its criteria for PENE, in which patients must exhibit 1) a marked, rapid physical/cognitive fatigue in response to exertion; 2) post-exertional exacerbation of other symptoms; 3) immediate or delayed post-exertional exhaustion; 4) prolonged recovery period of more than 24 hours; and 5) a lack of stamina that results in a substantial reduction in pre-illness activity level.

In the previous criteria, fatigue has been described as unexplained, persistent, and not due to ongoing exertion (Carruthers et al., 2003, Fukuda et al., 1994). In contrast, the ICC has redefined the role of fatigue as abnormal in response to exertion. This is the first time a relationship between fatigue and exertion has been introduced in CFS/ME, which may help differentiate the fatigue observed in CFS/ME from that observed in other chronic illnesses. The symptoms suggested in the ICC include all that were previously seen in the CCC, but additions include susceptibility to viral infections, respiratory difficulties, and intolerance of extreme temperatures. The ICC however, organized its symptom profile into three physiological groups. This consists of neurological impairments (at least one symptom from three subcategories); immune, gastro-intestinal, and genitourinary impairments (at least one symptom from three subcategories); and energy metabolism, ion transportation impairments (one symptom). Overall, the criterion is based on the proposal that neurological dysfunction results in faulty interaction between the CNS and the

immune, endocrine and autonomic systems, as well as metabolism and ion transportation at the cellular level.

Upon examination of the development of these three sets of definitions shows that CFS/ME varies from a fatiguing flu-like illness to one that involves the dysfunction of multiple systems of the body. The 1994 CDC has received criticism for maintaining its criteria despite new clinical findings on the illness (Sullivan et al., 2005, Komaroff and Buchwald, 1998b, Buchwald, 1996b, Levine, 1997, Jason et al., 2007). Incidentally, the 1994 CDC is based on criteria previously used for Epstein Barr Virus Syndrome during the 1980s, for which a direct association with the virus was never established (Holmes et al., 1988). The IACFS/ME International Consensus primers however, provide an overview on findings that have contributed to their suggested symptomatology. Further, criteria have evolved from a nominal list of symptoms to the use of symptom clusters, which enables unique patterns of symptoms to be identified in patients. The implications of this for research are discussed further in the review.

Currently the three definitions were primarily devised for assessment of adults and their application in assessment of paediatric and adolescents cases has been particularly limited: the 1994 CDC (Fukuda et al., 1994) is limited for use in adults, and the CCC only suggests reducing the minimal duration of illness to 3 months for children. The ICC (Carruthers et al., 2011) suggests prominent symptoms that may be found in children including headaches, neurocognitive impairments like dyslexia, pain, and joint hypermobility but its effectiveness in distinguishing cases in children has not been examined. A criterion exclusively for the assessment of paediatric cases of CFS/ME however, is available that adapted symptoms largely from the CCC for the assessment of cases under 18 years old (Jason et al., 2008b). This has been shown to effectively distinguish between paediatric cases and healthy controls (Jason et al., 2009). It is therefore, recommended that such specific criteria be adopted for the assessment of paediatric cases rather than applying criteria originally intended for evaluation of adults.

2.4 Laboratory and further investigations

In the absence of specific markers for CFS/ME, the identification of cases relies on differentiating whether symptoms are caused by another physical illness or disease. Recommended routine screening tests for each guideline are summarized in Table 2.2. In general, the guidelines recommend similar tests for screening the presence of rheumatic disease, inflammation, kidney, heart, liver, renal, and thyroid function. Additionally, the IACFS/ME and International Consensus primers have suggested additional blood tests to screen for haematological, autoimmune, endocrine and metabolic disorders.

Table 2.2: Summary of recommended routine screening tests

Guideline	CDC Toolkit	IACFS/ME Primer	International Consensus Primer
Laboratory tests			
Full blood count	x	x	x
Erythrocyte sedimentation rate		x	x
Electrolytes	x	x	x
C-reactive protein	x	x	x
Total protein	x		
Glucose	x	x	x
Phosphate	x	x	x
Calcium	x	x	x
Magnesium			x
Zinc			x
Vitamin D		x	x
B12 and Folate		x	x
Iron studies		x	x
Liver function tests	x	x	x
Renal function tests	x	x	x
Thyroid function tests	x	x	x
Antinuclear antibodies and/or rheumatoid factor	x	x	x
Urinalysis	x	x	x
Essential fatty acids			x
Coenzyme Q10			x
Immunoglobulins			x
Serotonin			x
Tissue transglutaminase test			x

As the guidelines have developed a broader panel of tests has been suggested to investigate specific abnormalities that have been associated with CFS/ME in the literature. These include screening for the presence of specific pathogens. Though a single universal agent has not been identified in patients, viral and non-viral agents have been reported to trigger 11% of CFS cases

(Hickie et al., 2006). It further suggests neurological testing for structural and functional abnormalities (Chen et al., 2008a), and sleep studies (Van Hoof et al., 2007). Moreover, the guidelines recommend monitoring for PENE (VanNess et al., 2007, Van Oosterwijck et al., 2010), as well as tilt table tests for the presence of orthostatic intolerance (Streeten et al., 2000). The International Consensus primer is also the first to include profiling of the immune system, particularly for reduction in NK cell function (Brenu et al., 2012) and a possible increase in cytoxicity (Broderick et al., 2010), as well as signs for intestinal dysbiosis (Sheedy et al., 2009).

2.5 Exclusionary and comorbid conditions

Diagnosis of CFS/ME is largely based on exclusion, and each guideline suggests that any treatable medical and psychiatric conditions must be ruled out before a case of CFS/ME is confirmed. Common exclusions specifically mentioned in all guidelines include multiple sclerosis, chronic hepatitis, hypothyroidism, lupus, cancer, alcohol and substance abuse, and major depressive disorder. Other illnesses may be considered exclusions but are not referred to directly across guidelines. For example, only hypothyroidism and not hyperthyroidism is suggested in the CDC toolkit. Diabetes is noted as an important exclusion in the CDC toolkit and International Consensus primer, but not mentioned in the IACFS/ME primer. Sleep disorders are not specifically referred to as exclusions in the International Consensus primer, though sleep studies are suggested in its protocol.

There are several non-exclusionary conditions that may be present before the onset of CFS/ME, or became associated with it (Table 2.3). All describe Fibromyalgia as a condition most closely associated with CFS/ME. Guidelines also agree in the presence of Irritable Bowel Syndrome and multiple chemical-sensitivities. It is also acknowledged that it is common for symptoms of secondary depression to overlap with CFS/ME, though this is not directly mentioned in the IACFS/ME. Compared to the 1994 CDC definition, the CCC and ICC have been shown to select patients with greater psychiatric comorbidity (Jason et al., 2004, Jason et al., 2011). It is suggested that the higher number of

symptoms required by these criteria may select patients with greater impairment to their mental health functioning than the 1994 CDC (Brown et al., 2013a).

Table 2.3: Summary of suggested comorbidities

Guideline	CDC Toolkit	IACFS/ME Primer	International Consensus Primer
Obesity	X		
Insulin resistance	X		
Metabolic syndrome	X		
Secondary depression	X		x
Fibromyalgia	X	x	x
Multiple chemical sensitivity	X	x	x
Irritable bowel syndrome	X	x	x
Irritable bladder syndrome		x	x
Interstitial cystitis		x	x
Temporomandibular joint syndrome		x	x
Migraine		x	x
Allergies		x	x
Sicca syndrome		x	x
Raynaud's phenomenon		x	x
Prolapsed mitral valve		x	x

There are particular differences between guidelines for example, metabolic syndrome is considered exclusionary in IACFS/ME and International Consensus primers but advised as a comorbid condition by the CDC toolkit. Such disparities could contribute significantly to the clinical variability found within the diverse picture of CFS/ME. For additional illnesses, the CDC toolkit is the only guideline to advise that CFS/ME patients are more likely to be obese. This can be controversial as obesity could explain chronic fatigue and impaired functioning reported in CFS/ME. A recent study has investigated the impact of obesity in CFS/ME, and found that overweight and obese 1994 CDC defined patients demonstrated poorer functioning than obese controls (Flores et al., 2013a). The implications of this in research settings are discussed further in the review.

In contrast to the examples suggested by the CDC toolkit, the IACFS/ME and International Consensus primers feature more extensive list of comorbid conditions. As a general rule, any medical condition that has been treated and controlled or physical abnormality that is not sufficient for an alternative diagnosis can be considered as a comorbid condition. Identifying symptoms

relating to these specific conditions however, may help characterize the symptoms that are attributed to CFS/ME.

2.6 Research applications

Though the clinical guidelines available were devised to aid physicians in their interpretation of the illness, their usefulness in improving consistency in research may be overlooked. The CDC toolkit, IACFS/ME and International Consensus primers all recommend that patient history, clinical, and laboratory examinations must be completed to fulfil criteria for research. A particular source of variability in epidemiological reports for example, has been the inconsistent application of case definitions (Jason et al., 2007). Reliance on self-reporting of symptoms alone, though useful for initial screening purposes can lead to inflated prevalence estimates (Johnston et al., 2013d). Far greater consistency however, is observed when studies involve clinical and laboratory investigations to assess criteria (Johnston et al., 2013d). It is therefore, recommended that research adopt a multi-disciplinary approach with the aid of physicians and psychiatrists to ensure that symptoms of CFS/ME are not due to exclusionary causes or mislabelled as a primary psychiatric disorder.

The guidelines however, vary significantly in their selection of patient sets for research. It is argued that the 1994 CDC definition is broadly inclusive and thus, more likely to select widely heterogeneous patient groups (Reeves et al., 2003, Jason and Richman, 2007). This has been demonstrated among distinct patient sets that all fulfil the definition, but have significantly different clinical measures (Kennedy et al., 2004). In contrast, the CCC and ICC have been shown to select cases with more severe impairments to physical functioning and cognitive symptoms (Jason et al., 2004, Nacul et al., 2011, Jason et al., 2011). Accordingly, fewer patients are known to fulfil the CCC and ICC compared to the 1994 CDC definition (Nacul et al., 2011).

There has been considerable debate as to whether more specific definitions have improved the ability to distinguish cases of CFS/ME from primary psychiatric illness (Jason and Richman, 2007). As discussed previously, greater

rates of psychiatric comorbidity have been identified in CCC and ICC patient subgroups. This was identified after initial psychiatric screening and exclusion of primary psychiatric conditions. It is therefore, important to differentiate that the reported lower mental health status is not indicative of primary psychosis and likely reflective of poorer physical health. A particular issue in broad guidelines is that they do not capture how the impact of the illness can range from mild to very severe. In the most severe cases, patients may be bed-bound for extremely long periods of time and unable to care for themselves, which poses a definite risk of poorer mental health. Psychiatrists therefore, have an important role in distinguishing between primary psychiatric disorders and those presenting with CFS/ME, as well as provide support in the management of the illness.

Further, the CDC toolkit lacks a standard protocol for applying its criteria and may be open to further interpretation than the other guidelines. Accordingly, those fulfilling the 1994 CDC definition may range from mild symptoms to those that are severely debilitated. The International Consensus primer (Carruthers et al., 2012b) is the first to suggest categories of symptom severity: mild cases experience a significant reduction in pre-morbid activity levels, moderate cases experience a 50% reduction, severe are mostly housebound, and very severe are mostly bedridden and requiring assistance. It further allows for sub grouping of symptoms according to prominent pathophysiology of neurological, immune, metabolic/cardio respiratory systems. Adoption of this basic classification system could have advantages when investigating patients with varying severity of clinical signs and symptoms and aligning laboratory data with clinical severity.

The IACFS/ME International primers include a standard worksheet to evaluate cases including important exclusionary illnesses, and comorbid considerations. Though useful to guide clinicians in diagnosis, such worksheets may lack the specificity required in a research environment. For example, the guidelines do not define how to measure a reduction in pre-morbid activity levels, or standard scales to measure the severity and frequency of symptoms. Accordingly, a patient with difficulties concentrating, infrequent headaches and

minor sleep disturbances could fulfil neurological criteria in the ICC. Hence, there is a need in research to verify that patients are indeed experiencing the same symptom profile, and evaluate severity and frequency in which they experience them. There also needs to be a standard list of exclusions and comorbidities to be considered in the evaluation of every case. Ambiguities such as to whether obesity, hyperthyroidism and metabolic disorders can be considered comorbid conditions can lead to confounding of symptoms and make it particularly difficult to study the effects of CFS/ME. Thus, it is important for research to clarify what were considered exclusionary parameters for the consistent selection of patient sets.

Based on the evaluation of each guideline, a framework for how they identify cases for research is proposed in Figure 2.1. The CDC toolkit reports higher rates of CFS, and cases that vary widely in their symptoms. This may only be practical for initial screening of cases in small samples. More specific guidelines may be more useful for research on the aetiology and pathophysiology of the disease. The criteria found in the Canadian guidelines has been found to select fewer patients with more severe symptoms (Jason et al., 2013). Meanwhile, the International Consensus Primer [3] has refined these criteria to identify a distinct illness with PENE as its primary feature. Accordingly, fewer cases have been found to fulfil the ICC in comparison to the Canadian, and also indicate more severe measures of physical and mental health (Brown et al., 2013a, Johnston et al., 2013a). Immune markers previously identified in 1994 CDC defined patients, were also identified in ICC patients, however salient differences in human neutrophil antigens has been identified (Brenu et al., 2013). Hence, the potential of the ICC to detect a distinct subgroup could improve the likelihood of finding a biomarker for the illness.

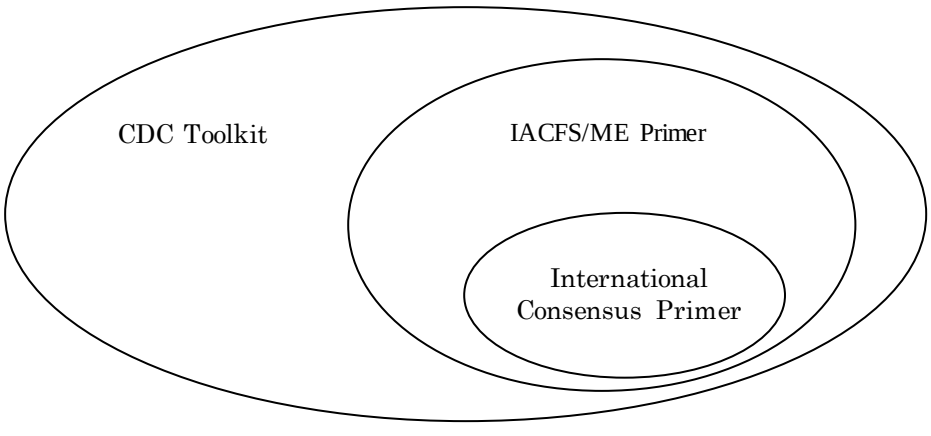

Figure 2.1: Conceptual framework for selection of CFS/ME cases according to different guidelines.

2.7 Conclusion

The identification of CFS/ME cases relies on the application of case definitions that involve a detailed examination of a patient's symptoms, laboratory and further investigations to aid in differential diagnosis, and careful consideration of comorbid disorders. The CDC toolkit is based on the broadest 1994 CDC definition of CFS/ME and may be overly inclusive in research settings. The IACFS/ME primer is based on the more specific CCC, while a revised version of this known as the ICC is featured in the International Consensus Primer. Substantial differences are found between guidelines, which can contribute to significant variations in reported findings on CFS/ME.

The guidelines are primarily intended for the evaluation of adult cases of CFS/ME and symptom criteria vary from 6 months of chronic fatigue and minor symptoms, to the application of symptom clusters to represent an illness that is multi-systemic in nature. Several ambiguities are also found among suggested comorbid and exclusionary conditions, such as hyperthyroidism, obesity and metabolic disorders. Though the guidelines are designed to aid in their application in clinical settings, they have an important role in research settings as it is recommended that a multidisciplinary approach is required where researchers include physician and psychiatric evaluation to accurately identify CFS/ME patients. Currently, the 1994 CDC definition remains the most widely used in CFS/ME research. The adoption of new guidelines may have the potential to identify subgroups of CFS/ME patients with predominant neurological, immune, or autonomic symptoms, which is of particular importance in investigations into potential biological markers. The guidelines however, remain largely subjective to a clinician's perspective. Unless standard and specific protocols are proposed that can be translated for use in a research

setting, definitions may continue to be interpreted and applied quite differently among research groups.

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Chapter 3: The adoption of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis clinical definitions to assess prevalence: A systematic review

Statement of Co-authorship

This chapter includes a co-authored paper. The bibliographic details of the co-authored paper, including all authors, are:

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My contribution to the paper involved the design of the study, provision of data, analysis, and preparation of the resulting manuscript.

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3.1 Abstract

Purpose: Prevalence estimates have been based on several clinical definitions of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME). This is a significant source of variability, and can lead to biased reporting if unsuitable definitions are used. The purpose is to provide a rigorous overview of their application in prevalence research.

Methods: A systematic review of studies reporting CFS/ME prevalence since 1990 was conducted and summarised according to study design and clinic definition used to ascertain cases.

Results: Thirty one studies of CFS/ME prevalence were retrieved. Six clinical definitions have been used to report prevalence. The first estimates of CFS/ME prevalence are based on dated definitions. The 1994 Centres for Disease Control and Prevention (CDC) definition (Fukuda et al., 1994) appears to have been adopted internationally, as a general standard. Only one study has reported prevalence according to a more recent, 2003 Canadian definition (Carruthers et al., 2003).

Conclusion: Advances in clinical definitions during the past 10 years has received little attention in prevalence research. As concerns have been raised on the specificity of the 1994 CDC definition, future assessments of prevalence need to adopt more recent developments, such as the newly available International Consensus Criteria (ICC) (Carruthers et al., 2011). This will improve the surveillance of more specific cases of CFS/ME.

Key words: Chronic Fatigue Syndrome; Myalgic Encephalomyelitis; Systematic Review; Prevalence; Case definition

3.2 Introduction

Several clinical definitions have been proposed for Chronic Fatigue Syndrome or Myalgic Encephalomyelitis (CFS/ME). Patients are commonly described as experiencing persistent or recurrent bouts of fatigue, accompanied by mainly flu-like symptoms such as muscle and joint pain, headaches, sore throat and

cognitive difficulties (Fukuda et al., 1994). More recently proposed models however, emphasise symptoms relating to dysfunction of the neuroimmunological system (Carruthers et al., 2003; Carruthers et al., 2011). Clinical definitions currently remain the predominant diagnostic tool available for CFS/ME and are used to ascertain cases in clinical research, including epidemiology.

Assessment of CFS/ME prevalence commenced in the late 1980s and has since relied on the quality of definitions that are available. A particular concern is that overly inclusive or broad criteria fail to select homogenous sets of patients (Reeves et al., 2005, Jason et al., 2009). Definitions also differ in their emphasis given to specific symptoms and inclusion of co-morbid and psychiatric conditions leading to substantial variability in reported prevalence (Bates et al., 1993, Kawakami et al., 1998, Lindal et al., 2002, Nacul et al., 2011).

The primary purpose of this systematic review is to provide a rigorous overview on reported CFS/ME prevalence according to the clinical definitions used. It is particularly interested in whether prevalence studies have adopted improved clinical definitions into their design. This will help evaluate the reliability of available estimates and how the role of clinical definitions in future surveillance of the disease can be improved.

3.3 Methods

Medline, Embase and PubMed Central databases were systematically searched using the Medical Subject Headings (MeSH) terms of 'Chronic Fatigue Syndrome' and 'prevalence'. Titles and abstracts were screened for potential studies whose primary outcome was to detect the prevalence of CFS/ME in community or primary care samples. Full texts were then examined for suitability. Secondary search was then commenced on reference lists of the studies selected for review. To capture the beginning of prevalence research and the progress of different countries, no restrictions were made to the date and language if detailed summaries in English were available. As this review focuses on CFS/ME prevalence in the general population, it did not include

assessment in high risk or special interest groups. Data were summarised according to sample setting (community, primary care, and special interest groups), sampling method (prospective vs retrospective), age grouping (adult vs paediatric studies) and the clinical definition used to ascertain cases.

3.4 Results

3.4.1 Literature search

The search returned 218 records, including 40 prevalence studies that were assessed for eligibility. Of these 9 exclusions were made: one study based on a case-control design that was considered unsuitable for detecting prevalence (Wessely et al., 1997); one study did not disclose which definition they used (Bazelmans et al., 1999); and 7 studies based on sampling of high risk or special interest groups outside general population surveillance (Buchwald et al., 1995, Minowa and Jiamo, 1996, Jason et al., 1998, Farmer et al., 2004, Huibers et al., 2004, Kim et al., 2008, Kang et al., 2003). The remaining 31 studies were published between 1990 and 2011 and summarised in Table 3.1. Of these, 19 were community based; 12 were primary-care based. Twenty nine used prospective survey methods and 2 used retrospective methods. Twenty five studies assessed cases in adults and 7 assessed cases in children and/or adolescents.

3.4.2 Clinical definitions used

In total, six different definitions have been used to report prevalence: the 1988 CDC, the 1990 Australian, the 1991 Oxford, the 1994 CDC, and the 2003 Canadian. Studies were also found to apply their own clinical definition (Ho-Yen and McNamara, 1991, Nacul et al., 2011) or applied an approximate version of a published definition (Bhui et al., 2011, Price et al., 1992). Early estimates were based on the 1988 CDC, Australian and Oxford definitions. Since 1997, estimates are largely based on the 1994 CDC definition. Only one

Table 3.1: Study design of studies reporting CFS/ME prevalence

Year	Author	Country	Age	Sample[I]	Method[II]	Clinical definition[III]
1990	Lloyd	Australia	all	P	P	Australian
1991	Ho-yen	UK	all	P	P	OCD
1992	Price	USA	18+	P	R	1988 CDC*
1993	Bates	USA	18+	P	P	1988 CDC Oxford Australian
1993	Gunn	USA	18+	P	P	1988 CDC
1995	Jason	USA	18+	C	P	1988 CDC
1995	Lawrie	UK	18+	P	P	Oxford
1997	Dobbins	US	12-17	P	P	1994 CDC
1997	Reyes	USA	18+	P	P	1988 CDC
1997	Versluis	Netherlands	NA	P	P	1988 CDC Oxford
1998	Kawakami	Japan	18+	C	P	1988 CDC 1994 CDC
1998	Steele	USA	18+	C	P	1994 CDC
1999	Jason	USA	18+	C	P	1994 CDC
2000	Jordan	US	5-17	C	P	1994 CDC
2002	Lindal	Iceland	19-75	C	P	1988 CDC Australian Oxford 1994 CDC
2003	Reyes	USA	18-69	C	P	1994 CDC
2003	Chalder	UK	5-15	C	P	1994 CDC
2004	Jones	US	12-17	C	P	1994 CDC
2004	Bierl	USA	18-69	C	P	1994 CDC
2005	Kim	Korea	18+	P	P	1994 CDC
2005	Yiu	Hong Kong	18-59	C	P	1994 CDC
2006	Jordan	US	5-17	C	P	1994 CDC
2007	Rimes	UK	11-15	C	P	1994 CDC
2007	Njoku	Nigeria	18+	C	P	1994 CDC
2007	Reeves	USA	18-59	C	P	1994 CDC
2009	Cho	Brazil UK	18-45	P	P	1994 CDC
2010	van't Leven	Netherlands	all	C	P	1994 CDC
2011	Bhui	UK	16-74	C	R	1994 CDC*
2011	Hamaguchi	Japan	20-78	C	P	1994 CDC
2011	Nijhof	Netherlands	10-15	C	P	1994 CDC
2011	Nacul	UK	18-64	P	P	1994 CDC Canadian OCD

I P, primary care; C, community sample II P, prospective; R, retrospective III OCD, author applied own case definition; CDC, Centre for Disease Control and Prevention
* author applied approximate version of definition

study examined prevalence according to the 2003 Canadian definition. Furthermore, all 7 reports of prevalence in paediatrics found in this review were

based on the 1994 CDC definition for adults. Six of these were published after the 2003 Canadian definition for CFS/ME in children was released. After the publication of these studies, the 2011 International Consensus Criteria (ICC definition) (Carruthers et al., 2011) has become available.

3.5 Discussion

3.5.1 Clinical definitions in present studies

This review found six different clinical definitions have been used during the development of prevalence studies for CFS/ME. Typically, CFS/ME is described with persistent or recurrent fatigue for a minimal duration of 6 months but each differs significantly in its requirement of accompanying symptoms.

The 1988 CDC definition described fatigue of at least six months duration as the major criterion and eight flu-like symptoms such as mild fever, sore throat, painful lymph nodes and headaches, as minor criteria. It also strictly excluded psychiatric conditions including anxiety and depression. This CDC definition was criticised for its emphasis on fatigue, which is not unique to CFS/ME and may apply to other fatiguing illness (Matthews et al., 1988). However, comparison with other definitions suggests it has been the most restrictive, as it reports the lowest estimates of prevalence (Bates et al., 1993, Kawakami et al., 1998, Lindal et al., 2002).

The Australian definition described fatigue accompanied by neuropsychiatric dysfunction. This definition was considered to contribute to bias in selecting CFS/ME patients with psychiatric disorders (Komaroff and Buchwald, 1998a). Ho-yen et al (Ho-Yen and McNamara, 1991) applied their own similar definition but the minimal duration of illness was reduced to 3 months and excluded only known medical and psychiatric conditions (Ho-Yen, 1990). This may be the reason for a considerably higher prevalence of 0.15% detected in Scotland (Ho-Yen and McNamara, 1991), compared to only 0.04% prevalence in Australia using the former definition (Lloyd et al., 1990). The 1991 Oxford definition removed accompanying symptoms to fatigue altogether; describing CFS/ME as mental and physical fatigue associated with an infection

(Sharpe et al., 1991). As only one symptom is required, it was criticized for not distinguishing CFS/ME patients from those without the disease (Jason et al., 2012).

The 1994 CDC definition has generally been adopted in the literature as a standard definition for CFS/ME. Compared to the 1988 version, the required number of symptoms was reduced from eight to four (Fukuda et al., 1994). Psychiatric exclusions were also less restrictive because it permitted anxiety and less severe forms of depression. It is argued however that the definition is too broad and vague in its requirements, leading to the inconsistent selection of cases in clinical research (Reeves et al., 2003). Further investigation on its specificity has found significant differences in simple clinical measurements between groups of patients that fulfil the definition (Kennedy et al., 2004).

Furthermore, retrospective studies have been found to apply approximate versions of a clinical definition to general population health surveys to report the prevalence of CFS/ME. Bhui et al (Bhui et al., 2011) for example, attempted to approximate 1994 CDC by defining cases of CFS/ME as fatigue; concentration or memory problems; sleep issues; and pain. This only meets 3 of the 8 possible symptoms in addition to fatigue specified by the 1994 CDC definition. Therefore, caution must be taken when interpreting estimates based on approximated clinical definitions of CFS/ME.

None of the above definitions discussed appear to capture the prevalence of those with the most severe clinical manifestations. Unlike previous definitions, the 2003 Canadian features explicit descriptions of post-exertional malaise; sleep dysfunction; pain; neurocognitive impairment; as well as autonomic, neuroendocrine and immune manifestations (Carruthers et al., 2003). Compared to patients that only meet the 1994 CDC definition, patients fulfilling the Canadian definition are found to experience more severe physical and cognitive symptoms (Jason et al., 2012, Nacul et al., 2011, Jason et al., 2009). The Canadian definition is also the first to offer an alternative definition for paediatric cases of CFS/ME and has been shown to effectively distinguish between paediatric cases and healthy controls (Jason et al., 2009).

Despite its availability in 2003, only one study has reported a prevalence of 0.11% in the UK for adults (Nacul et al., 2011) and recent studies of prevalence of paediatric CFS/ME continue to rely on the 1994 CDC definition for adults (Dobbins, 1997, Jordan, 2000, Chalder et al., 2003, Farmer et al., 2004, Jones et al., 2004, Jordan, 2006, Rimes et al., 2007, Nijhof et al., 2011). A potential reason for the Canadian definition's late adoption is that the CDC may be easier and less timely to administer, as it requires the verification of less symptoms.

3.5.2 Clinical definitions in future studies

The findings of the review highlight three important issues in the development of prevalence studies. 1) Since definitions have changed over time, early estimates cannot be compared to recent ones. Accordingly, it is not possible to measure accurately how prevalence has changed over time. 2) The 1994 CDC definition has been used as a standard definition for CFS/ME, while new developments in clinical definitions have received very little attention in prevalence research. This could be a potential source of bias in reporting prevalence. 3) Reports of paediatric prevalence may not be accurate, because they are based on a definition designed for adults. To address these issues in future assessment, it is proposed that the 2011 ICC definition be systematically applied in prevalence research. The potential for ICC to diagnosis further subgroups of CFS/ME in comparison to the 1994 CDC is displayed in Figure 3.1.

The ICC definition is the latest version of the 2003 Canadian definition that introduces a number of distinct changes to how CFS/ME is defined. To diagnose cases, the symptom of fatigue is no longer required and an emphasis is made on post-exertional neuroimmune exhaustion (PENE) instead. Though previous definitions described 'malaise', this was viewed as a vague and inaccurate term to describe the physical response to exertion. A minimal duration of illness is also no longer required to allow early diagnosis. Furthermore, it is the first to distinguish severity of cases; proposing a 50% reduction in previous activity levels as mild, moderate as mostly housebound, severe as mostly bedridden and very severe as totally bedridden. Furthermore, a

useful tool in administering the ICC is the availability of a clinical primer to assist health professionals in the interpretation of symptoms to diagnosis ME (Wallesch, 2006). Accordingly, its use may be particularly effective in prevalence studies that are conducted in a primary care setting where clinicians are available to assess cases.

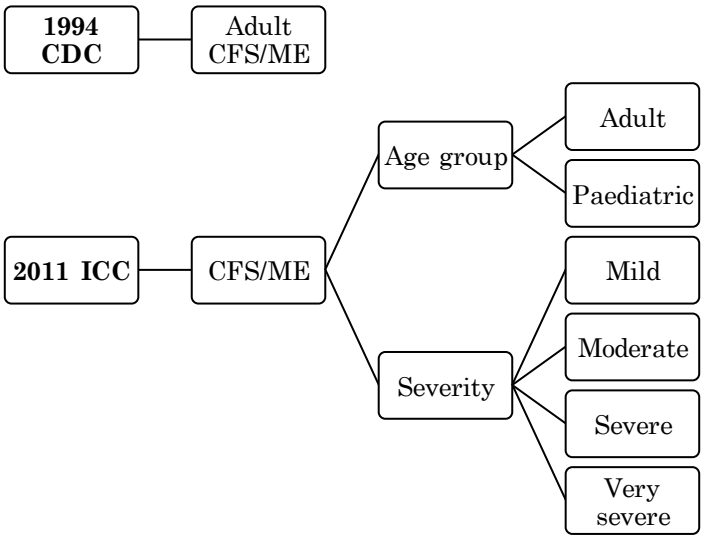

Figure 3.1: The 1994 CDC vs 2011 ICC definition in assessment of cases
The 2011 ICC definition specifies additional criteria for the evaluation of paediatric cases and cases of different severity. Abbrev: CDC, Centres for Disease Control; ICC, International Consensus Criteria; CFS/ME, Chronic Fatigue Syndrome/Myalgic encephalomyelitis

3.6 Conclusion

Available estimates of CFS/ME prevalence are largely based on definitions that emphasise prolonged fatigue and broad cognitive difficulties and flu-like symptoms. Recent developments in definitions however, have moved away from these original models and feature more specific neuroimmunological symptoms. This however, has received little attention in prevalence studies as the 1994 CDC continues to be used as the standard definition of CFS/ME in recent studies. This review proposes that a systematic approach be taken in future studies using the 2011 ICC definition to identify more specific cases of CFS/ME. This can help make prevalence studies reproducible in different countries and lead to more effective surveillance of the disease, which can provide further insight on socio-demographic characteristics of the illness.

Chapter 4: The prevalence of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: A meta-analysis

Statement of Co-authorship

This chapter includes a co-authored paper. The bibliographic details of the co-authored paper, including all authors, are:

Johnston, S., Brenu, E. W., Staines, D., & Marshall-Gradisnik, S. (2013). *Clin Epidemiol, 5,* 105-110.

My contribution to the paper involved the design of the study, provision of data, analysis, and preparation of the resulting manuscript.

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Samantha Claire Johnston

(Countersigned) _____ (Date) _____

Corresponding author of paper: Samantha Claire Johnston

(Countersigned) _____ (Date) _____

Supervisor: Sonya Marshall-Gradisnik

4.1 Abstract

Purpose: To perform a meta-analysis to examine variability among prevalence estimates of CFS/ME, according to method of assessment used.

Methods: Databases were systematically searched for studies on CFS/ME prevalence in adults that applied the 1994 Centres for Disease Control (CDC) case definition (Fukuda et al., 1994). Estimates were categorized into two methods of assessment: self-reporting of symptoms vs. clinical assessment of symptoms. Meta-analysis was performed to pool prevalence by assessment using random effects modeling. This was stratified by sample setting (community or primary care) and heterogeneity was examined using the I^2 statistic.

Results: Of 218 records found, 14 studies were considered suitable for inclusion. The pooled prevalence for self-reporting assessment was 3.28% (95%CI: 2.24-4.33) and 0.76% (95%CI: 0.23-1.29) for clinical assessment. High variability was observed among self-reported estimates, while clinically assessed estimates showed greater consistency.

Conclusion: The observed heterogeneity in CFS/ME prevalence may be due to differences in method of assessment. Stakeholders should be cautious of prevalence determined by the self-reporting of symptoms alone. The 1994 CDC case definition appeared to be the most reliable clinical assessment tool available at the time of these studies. Improving clinical case definitions and their adoption internationally will enable better comparisons of findings and inform health systems about the true burden of CFS/ME.

Keywords: Chronic Fatigue Syndrome, Myalgic Encephalomyelitis, prevalence, meta-analysis

4.2 Introduction

Chronic fatigue syndrome or Myalgic Encephalomyelitis (CFS/ME) is most commonly characterized as fatigue for more than 6 months accompanied by symptoms such as muscle and joint pain, sore throat, tender lymph nodes, and

cognitive difficulties (Fukuda et al., 1994). It is not relieved by rest and results in a substantial reduction in patients activity levels prior to onset.

Studies on its prevalence have been available since 1990. While most reports have come from the United States and Europe, increasing estimates are emerging from Asia and developing countries such as Nigeria (Kawakami et al., 1998, Kim et al., 2005, Njoku et al., 2007, Hamaguchi et al., 2011). Prevalence varies from as low as 0.2% to as high as 6.41%.(Yiu and Qiu, 2005, Nacul et al., 2011). A previous review suggested that the inconsistency is more likely due to differences in study design rather than true differences in prevalence (Ranjith, 2005). Prior to epidemiological surveys, prevalence was suggested based on clinical reviews of patients in tertiary care (Murdoch, 1987). The first studies to use prospective sampling methods were based on physician referrals (Lloyd et al., 1990, Ho-Yen and McNamara, 1991, Gunn et al., 1993, Reyes et al., 1997).

Studies gradually began to directly screen samples from primary care clinics (Bates et al., 1993, Lawrie and Pelosi, 1995, Reyes et al., 1997, Versluis et al., 1997, Wessely et al., 1997, Cho et al., 2009) and the wider community (Price et al., 1992, Jason et al., 1995, Kawakami et al., 1998, Steele et al., 1998, Jason et al., 1999, Lindal et al., 2002, Reyes et al., 2003b, Bierl, 2004, Yiu and Qiu, 2005, Njoku et al., 2007, Reeves et al., 2007, van't Leven et al., 2010, Bhui et al., 2011, Hamaguchi et al., 2011) through questionnaires and structured interviews. In contrast, larger population based studies firstly screen medical databases for potential cases (Versluis et al., 1997, Nacul et al., 2011).

A particular issue in the development of prevalence studies is case definitions that differ fundamentally with respect to inclusion criteria for comorbid and psychiatric conditions. Several studies have demonstrated the difference in prevalence detected according to the case definition used (Bates et al., 1993, Wessely et al., 1997, Kawakami et al., 1998, Lindal et al., 2002, Nacul et al., 2011). In Iceland for example, prevalence was estimated as 4.8%, 2.4% and 1.4% using the Australian, Oxford, and 1994 CDC criteria, respectively (Lindal et al., 2002). Even when the same case definition is applied across studies, different methods have been used to ascertain cases. Many studies rely on the

self-reporting of symptoms alone (Price et al., 1992, Lawrie and Pelosi, 1995, Kawakami et al., 1998, Steele et al., 1998, Lindal et al., 2002, Bierl, 2004, Yiu and Qiu, 2005, Njoku et al., 2007, van't Leven et al., 2010) while others complete clinical assessment of symptoms (Bates et al., 1993, Jason et al., 1995, Wessely et al., 1997, Jason et al., 1999, Reyes et al., 2003b, Kim et al., 2005, Reeves et al., 2007, Hamaguchi et al., 2011, Nacul et al., 2011). The effect of study design on prevalence however, has not been examined.

This study performed a meta-analysis to assess consistency between estimates and this paper presents its findings. The aim was to verify whether prevalence varied according to method of assessment used to detect cases. It was hypothesized that prevalence estimates relying on the self-reporting of symptoms would, on average be higher and less consistent than estimates based on clinical assessment. This was completed using guidelines by the Meta-analysis for Observational Studies in Epidemiology (MOOSE) Group (Stroup et al., 2000).

4.3 Method

4.3.1 Literature search

Systematic search of Medline, Embase and Pubmed Central databases was conducted using Medical Search Headings (MeSH terms) 'Chronic Fatigue Syndrome' (which also captures myalgic encephalomyelitis) and 'prevalence'. No limit was applied to years published or language. The strategy also included secondary search of reference lists of records retrieved from the databases.

4.3.2 Selection of studies

Titles and abstracts were screened for potential studies and full text articles were assessed for suitability. The outcome of interest was prospective studies on the point prevalence of CFS/ME, as defined by the authors of each study. Period prevalence was not considered as it may result in inflated prevalence estimates when compared to point prevalence. Selected studies were based on community or primary care samples, where the condition is most often

presented. Studies on secondary and tertiary care patients were excluded as high-risk groups, as well as groups of special interest that did not represent the general population such as veterans and nurses.

Studies published in languages other than English were also included if detailed English summaries were available. Only studies that applied the 1994 CDC case definition were selected. This was identified as the most widely applied criteria among prevalence studies. This case definition has been the most widely accepted definition available at the time of these studies and is also the current criteria used by the CDC and more selective than previously proposed Australian (Lloyd et al., 1990) and Oxford criteria (Sharpe et al., 1991). Furthermore, only studies on samples aged 18 years and above were included as the 1994 CDC definition was designed for the detection of CFS/ME in adults (Fukuda et al., 1994).

4.3.3 Data extraction and analysis

Data were extracted on sample size, response rate, number of cases detected, method of assessment (self-reporting vs. clinically assessment) and sample setting (community vs. primary care). Sample size was calculated as the total number of participants invited to the study minus the number of non-responders. Prevalence was tabulated as the number of cases detected divided by sample size, along with standard errors. All estimates were expressed as percentage of the population. Separate tabulations were made according to method of assessment, sample setting, age and gender. The inverse variance method by DerSimonian and Laird (DerSimonian and Laird, 1986) adjusted for random effects was used to calculate pooled prevalence and 95% confidence intervals for self-reported and clinically assessed symptoms of CFS/ME. Heterogeneity between studies was tested using the I^2 statistic. Sensitivity analysis was performed to test the influence of possible outliers. Meta-analysis was performed in STATA v.10.0. Studies that reported prevalence for more than one study site or for both methods of assessment were treated as separate studies for the purpose of modeling.

4.4 Results

The literature search found 218 records, including 26 prevalence studies that were further assessed for eligibility (Figure 4.4.1). Of these, 11 exclusions were made: 10 did not use the 1994 CDC case definition for CFS/ME (Lloyd et al., 1990, Ho-Yen and McNamara, 1991, Price et al., 1992, Bates et al., 1993, Gunn et al., 1993, Jason et al., 1995, Lawrie and Pelosi, 1995, Reyes et al., 1997, Versluis et al., 1997, Bhui et al., 2011) (including 3 reporting period prevalence (Gunn et al., 1993, Reyes et al., 1997, Versluis et al., 1997); 1 study recruited participants with acute viral illness as part of a case control design (Wessely et al., 1997). During sensitivity analysis, a further study (Nacul et al., 2011) with a statistical weight of more than 90% was excluded from the investigation.

Fourteen studies published between 1995 and 2011, were considered suitable for meta-analysis. Eleven were based on community samples and 3 on primary care samples. Most studies reported CFS/ME cases based on the self-reporting of symptoms alone (Kawakami et al., 1998, Steele et al., 1998, Lindal et al., 2002, Bierl, 2004, Yiu and Qiu, 2005, van't Leven et al., 2010, Jason et al., 1995). Three studies reported cases after clinical assessment of symptoms (Kim et al., 2005, Cho et al., 2009, Hamaguchi et al., 2011) while four studies provided estimates for both methods (Jason et al., 1999, Reyes et al., 2003b, Njoku et al., 2007, Reeves et al., 2007). Including one study that contributed estimates for two separate study sites (UK and Brazil), a total of 19 estimates were tested by meta-analysis. Insufficient data was found in more than 50% of studies to allow summaries of age-gender specific prevalence to be calculated.

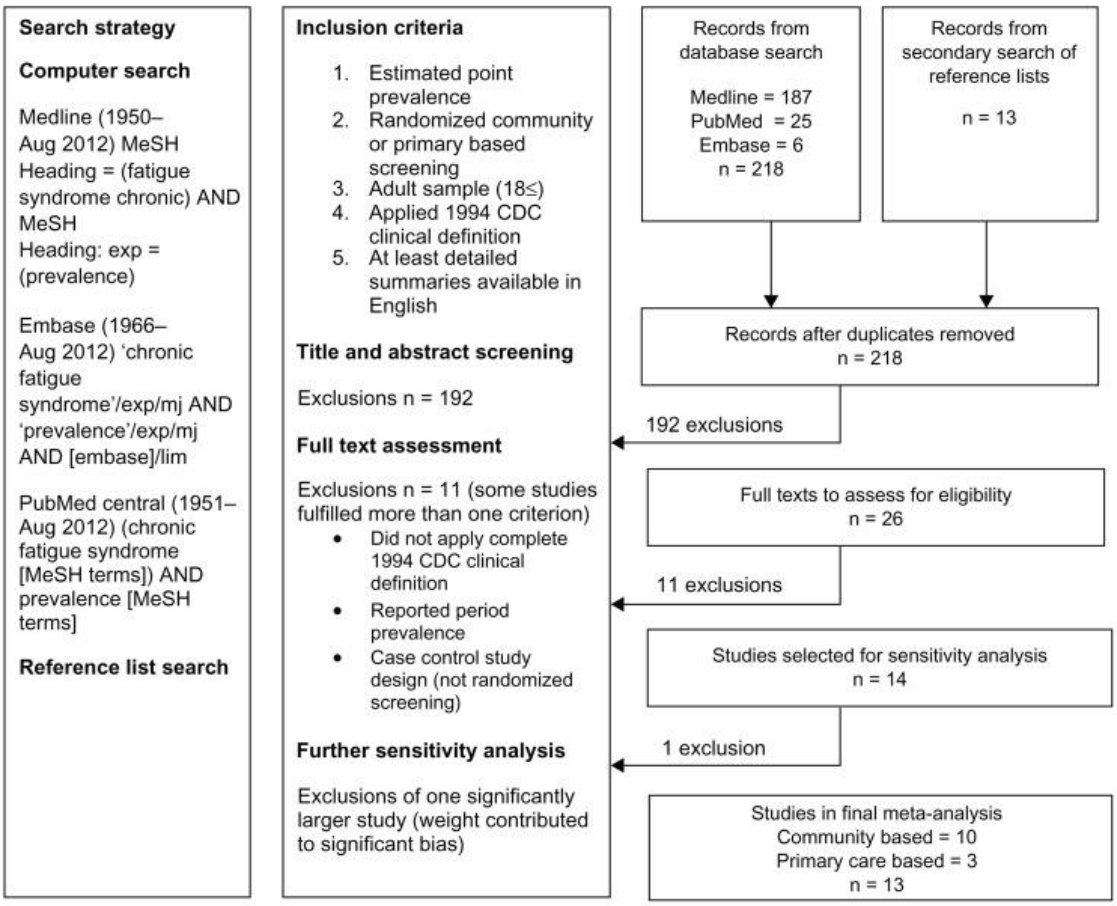

Figure 4.1: Flow chart for the selection of prevalence studies for the meta-analysis

The overall, pooled prevalence for self-reported CFS/ME was 3.48% (95%CI: 2.36-4.60) and high heterogeneity was observed (I^2=58%). All samples were community-based (Figure 4.2). The overall, pooled prevalence for CFS/ME detected with clinical assessment was lower at 0.76% (95%CI: 0.23-1.29) and no heterogeneity was detected (I^2=0%) (Figure 4.3). Heterogeneity remained lower than self-reporting studies when estimates were systematically removed during sensitivity analysis. Prevalence however, was lower in community samples (0.87%; 0.32-1.42) than in primary care samples (1.72%; 1.40-2.04). Low heterogeneity (I^2=*19%*) was found among community samples. Moderate heterogeneity was detected between the three primary care samples (I^2=*48%*).

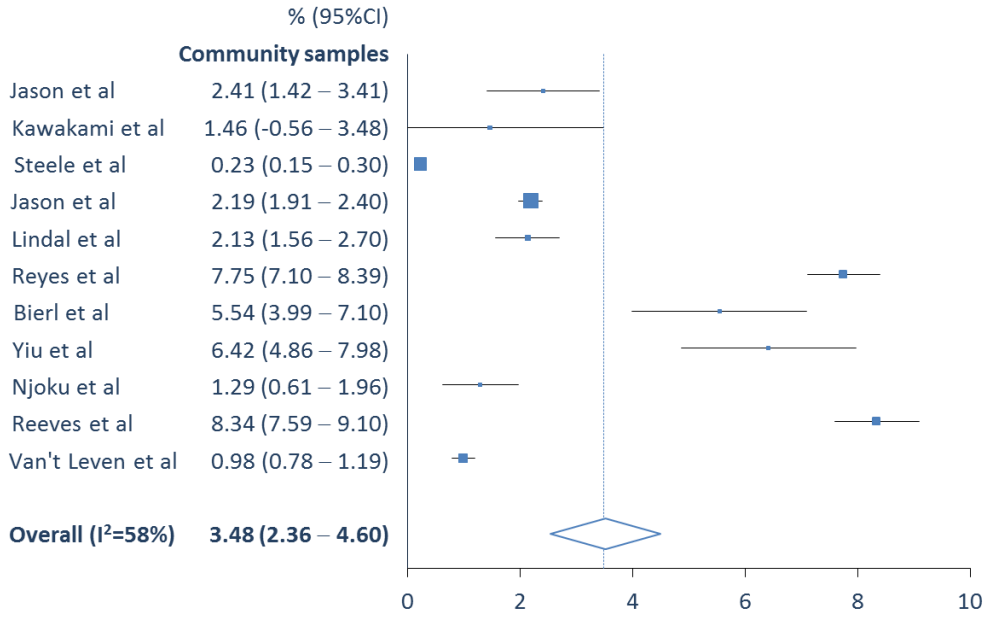

Figure 4.2: Flow chart for the selection of prevalence studies for the meta-analysis

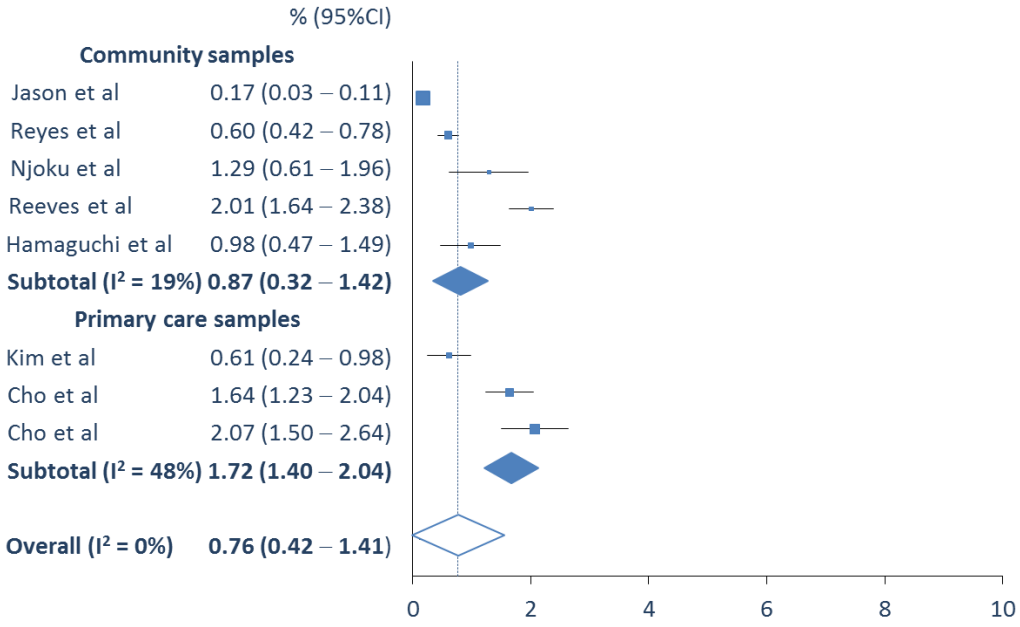

Figure 4.3: Flow chart for the selection of prevalence studies for the meta-analysis

4.5 Discussion

This review has demonstrated that high heterogeneity is found among prevalence estimates that rely on the self-reporting of symptoms. This was based on community samples only as available estimates from primary care samples were not eligible for this meta-analysis. Homogeneity however, was found

between studies that completed clinical assessment of symptoms. Furthermore, the findings illustrate that prevalence estimates obtained from self-reporting alone are higher than estimates involving clinical assessment.

Those attending primary care clinics may be a higher risk group than the general community. Slightly higher prevalence was found in primary care, but this was more likely due to the limited availability of studies. This also made the heterogeneity detected among primary care samples highly sensitive to lower prevalence detected in a Korean sample (Kim et al., 2005). However, the variability among community samples that used clinical assessment was still low compared to community samples relying on self-reporting.

This systematic review used specific inclusion criteria to minimise biased selection of studies. The majority of exclusions were studies based on dated definitions of CFS/ME. A UK study (Nacul et al., 2011) based on nationwide screening was also removed due to its large statistical weighting. If included, the results of the remaining studies would not have been detected by the meta-analysis. Prevalence figures were adjusted for no response or participation. This may have resulted in higher estimates as it assumes non-responders are not less likely to have CFS/ME.

Although there are studies that rely on self-reporting to report an official prevalence of CFS/ME (Yiu and Qiu, 2005, Kawakami et al., 1998, Lindal et al., 2002, van't Leven et al., 2010) many use it as an initial screening technique to source potential cases of CFS/ME and assess the feasibility of conducting larger epidemiological surveys. In such cases, those that report symptoms fulfilling the clinical definition of CFS/ME have often been referred to as CFS/ME-like cases (Reyes et al., 2003b, Reeves et al., 2007, van't Leven et al., 2010, Steele et al., 1998, Bierl, 2004). It is not uncommon for studies to apply further tools to help verify suspicions of CFS/ME such as empirical criteria (Reeves et al., 2005) validated health surveys (Shea and Barney, 2007) fatigue scores (Albersts et al., 2001) and depression scales (House et al., 2006). Some studies have then proceeded with clinical diagnosis of CFS/ME. Different approaches to clinical assessment can be found; one study evaluated all participants as part of a

random health check of the population (Hamaguchi et al., 2011). Some studies evaluated those reporting CFS/ME symptoms (Kim et al., 2008, Cho et al., 2009) while others only evaluated a sample reporting CFS/ME symptoms (Jason et al., 1999, Reyes et al., 2003b, Njoku et al., 2007, Reeves et al., 2007). The latter may have resulted in conservative estimates as cases may have been detected in those not assessed.

The differences found in heterogeneity due to method of assessment highlight the need for collaborative research in CFS/ME prevalence where similar methods are applied across study sites. This has only been demonstrated by one study that found similar prevalence estimates in Brazil (1.64%; 95%CI: 1.23-2.04) and the UK (2.07%; 1.50-2.64) (Cho et al., 2009). The meta-analysis particularly illustrates that prevalence is more consistent across samples when clinical assessment is involved. Therefore, it is recommended that studies combine the use of a standard case definition with clinical verification of symptoms. More specific definitions however, are now available such as the recently released International Consensus definition (Carruthers et al., 2012c). Their use to assess prevalence should also help produce more reliable estimates in the future.

4.6 Conclusion

Prevalence estimates for CFS/ME based on self-reporting alone should be viewed with caution. Clinically valid diagnoses are vital in undertaking accurate prevalence studies for CFS/ME. The findings of this study are based on CFS/ME as defined by the CDC. As new advances are made in clinical case definitions, for example through the International Consensus definition, more valid prevalence studies may be expected.

Disclosures

The author reports no conflicts of interest in this work.

Chapter 5: A comparison of health status in varying cases of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis

Statement of Co-authorship

This chapter includes a co-authored paper. The bibliographic details of the co-authored paper, including all authors, are:

Johnston, S., Brenu, E. W., Hardcastle, S., Huth, T., Fuller, K., Staines, D., & Marshall-Gradisnik, S. (2014). *Health Quality of Life Outcomes, 12, 64*, 371-376.

My contribution to the paper involved the design of the study, provision of data, analysis, and preparation of the resulting manuscript.

(Signed) _____ (Date) _____

Samantha Claire Johnston

(Countersigned) _____ (Date) _____

Corresponding author of paper: Samantha Claire Johnston

(Countersigned) _____ (Date) _____

Supervisor: Sonya Marshall-Gradisnik

5.1 Abstract

Background: Several diagnostic criteria are available for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) that vary significantly in their symptom criteria. The purpose of this study is to determine whether simple biological and clinical measures differed between CFS/ME patients meeting the 1994 Centres for Disease Control and Prevention (CDC) criteria, the International Consensus Criteria (ICC), and healthy controls.

Methods: A total of 45 CFS/ME patients and 30 healthy controls from the South East Queensland region of Australia provided a blood sample, reported on their current symptoms, on aspects of their physical and social health using the Short-Form General Health Survey (SF-36), and the World Health Organisation Disability Adjustment Schedule 2.0 (WHO DAS 2.0) and were examined for differences using independent sample t-testing.

Results: Patients fulfilling the ICC reported significantly lower scores ($p<0.05$) for physical functioning, physical role, bodily pain, and social functioning than those that only fulfilled the 1994 CDC criteria. ICC patients reported significantly greater ($p<0.05$) disability across all domains of the WHO DAS 2.0.

Conclusions: These preliminary findings suggest that the ICC identifies a distinct subgroup found within 1994 CDC patients, with more severe impairment to their physical and social functioning.

Keywords: Chronic Fatigue Syndrome; Disability; Myalgic Encephalomyelitis; Short Form Health Survey.

5.2 Introduction

The term Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) first appeared in the literature in 1988 when the Centres for Disease Control and Prevention (CDC) described an illness of debilitating fatigue accompanied by a various combination of symptoms (Holmes et al., 1988). Throughout the 1950s to 1980s however, outbreaks of CFS/ME-like illness have been reported as Bornholm disease (Hopkins, 1950), Iceland disease (Acheson, 1959), the Royal

Free Hospital epidemic (Psychol), as well as Chronic Epstein Barr Virus Syndrome (Buchwald et al., 1987). In recent decades, several formal case definitions have been released for CFS/ME (Carruthers et al., 2011, Carruthers et al., 2003, Fukuda et al., 1994, Sharpe et al., 1991, Ho-Yen, 1990, Lloyd et al., 1990, Reeves et al., 2005), and each differ significantly in the symptoms they emphasise, as well as their exclusion criteria (Johnston et al., 2013b). The most common definition is the 1994 CDC, which requires the presence of debilitating fatigue of 6 months, and at least four of eight, mostly flu-like symptoms (Fukuda et al., 1994). It was primarily developed for the selection of adult cases for research however, concerns have been raised on its selection of widely heterogeneous patients (Jason and Richman, 2007, Reeves et al., 2003).

A more stringent definition, known as the Canadian Consensus Criteria was released in 2003 (Carruthers et al., 2003), primarily for diagnosis in clinical settings. Criteria included core symptoms found in the 1994 CDC such as debilitating fatigue of 6 months, post-exertional malaise, sleep dysfunction, and pain, as well as symptoms relating to dysfunction of the neurological, autonomic, neuroendocrine, and immune systems. Its application in research however, suggests that patients fulfilling the Canadian definition have more severe impairment to their physical functioning and cognition than 1994 CDC patients (Nacul et al., 2011, Jason et al., 2004).

The Canadian definition was revised in 2011 and renamed the International Consensus Criteria (ICC) (Carruthers et al., 2011). The most significant change is its removal of criteria for fatigue, and emphasises that the cardinal feature of the illness is a low threshold of fatigability that it refers to as post-exertional neuroimmune exhaustion (PENE). Accompanying symptoms are then categorised into three pathophysiologies relating to dysfunction of the neurological system, immune and gastro-intestinal system, and deregulation of energy metabolism and ion transportation. This latest definition has yet to be applied regularly in CFS/ME research.

A major criticism of the 1994 CDC definition is that it has remained the most common criteria for CFS/ME due to consensus (Sullivan et al., 2005). The

ICC however, was proposed based on collective empirical findings on dysfunction found in CFS/ME patients fulfilling broader definitions of the illness (Chen et al., 2008b, Cook et al., 2001, Streeten et al., 2000, Tirelli et al., 1998, Fletcher et al., 2010, Ngonga and Ricevuti, 2009, Mihaylova et al., 2007, Klimas et al., 1990, Myhill et al., 2009, Pieczenik and Neustadt, 2007, Behan et al., 1991). These findings however, may be more prominent in a more homogenous sample. The potential of the ICC to identify a distinct subgroup of CFS/ME may therefore, enhance the opportunity of discovering a unique biological marker for the illness. The aim of this study was to compare patients fulfilling the 1994 CDC definition, the ICC definition, and healthy controls. It examined whether differences could be found in standard blood tests for screening of the disease that are recommended for differential diagnosis of CFS/ME (Friedberg et al., 2012a, Carruthers et al., 2012c, Centers for Disease Control and Prevention, 2006). It also examined impairments using the Short Form 36 Item Health Survey (SF-36) (Ware Jr and Sherbourne, 1992), and the World Health Organisation's Disability Adjustment Schedule 2.0 (WHO DAS 2.0) (World Health Organisation, 2001). The SF-36 has previously been examined in patients fulfilling the 1994 CDC (Fukuda et al., 1994) and Canadian criteria (Hardt et al., 2001, Jason et al., 2013). The WHO DAS 2.0 assesses patients according to its framework for the International Classification for Functioning, Disability and Health (ICF), but has yet to be applied in CFS/ME patients (World Health Organisation, 2002). These findings provide the first preliminary data available standard biological and clinical measures in CFS/ME patients complying with the 1994 CDC and ICC definitions.

5.3 Method

The study involved a blood sample and cross-sectional survey of participants self-reporting a current diagnosis of CFS/ME, and healthy controls, aged 18 to 64 years. Participants were part of a larger study examining immunological markers and were recruited from support networks in the South East Queensland region. Written consent was obtained from all eligible before obtaining a blood sample to measure their full blood count (FBC), erythrocyte

sedimentation rate (ESR) and electrolytes. Participants were also required to complete a hard copy of self-reporting measures. This included a symptom checklist developed by the authors to ascertain cases fulfilling the 1994 CDC, Canadian and International criteria. Participants were also asked to report on all other diagnoses including psychiatric conditions as these may be considered an exclusionary condition according to study criteria.

To be confirmed as a CFS/ME patient, current symptoms had to comply with the 1994 CDC (Fukuda et al., 1994), Canadian (Jason et al., 2013), or the International (Carruthers et al., 2011) criteria. Healthy controls were defined as participants with no reported signs of illness. Participants also completed self-reporting measures of their health according to the SF-36 (Ware Jr and Sherbourne, 1992) and the WHO DAS 2.0 (World Health Organisation, 2001) surveys. The SF-36 investigates eight subscales according to: physical functioning, role limitations due to physical problems, bodily pain, general perception of physical health, vitality, social functioning, role imitations due to emotional problems, and general perception of mental health (Ware Jr and Sherbourne, 1992). Scoring ranged between 0 and 100, with lower values representing more impairment. The WHO DAS 2.0 (World Health Organisation, 2001) consists of six domains to assess difficulties in health relating to communication, mobility, self-care, interpersonal relations, life activities, and participation in society, over the past 30 days. Scoring also ranged between 0 and 100, with higher values indicating greater impairment.

It was observed that all patients that complied with the ICC also fulfilled the 1994 CDC criteria. Based on this, the study used three independent groups for analysis: patients conforming only to the 1994 CDC criteria, patients that fulfilled the ICC, and healthy controls. Five cases in the 1994 CDC group were found to also comply with the Canadian, but not the ICC. Due to low statistical power of this sample, these cases remained in the 1994 CDC group for analysis. SPSS v.22 was used to compare mean scores on the SF-36 and WHO DAS 2.0 between 1994 CDC and ICC patient groups, and between all patients and healthy controls, using independent sample t-testing. Categorical variables were

analysed using chi-squared test when appropriate. Results were considered significant at the $p<0.05$ level and highly significant at the $p<0.001$ level. The study was approved by the Griffith University Human Research Ethics Committee.

5.4 Results

Of 45 self-reporting CFS/ME patients recruited into the study, 4 did not comply with any of the study criteria and were excluded from analysis. Of the 41 patients included, 19 reported symptoms that only fulfilled the 1994 CDC criteria, and 22 fulfilled the ICC. The 30 healthy controls recruited remained in the study as they indicated no signs of illness. Basic characteristics and standard blood results for each study group are presented in Table 5.1. The age distribution was similar between the three study groups, but a significantly higher number of females ($p<0.05$) was found in the ICC patients. The mean duration of illness of approximately 19 years was the same among the two patient groups. Significant differences ($p<0.05$) were found between all patients and healthy control groups in Haemoglobin, Haematocrit, and Red Cell Count with higher levels found in healthy controls. No difference however, was found between 1994 CDC and ICC patients across these markers.

The results for the SF-36 are presented in Table 5.2. CFS/ME patients complying with either of the study criteria reported significantly lower scores ($p<0.05$) for all eight SF-36 subscales, when compared to healthy controls. Among the patients, those that fulfilled the ICC reported significantly lower scores (<0.05) for physical functioning, physical role, bodily pain, and social functioning than those that only fulfilled the 1994 CDC criteria.

Table 5.1: Characteristics of 1994 CDC patients, ICC patients, and healthy controls

Parameters	**1994 CDC patients (n=19)**	**ICC patients (n=22)**	**Healthy controls (n=30)**	**Sig**
Age, mean (SD)	50.7 (7.4)	49.3 (13.2)	49.7 (10.9)	
Gender (% female)	68%	95%	66%	<0.05[a]
Illness duration (years), mean (SD)	18.9 (13.6)	19.0 (10.2)	n/a	

Haemoglobin (g/L)	134.9 (13.6)	132.9 (11.9)	140.7 (12.6)	<0.05[b]
White cell count ($x10^9$/L)	6.1 (1.5)	6.1 (1.9)	6.0 (1.5)	
Platelets ($x10^9$/L)	247.9 (66.8)	276.7 (68.5)	235.5 (48.2)	
Haematocrit	.41 (0.04)	.40 (0.03)	.43 (0.03)	<0.05[b]
Red cell count ($x10^{12}$/L)	4.45 (0.4)	4.40 (0.4)	4.65 (0.43)	<0.05[b]
Mean corpuscular volume ($x10^9$/L)	91.8 (3.6)	91.6 (2.9)	92.0 (2.5)	
Neutrophils ($x10^9$/L)	3.75 (1.3)	3.48 (1.6)	3.81 (1.28)	
Lymphocytes ($x10^9$/L)	1.83 (0.4)	2.04 (0.8)	1.72 (0.43)	
Monocytes ($x10^9$/L)	.30 (0.1)	.34 (0.1)	.32 (0.12)	
Eosinophils ($x10^9$/L)	.17 (0.1)	.15 (0.1)	.15 (0.11)	
Basophils ($x10^9$/L)	.03 (0.03)	.03 (0.03)	.03 (0.02)	
ESR (mm/Hr)	15.5 (11.2)	15.7 (13.8)	10.2 (8.4)	<0.05[b]
Sodium (mmol/L)	138.6 (1.3)	130.8 (30.0)	138.2 (1.8)	
Potassium (mmol/L)	4.0 (0.3)	9.3 (23.2)	4.0 (0.3)	
Chloride (mmol/L)	104.1 (2.0)	99.6 (17.5)	103.6 (2.5)	
Bicarbonate (mmol/L)	26.7 (2.1)	24.7 (5.3)	26.5 (2.6)	
Anions (mmol/L)	7.9 (1.3)	8.6 (2.5)	8.3 (1.7)	

[a]Significant difference between 1994 CDC and International patient groups
[b]Significant difference between all patient and healthy control groups

Table 5.2: SF-36 Scores of 1994 CDC defined patients, ICC defined patients, and healthy controls. Lower scores indicate greater impairment.

Scores	1994 CDC patients	ICC patients	Healthy controls	1994 CDC vs ICC	1994 CDC vs Controls	ICC vs Controls
Physical functioning	58.7 (20.9)	35.0 (23.3)	96.1 (8.4)	p=0.002	p=0.000	p=0.000
Physical role	21.1 (29.2)	1.25 (5.6)	96.4 (14.8)	p=0.005	p=0.000	p=0.000
Bodily pain	62.9 (24.6)	44.8 (26.2)	94.3 (9.6)	P=0.030	p=0.000	p=0.000
General health	36.8 (21.3)	31.3 (21.5)	82.5 (9.6)	p>0.05	p=0.000	p=0.000
Vitality	26.6 (15.4)	19.2 (18.0)	67.6 (15.9)	p>0.05	p=0.000	p=0.000
Emotional role	52.6 (46.2)	47.4 (48.8)	92.0 (21.2)	p>0.05	p=0.000	p=0.000
Social functioning	26.8 (21.4)	26.8 (21.4)	94.9 (10.6)	p=0.002	p=0.000	p=0.000
Mental health	66.2 (21.2)	62.5 (22.9)	79.1 (14.6)	p>0.05	p=0.018	p=0.003

Table 5.3 presents the results of the WHO DAS 2.0. 1994 CDC patients indicated significantly higher scores ($p<0.05$) for all disability domains compared to healthy controls, except for self-care. ICC patients however, differed significantly across all domains. Between 1994 CDC and ICC patients $p<0.001$ for cognition, mobility, self-care, and getting-along, and $p<0.05$ for life activities, and participation.

Table 5.3: WHO DAS 2.0 scores in 1994 CDC patients, ICC patients, and healthy controls. Higher scores indicate greater impairment.

Scores	1994 CDC patients	ICC patients	Controls	1994 CDC vs ICC	1994 CDC vs Controls	ICC vs Controls
Cognition	22.6 (16.2)	43.5 (17.6)	4.0 (5.6)	p=.000	p=0.000	p=0.000
Mobility	27.1 (17.6)	48.2 (15.5)	1.4 (3.0)	p=.000	p=0.000	p=0.000
Self-care	4.0 (9.6)	22.2 (16.5)	16.5 (0.7)	p=.000	p>0.05	p=0.000
Getting along	15.6 (15.2)	44.2 (22.7)	22.7 (5.5)	p=.000	p=0.007	p=0.000
Life activities	39.9 (25.9)	63.1 (23.8)	23.8 (6.3)	p=.010	p=0.000	p=0.000
Participation	38.2 (20.4)	53.9 (16.5)	16.5 (3.6)	p=.011	p=0.000	p=0.000

5.5 Discussion

This is the first study to examine CFS/ME patients that fulfil the ICC definition in an Australian sample. As all ICC defined patients were found to also comply with 1994 CDC criteria, the preliminary findings of this study support findings that ICC patients can be classified as a subgroup found within the broader category of CFS/ME (Brown et al., 2013b). Though broad criteria may be particularly useful for the identification of potential cases among small samples, it could inadvertently select those that do not have the illness (Kennedy et al., 2004). The symptoms of chronic fatigue, post-exertional malaise, short-term memory and concentration problems reported in 1994 CDC defined CFS/ME cases are found to overlap with cases of depression (Jason et al., 2001). The Canadian definition however, has been shown to effectively differentiate between those with CFS/ME and depression (Jason et al., 2007). With its use of more specific criteria, 96% of self-reporting cases met the 1994 CDC, and 77% of patients complied with the Canadian (Jason et al., 2013). The findings of this study are based on a similar method of recruitment and case ascertainment, and are consistent with this pattern as 91% of self-reporting cases only fulfilled the 1994 CDC, 60% also fulfilled the Canadian, and 49% fulfilled the 1994 CDC, Canadian and ICC.

An important consideration is a consistent method of applying criteria (Jason et al., 2007). Reliance on self-reporting versus evaluation of cases by a physician can be a particular source of variability in reported cases (Johnston et al., 2013d). The symptom checklist used to verify the study criteria is limited to self-reporting, although this may be a useful tool for the initial screening of cases for research. Like the Canadian definition, the ICC was devised for clinical applications. Accordingly, the International Primer was published in 2012

(Carruthers et al., 2012c), to aid clinicians in their evaluation of symptoms according to the ICC. The availability of this tool could contribute to the selection of homogenous patient sets in research settings and help exclude other causes of illness.

As part of recruitment however, this study screened patients for chronic conditions such as heart disease, diabetes, and primary psychiatric disorder, as well as conducted standard blood tests as part of routine screening of disease. While all CFS/ME patients were found to have different results from controls in some parameters, no difference was found between the 1994 CDC and ICC patient groups. If the ICC identifies a subgroup with a more homogenous clinical presentation, salient differences may be found in more specific biological markers than the ones examined in this study.

The SF-36 used to evaluate the study groups is widely recognised as a valid and reliable tool for assessment of physical and social functioning in chronic illnesses [21], and has previously demonstrated impairment in 1994 CDC cases of CFS/ME (Hardt et al., 2001, Buchwald et al., 1996, Komaroff et al., 1996). It has been used to contrast between patients fulfilling the 1994 CDC and Canadian definitions (Jason et al., 2013). Recently, ICC defined patients in a US sample reported greater impairment to their physical functioning, bodily pain, and role limitations due to their physical health, as well as a greater impact on their social functioning (Brown et al., 2013b). The findings of this preliminary study are highly consistent, as significant difference was only found between the 1994 CDC and ICC patients in the same subscales. The WHO DAS 2.0 was also found to support the findings from the SF-36 in this study. All CFS/ME patients reported higher levels of disability than healthy controls, with ICC patients reporting greater impairment in all aspects of their physical and social functioning. The greatest difference was reported in cognition, mobility, ability to self-care, and maintaining daily activities.

The 1994 CDC definition for CFS/ME can represent an illness that ranges from mild impairment to daily activities to severe cases where patients are bedridden and unable to care for themselves. For many chronic illnesses, the

most severe cases often present themselves to primary or secondary care and mild cases often go unreported. The characteristics of CFS/ME can be quite the opposite, as the most debilitating cases can leave patients housebound or bedridden and can often be overlooked by clinicians and researchers alike. The use of broad criteria with symptoms that overlap with other conditions can also make cardinal features of CFS/ME difficult to identify. The current study suggests that the ICC may identify a more severe subgroup found within traditional CFS/ME and this may be consistent across samples in different geographic locations. Further research is required on the consistent application of the ICC in conjunction with the 1994 CDC in larger patient groups and analysis of critical symptoms. This could contribute to more accurate and homogenous patient sets for further research on the aetiology and underlying pathomechanism of the illness.

The ICC has suggested that this subgroup should be referred to exclusively as Myalgic Encephalomyelitis (ME) patients. This proposal however, remains controversial as the term implies inflammation of the central nervous system that is not necessarily exhibited in all cases that fulfil the criteria. The term ME alone, may be viewed as pathogen-related initiation associated with onset as seen in bacterial, viral or parasitic infection and resultant inflammation of the nervous system. However use of the term in this context may result in misleading assignation of the syndrome directly and solely to an infectious agent. This has been seen previously in the ill-fated XMRV expedition. Alternatively the identification of this illness as due to immune dysfunction following infection or other initiating event represents a paradigm in closer fit with observable clinical signs and laboratory findings. Ongoing discoveries in immune dysfunction are likely to harmonise with more accurate case definitions over time.

5.6 Conclusion

The preliminary findings of this study suggest that the ICC has the sensitivity required to identify a subgroup of patients among broadly defined 1994 CDC patients. Though no difference was found between standard blood tests between

1994 CDC and ICC defined patients, ICC patients still reported greater impairment to their physical functioning, cognition, ability to maintain daily activities and care for themselves, as well as more severe social consequences to their health. Further study on the potential of the ICC to provide homogenous sets of patients will be important for examining whether more specific biological markers can be found for the illness.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SJ Contributed to the study design, data collection and analysis for this study. SJ, EB, DS, SM Contributed to the drafting and revisions of this manuscript. SH, TH, KF and EB Contributed to blood collection, and biological analysis for this study.

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Chapter 6: An evaluation of differential diagnosis in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An Australian registry for CFS/ME Study

Statement of Co-authorship

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My contribution to the paper involved the design of the study, provision of data, analysis, and preparation of the resulting manuscript.

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6.1 Abstract

Aim: Differential diagnosis has a crucial role in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME). As patients often present with various health issues, it is crucial to differentiate between secondary conditions, and those that should be considered alternative primary diagnoses. The aim of this study was to evaluate accompanying health conditions in those diagnosed with CFS/ME by a primary care physician.

Methods: Participants reporting a diagnosis of CFS/ME were obtained from a university research registry. As part of a larger epidemiological study, all subjects completed a self-reporting questionnaire reviewing the history of illness, health service use, accompanying diagnoses, and a 53-item checklist regarding fatigue and accompanying symptoms. Participants were categorised in four groups based on published criteria: CFS, ME, chronic fatigue (CF) only, and other fatiguing illnesses.

Results: A sample of 515 participants was eligible, with 127 (24.7%) categorised as CFS, 164 (31.8%) as ME (whom also met CFS criteria), 86 (16.5%) as CF only, and 139 (27%) as other fatiguing illnesses. In both CFS and ME groups, secondary insomnia, irritable bowel syndrome, sinusitis, and orthostatic intolerance were highly common (>20%). Other common coexisting diagnoses in both CFS and ME included postural orthostatic tachycardia syndrome (12.6% – 16.5%), and neutrally mediated hypotension (7.1% – 9.8%). Considerably less coexisting diagnoses were reported by the CF only (<10%) than all other categories.

Conclusions: In terms of diagnosis, significant improvements in general practice are needed to differentiate diagnoses of CFS, ME, chronic fatigue, and other fatiguing illnesses. Further, several potential CFS subgroups according to their coexisting conditions were identified, that may be targeted for improved management of the illness.

Keywords: Chronic Fatigue Syndrome; Myalgic Encephalomyelitis; Chronic Fatigue; Primary Care

6.2 Introduction

Chronic Fatigue Syndrome (CFS) is a debilitating illness receiving increasing attention in primary care. Worldwide, it is estimated to have a prevalence of 0.76% (95% CI: 0.23-1.29) in primary care practice (Johnston et al., 2013c). The cause of CFS has yet to be established and is thus diagnosed according to symptom based criteria. The most common is the Fukuda et al. (1994), which requires the presence of severe fatigue for at least 6 months that significantly reduces activities of daily life. This must be accompanied by at least four minor symptoms that are mostly attributed to flu-like illnesses. The Fukuda et al. (1994) criteria share substantial overlap with the Carruthers et al. (2011) criteria proposed for Myalgic Encephalomyelitis (ME) that requires additional symptoms. The Carruthers et al. (2011) is largely based on several potential aetiologies that have been proposed for the illness pertaining to neurological, immune, and metabolic dysfunction (Morris and Maes, 2013).

The key characteristic of both criteria is that the fatigue is not the result of ongoing exertion and is unexplained by other medical or psychological conditions. In CFS, relatively normal physical tasks exacerbate fatigue that cannot be substantially alleviated by rest thus, resulting in prolonged recovery periods. This can often be difficult to distinguish as fatigue is an extremely common complaint in primary care, estimated in between 5 to 15% of cases (Bates et al., 1993, Buchwald et al., 1995, Cathebras et al., 1992, McDonald et al., 1993, Pawlikowska et al., 1994) and is also a major part of other chronic diseases. Thus, it is essential that a diagnosis of CFS is considered only when all other explainable causes of fatigue that may be active, relapsing or not completely resolved by treatment are ruled out. This includes, and is not limited to the exclusion of sleep disorders, endocrine disorders such as hypothyroidism, and diabetes, cancers, anaemia, chronic infections such as hepatitis, autoimmune disorders, endocrine disorders, gastrointestinal disease, cancers and primary psychoses (Working Group of the Royal Australasian College of Physicians, 2002b, Centers for Disease Control and Prevention, 2006). The fatigue should also not be explained by secondary event or environmental stressors that result

in unusual stress, major anxiety, major depression and inactivity. Hence, diagnosis must pursue thorough history taking, physical examination, and routine laboratory investigations in patients who have symptoms that meet criteria (Baker and Shaw, 2007, Working Group of the Royal Australasian College of Physicians, 2002b)

Accordingly, a condition that does not explain ongoing problems with debilitating fatigue may be considered a coexisting condition. The most common suggested comorbidities include fibromyalgia (FM), irritable bowel syndrome (IBS), or postural orthostatic tachycardia syndrome (POTS) (Johnston et al., 2014d). FM is considered the largest overlapping illness requiring the presence of chronic pain for more than 3 months with accompanying symptoms such as sleep disturbance and fatigue. Studies have specifically investigated this overlap in diagnosis and found that up to 70% of CFS patients fulfilled the American College of Rheumatology criteria for FM (Buchwald, 1996a, Buchwald and Garrity, 1994b, White et al., 1999b, White et al., 1999a). Specific investigation into the presence of POTS, a condition associated with orthostatic intolerance (Thieben et al., 2007, Raj, 2006) reported its prevalence in 11% of CFS patients enrolled in a specialised clinic (Reynolds et al., 2014). Further studies have reported CFS in 14% of irritable bowel syndrome cases (Aaron et al., 2001, Whitehead et al., 2002). Hence within the construct of CFS, an array of other conditions may be present, contributing to the challenges of accurate diagnosis and management.

Though the role of differential diagnosis is so crucial in CFS, no study to date has examined the frequency of coexisting conditions among patients specifically diagnosed with CFS. The aim of this study investigate those that have received a diagnosis by a primary care physician for: 1) whether their reported symptoms aligned with available formal criteria for CFS and ME; 2) the frequency of coexisting conditions; 3) whether reported conditions were present and active that would exclude a diagnosis of CFS. The findings will help provide clarification for both general practice and the patient community to the

conditions that coexist with CFS and conditions that should be considered an alternative primary diagnosis.

6.3 Methods

6.3.1 Participants

The Australian Registry for CFS/ME (ARCFS) is a volunteer, university based registry for those diagnosed with CFS or ME. This study selected adults (≥ 18 years old) reporting a formal diagnosis of CFS or ME by a general practitioner across Australia and were referred to the registry from participation in immunological studies at the National Centre for Neuroimmunology and Emerging Diseases, and CFS community support networks. This study was approved by the Griffith University Human Research Ethics Committee (MSC0413HREC).

6.3.2 Data collection

The ARCFS was open for registration in August 2013. After providing initial consent, participants completed a series of self-reported questionnaires online or by a hardcopy about their socio-demographic background, medical history including all diagnoses, and health service use, and symptomatology, and lifestyle. Online data was collected and managed using the LimeSurvey electronic data capture tool, and hosted by Griffith University. Data from hardcopy versions were subsequently entered into this program.

The symptom checklist consisted of a total of 53 symptoms derived from the Fukuda et al. (1994), and Carruthers et al. (2011) criteria, which was based on systematic literature review (Johnston et al., 2013f) and by author consensus. Participants then selected symptoms from the checklist that had accompanied their onset of fatigue and had persisted or recurred throughout their illness and is outlined in Table 6.1. Lifestyle questions addressed substance use including smoking andalcohol consumption.

Table 6.1: Symptom criteria applied for classifying CFS and ME

Criteria	Fukuda et al. (1994) criteria for CFS	Carruthers et al. (2011) criteria for ME
Major	Fatigue	Fatigue

	Unexplained ≥6 months Persistent or relapsing new or definite onset Not due to ongoing exertion Not alleviated by rest Substantially interferes with daily activities/work	Marked fatigue in response to exertion Post-exertional symptom exacerbation Post-exertional fatigue is immediate or delayed Prolonged recovery period Substantially interferes with daily activities/work
Minor	Accompanying symptoms Post-exertional malaise lasting more than 24 hours Unrefreshing sleep Significant impairment of short terms Muscle pain Joint pain without swelling/redness Headaches of new type Tender lymph nodes Sore throat	Accompanying symptoms Neurological (1≤ symptom(s) from all four subcategories): Neurocognitive impairments Pain Sleep disturbance Neurosensory, perceptual and motor disturbances Immune, Gastro-intestinal & Genitourinary (1≤ symptom(s) from three subcategories): Flu-like symptoms Susceptibility to viral infections Gastro-intestinal tract disturbances Genitourinary disturbances Sensitivities Energy production/transportation impairments (1≤ symptom(s) from any subcategory): Cardiovascular Respiratory Loss of thermostatic stability Intolerance of extremes of temperature

6.3.3 Data analysis

Participants were grouped according to four categories: CFS, ME, CF, and other fatiguing illnesses (other). CFS patients were defined as those reporting symptoms according to the Fukuda et al. (1994) criteria that required the presence of debilitating fatigue for at least 6 months and at least four of the following: post-exertional malaise, difficulties with short term memory or concentration, unrefreshing sleep, sore throat, muscle pain, joint pain, headaches, and tender lymph nodes. ME were classified as patients reporting symptoms that complied with the Carruthers et al. (Carruthers et al., 2011) criteria. This requires patients to meet requirements for post-exertional fatigue, which is referred to in the criteria as post-exertional neuroimmune exhaustion (PENE). Participants should further meet a required threshold of symptoms from three additional categories.

CF was defined as those that only met criteria for chronic fatigue (of at least 6 months duration) but did not meet minor criteria accompanying symptoms and was thus, categorised as having chronic fatigue only. Other was defined as participants who reported symptoms of CFS or ME but reported a diagnosis that was active, recurrent, or not completely resolved that was considered exclusionary to a diagnosis of CFS according to the criteria. Those reporting excessive substance use or alcohol consumption were excluded from this study. Overall, the primary outcomes of interest for this study were symptomatology, accompanying diagnoses, and health service use. Descriptive statistics and frequency analyses were used to collate this data and all analysis was conducted using SPSS version 22.

6.4 Results

6.4.1 Participant characteristics

Of the eligible 515 ARCFS participants, 127 (24.7%) categorised as CFS, 164 (31.8%) as ME (whom also met CFS criteria), 86 (16.5%) as CF only, and 139 (27%) as other fatiguing illnesses. Responders were more likely to be female, and between the ages 45 and 54 across all categories (Table 6.2). Few participants were over 65 years of age except those with other diagnoses (20.6%). CFS and ME participants were significantly less likely to be obese than CF, and other fatiguing illnesses. The majority of all participants in each group had been diagnosed with CFS within the past 5 years.

Table 6.2: Basic characteristics of CFS, ME, CF, and other participants

Characteristics	CFS	ME	CF	Other*
	N = 127	N = 164	N = 86	N = 139
Age				
18 – 24	6 (5.0)	16 (9.5)	2 (2.6)	4 (2.9)
25 – 34	20 (16.0)	26 (15.9)	13 (14.8)	14 (10.3)
35 – 44	25 (20.0)	47 (28.6)	13 (14.8)	14 (10.3)
45 – 54	36 (28.0)	38 (23.0)	29 (33.9)	41 (29.4)
55 – 64	31 (24.0)	30 (18.3)	22 (26.1)	37 (26.5)
65 ≤	9 (7.0)	8 (4.8)	7 (7.8)	29 (20.6)
Gender				
Male	36 (28.1)	40 (24.7)	17 (0.2)	20 (14.7)
Female	91 (71.9)	119 (75.3)	68 (0.8)	119 (85.3)
BMI				
Underweight (<18.5)	29 (22.7)	8 (4.9)	19 (22.7)	25 (18.2)
Normal (18.50 – 24.9)	32 (25.6)	59 (36.0)	7 (8.5)	45 (32.4)
Overweight (25.0 – 29.9)	47 (37)	25 (15.2)	8 (9.8)	36 (26.1)
Obese moderate (30.0 – 34.9)	19 (15)	15 (9.1)	13 (15)	45 (32.5)
Obese severe (35.0 – 39.9)	7 (5.3)	10 (6.0)	0 (0)	59 (42.1)
Obese very severe (≥40.0)	0 (0)	2 (1.2)	21 (25)	70 (50)
Years since diagnosis				
<5	44 (34.8)	71 (43.2)	26 (30)	31 (36.5)
5 – 9	20 (15.7)	34 (20.7)	11 (13.3)	13 (15.4)
10 – 14	19 (14.6)	16 (9.9)	9 (10)	8 (9.6)
14 – 19	23 (18)	21 (12.6)	17 (20)	10 (11.5)
20 – 25	13 (10.1)	10 (6.3)	14 (16.7)	13 (15.4)

All values are expressed as frequencies n(%)
*Other fatiguing illnesses

6.4.2 Coexisting diagnoses

The frequency of comorbidities reported by participants are summarised in Table 6.3. Secondary insomnia (46.5% - 67.5%), irritable bowel syndrome (41.7% – 70.5%), and sinusitis (31.5% – 57.6%) were highly common across CFS, ME and other fatiguing illnesses. Orthostatic tolerance and POTS were also of significance, particularly in ME (reported in more than 32.3% and 16.5% of cases, respectively). Hypertension was also significantly higher in CFS (5.5%). Ataxia was also reported higher in participants with ME (5.5%), and those with other diagnoses (5.0%) in comparison to CFS and CF.

Table 6.3: Frequency of comorbid diagnoses in CFS, ME, CF only, and other participants

Comorbid diagnoses	CFS		ME		CF		Other*	
	n	%	n	%	n	%	n	%
Insomnia**	59	46.5	102	62.2	6	7.0	94	67.6
Irritable bowel syndrome	53	41.7	90	54.9	9	10.5	98	70.5
Sinusitis	40	31.5	79	48.2	3	3.5	80	57.6
Orthostatic intolerance	26	20.5	53	32.3	3	3.5	32	23.0
Postural orthostatic tachycardia syndrome	16	12.6	27	16.5	1	1.2	26	18.7
Neurally mediated hypotension	9	7.1	16	9.8	3	3.5	13	9.4
Hypertension	7	5.5	4	2.4	2	2.3	5	3.6
Fibromyalgia	6	4.7	9	5.5	5	5.8	11	7.9
Migraine	4	3.1	2	1.2	2	2.3	2	1.4
Non-melancholic depression	4	3.1	4	2.4	5	5.8	8	5.8
Multiple chemical sensitivities	3	2.4	3	1.8	2	2.3	4	2.9
Osteoarthritis	3	2.4	4	2.4	1	1.2	9	6.5
Osteoporosis	2	1.6					2	1.4
Temporomandibular joint disorder	2	1.6	2	1.2				
Skin condition	2	1.6	3	1.8	2	2.3	3	2.2
Ataxia	2	1.6	9	5.5	1	1.2	7	5.0
Hypermobility	2	1.6	4	2.4	1	1.2		
Anxiety	1	0.8						
Disc prolapse	1	0.8	1	0.6				
Osteopenia			1	0.6			1	0.7
Scoliosis			1	0.6				

*Other fatiguing illnesses

**Participants reporting insomnia as part of their symptoms and not a separate diagnosis. Those reporting a diagnosis of primary insomnia were classified as having a sleep disorder

6.4.3 Exclusionary diagnoses

Of the 139 participants with other fatiguing illnesses, the most common reasons for CFS exclusion included heart disease (23%), diabetes mellitus (23%), and primary sleep disorders such as sleep apnoea (20.1%) (Table 6.4). Primary psychiatric disorders were also common such as post-traumatic stress disorder, bipolar disorder, melancholic depression, and major anxiety (11.5%). Celiac disease, active adult asthma, autoimmune disorders and hypothyroidism were also highly exclusionary diagnoses, also among those reporting only CF symptoms.

Table 6.4: Frequency of alternative primary diagnoses in CF only, and other

Exclusionary diagnoses*	CF		Other	
	n	%	n	%
Cardiovascular disease	1	1.2	32	23
Diabetes mellitus	.	.	32	23
Sleep disorder	1	1.2	28	20.1
Primary psychiatric disorder	6	7	16	11.5
Celiac disease	1	1.2	14	10.1
Asthma	4	4.7	13	9.4
Autoimmune disorder	7	8.1	12	8.6
Hypothyroid	10	11.6	8	5.8
Cancer	1	1.2	7	5
Endometriosis			7	5
Haemochromatosis	1	1.2	5	3.6
Hyperaldosteronism	1	1.2	5	3.6
Neurological disorder			4	2.9
Anemia			2	1.4
Chronic obstructive pulmonary disease			1	0.7
Inflammatory bowel disease			1	0.7
Gastro-esophageal reflux disease	1	1.2	1	0.7
Lupus			1	0.7
Sarcoidosis			1	0.7
Chronic kidney disease				

*Diagnosis considered exclusionary according to Fukuda et al. 1994 CFS criteria

6.4.4 Management

All groups were largely managed by a general practitioner (Table 6.5). Participants across all groups also utilised physiotherapists, psychologists, dieticians on average, more than two times a year. Visits to complementary and alternative health services including massage therapy and acupuncture were also common (≥ 2 visits per year).

Table 6.5: Average visits to health professionals and services during the past 12 months*

Health professional	CFS	ME	CF only	Other
General practitioner	9.9 (9.3)	12.6 (23.7)	11.9 (10.4)	8.2 (7.3)
Neurologist				
Physiotherapist	2.5 (5.2)	2.3 (5.1)	2.8 (5.7)	2.4 (6.5)
Occupational therapist	0.3 (1.4)	0.2 (0.9)	0.2 (0.7)	
Chiropractor	1.6 (7.9)	1.3 (4.1)	1.8 (4.6)	0.5 (2.1)
Psychologist/psychiatrist	2.4 (4.9)	2.9 (6.1)	4.2 (8.9)	2.1 (3.8)
Social worker			1 (3)	1 (3)
Surgeon			1 (2)	1 (2)
Acupuncturist	0.9 (4)	3.5 (11.4)	2.1 (6.8)	0.4 (1.3)
Podiatrist				1 (2)
Osteopath	1.3 (4.1)	0.8 (4.6)	1 (3)	0.7 (1.8)
Urologist				
Massage therapist	2.3 (4)	2.6 (5.4)	4 (7.9)	3.7 (8.4)
Dietician	2.3 (4.2)	4.3 (16.8)	3.4 (6.6)	1.9 (4.8)

* Values expressed as mean (SD)

6.5 Discussion

6.5.1 Diagnosis

Consistent with the literature, those diagnosed with CFS/ME symptoms were most likely to be in their mid-40s, and female (Buchwald et al., 1994, Ciccone and Natelson, 2003, Jason et al., 2003, Reeves et al., 2007). There were no significant differences however, detected between groups particularly for gender, suggesting this may be related to health seeking behaviour, which tends to be higher in females than males rather than CFS/ME being a female related illness (Tseng and Natelson, 2004). Several further claimed to have been diagnosed with the condition prior to when Fukuda et al. (1994) criteria applied in this study was published, and may have either associated their present claims of CFS with a prior diagnosis such as glandular fever, or were diagnosed according to previous clinical descriptions such as the Holmes et al. (1988) criteria or the Lloyd et al. (1990).

The findings of this study particularly support the proposed Carruthers et al. (2011) criteria for ME that specifically suggest the presence of insomnia, sinusitis, orthostatic intolerance, POTS, and neurally mediated hypotension as common perturbations. As the above mentions are clinically measureable, testing for their presence may have a significant role in the systematic diagnosis of CFS and ME. Irritable bowel syndrome was also extremely common in this sample, which is consistent with the literature as one of the most common syndromes seen by gastroenterologists and general practice, and is estimated to have a worldwide prevalence of 10 to 15% (Drossman et al., 2002). Contention is however, found in the literature as to whether IBS is exclusionary. Though suggested as a highly common comorbidity according to both CFS and ME criteria adopted for this study, the Australian Royal College of General Practice (2002b) guidelines consider IBS as a differential diagnosis to CFS. Further coexisting illnesses that are often suggested in the literature such as fibromyalgia, multiple chemical sensitivities, temporomandibular joint disorder, and hypermobility (Carruthers et al., 2011) were reported at a very low frequency in this sample. This may be attributable as illnesses less likely to be

diagnosed in primary care practice due to limited formal guidelines, and inconsistent evidence across the literature.

Differential diagnosis is evidently lacking in either the diagnosis or ongoing management of those that have adopted a diagnosis of CFS or ME. This was apparent in over a quarter of the study participants that had a major disease in which fatigue has a significant role, which still considered themselves as CFS or ME candidates rather than experiencing secondary chronic fatigue. According to an Australian Paediatric Network study, 56% of general practitioners did not base their diagnosis of paediatric cases of CFS on any case definition (Knight et al., 2014). Hence, it is highly possible that general practitioners are not distinguishing CFS from a state of chronic fatigue. This behaviour is also reflected in the participants reporting only experiencing symptoms of fatigue that had also adopted diagnosis of CFS or ME.

6.5.2 Management

The finding of several highly common coexisting conditions have important potential in terms of management, as targeting these in management could significantly reduce the overall impact of CFS and ME (Johnston et al., 2014c). The evidence also support a model of care based on identifying subgroups of CFS, which have been summarised in Figure 6.1. Accordingly, a patient would receive a suitable intervention that is targeted towards a specific symptom profile such as neurological, gastrointestinal, immunological, cardiovascular, or autonomic, for example dietary interventions for those with IBS, and antiviral therapy for those presenting with persistent chronic infection.

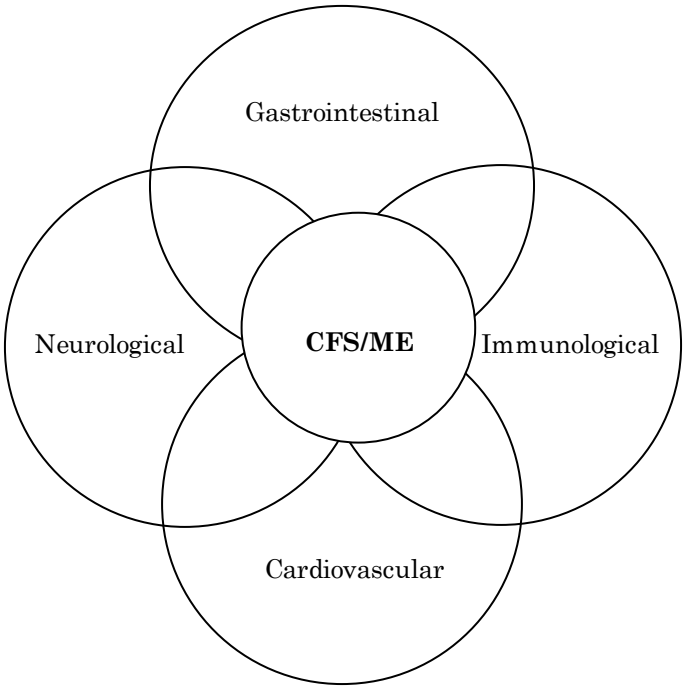

Figure 6.1: Potential subgroups for targeted CFS and ME management

As a chronic condition it is likely to develop other subsequent conditions or alternative diagnoses after being considered as CFS. Although this study did not measure when other diagnoses developed or if they were present prior to CFS, participants stated the diagnoses were active, reoccurring, or not entirely resolved. Accordingly, it is imperative that those diagnosed with CFS be particularly vigilant about the presence of new symptoms. It is highly evident in the findings of this study that those diagnosed with CFS are at risk of attributing symptoms that may be of a major disease such as cardiovascular disease, autoimmune disease and endocrine disorders as part of their experience of CFS. There are also many conditions that share many common features of CFS, especially when not adequately managed such as hypothyroidism.

Those that had reported major depression and anxiety were considered as having an alternative primary care diagnoses. Given the chronically debilitating nature of the illness, patients are greatly at risk of developing severe depression, such as those that are housebound or bedridden for extensive periods and those with limited social support. According to a sample of 166 deceased individuals with CFS, 20% were reported to have died from suicide (Jason et al., 2006). Hence, depression should be taken into primary account when managing their health, as

improved mental health would significantly impact on the prognosis, management, and expectations for their health.

With regards to health service use, all groups (CFS, ME, CF and other illnesses) were largely managed by general practitioners. It was also evident that patients consulted with physiotherapists, psychologists, dieticians and complementary and alternative therapists such as acupuncturists and massage therapists for management of their condition. Hence, CFS, ME and fatigue related conditions are of significant primary health care concern, and may benefit greatly from a multidisciplinary approach

6.5.3 Strengths, limitations and future directions

A particular strength of this study was the large sample size. The option of participating in the registry via online, as well as hardcopy also has the potential to capture participants that are housebound by their illness and would normally be unable to attend a site visit to participate in research. A limitation to consider is reliance on self-reported data and the findings of this should be regarded as the result of a preliminary screening. Particular examples include patients reporting conditions that require a physician to verify such as insomnia, neutrally mediated hypotension, postural orthostatic tachycardia syndrome, and ataxia. For these particular conditions, the questionnaire employed by this study asked whether patients had been formally diagnosed by a physician as opposed to whether they experienced these as a symptom (Appendix 2). Accordingly, the future direction of this study would be to recruit those reporting CFS symptoms for secondary screening with a physician. However, for the purposes of a research registry, the high response has given significant insight into diagnostic, management, and illness perception of candidates for CFS and ME in Australia. Thus, this study is an initial platform for more specific studies into the prognosis, management, and epidemiological investigations that are currently being undertaken by the authors.

6.6 Conclusion

This is the first study to investigate other diagnoses among those reporting CFS/ME symptoms in Australia. The main findings are that: (i) A significant subgroup of those reporting CFS symptom criteria also fulfil symptom criteria for ME supporting a previous proposal that ME maybe a clinical subgroup found within the broad spectrum of CFS. (ii) Further to this, several potential subgroups of CFS patients are apparent including those with sleep disturbances such as insomnia; immunological perturbations and gastrointestinal disturbance such as sinusitis and irritable bowel syndrome; and cardiovascular anomalies such as orthostatic intolerance and POTS. (iii) A diagnosis of CFS/ME is prevalent in Australian general practice, though a significant proportion is likely to be experiencing secondary chronic fatigue as a result of another primary diagnosis. (iv) A significant proportion of those reporting to have CFS/ME only meet major criteria for chronic fatigue, but not the myriad of symptoms that accompany these illnesses. This highlights the need for improvement in general practitioner awareness and knowledge of guidelines for the diagnosis and management of CFS/ME, which will in turn improve patient's own management and understanding of their health.

Competing interests

The authors declare that they have no competing interests.

Author contributions

SJ Contributed to the study design, data collection, analysis and drafting of this manuscript. EB, DS, SM Contributed to drafting and revisions of this manuscript.

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Chapter 7: Epidemiological characteristics of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis in Australian patients

Statement of Co-authorship

This chapter includes a co-authored paper. The bibliographic details of the co-authored paper, including all authors, are:

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My contribution to the paper involved the design of the study, provision of data, analysis, and preparation of the resulting manuscript.

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Supervisor: Sonya Marshall-Gradisnik

7.1 Abstract

Background: No epidemiological investigations have previously been conducted in Australia according to current clinical definitions of CFS/ME. The aim of this study was to describe sociodemographic and illness characteristics of Australian patients with CFS/ME.

Methods: A cross-sectional survey on the medical history of patients enrolled in an Australian CFS/ME research database between April 2013 and April 2015. Participants were classified according to Fukuda and International case definitions.

Results: A total of 535 patients diagnosed with CFS/ME by a primary care physician were identified. The mean age of all patients was 46.41 years (SD 11.97) and majority female (78.61%), Caucasian and highly educated. Of these, 30.28% were classified as Fukuda cases. A further 31.96% were classed as International cases. A further 14.58% had atypical chronic fatigue but did not meet case definitions and 23.18% were considered non-cases. Within CFS/ME cases, the most common triggers included cold or flu, gastrointestinal illness, and periods of undue stress. Of 54 symptoms surveyed, fatigue, cognitive and short term memory symptoms, headaches, muscle and joint pain, unrefreshed sleep, sensory disturbances, muscle weakness, and intolerance to extremes of temperature were the most commonly occurring symptoms (reported by more than two thirds of patients). Significant differences in symptom occurrence between Fukuda and International defined cases were also identified.

Conclusion: This is the first study to summarise sociodemographic and illness characteristics of a cohort of Fukuda and International definedAustralian CFS/ME patients. This is vital for identifying potential risk factors and predictors associated with CFS/ME and for guiding decisions regarding health care provision, diagnosis and management.

Keywords: Chronic Fatigue Syndrome; Myalgic Encephalomyelitis; Chronic Fatigue; Diagnosis; Epidemiology

7.2 Introduction

Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) is a disabling condition that significantly interrupts individuals during critical years of social and economic productivity. It is most often characterised by Fukuda et al. (1994) symptom criteria that includes medically unexplained fatigue accompanied by at least four of the following: post-exertional malaise, short term memory loss or concentration difficulty, unrefreshed sleep, headache, muscle pain, joint pain, sore throat, and tender lymph nodes. Alternative criteria such as the International (Carruthers et al., 2011) disclose a further range of neurological, immunological, gastrointestinal, and autonomic symptoms. The aetiology or pathomechanism behind this illness however, remains unknown.

In the United Kingdom (UK), Fukuda defined cases have a prevalence of 0.19% (Nacul et al., 2011). The economic consequence is estimated as GBP120.2 million annually due to lost productivity (Collin et al., 2011). In the United States (US), the prevalence of Fukuda defined cases has been reported as 0.24% (Reyes et al., 2003b), and is estimated to cost USD9.1 billion annually in productivity losses (Reynolds et al., 2004). This represents a sizeable economic burden for a select population.

Despite the evidence demonstrating the public health impact abroad, the characteristics of an Australian CFS/ME population has not been summarised. An early study based on a primary care practice survey in the Richmond Valley, a rural district in the state of New South Wales suggested a prevalence of 0.04% (Lloyd et al., 1990). This was based on the author's case definition that required fatigue of at least 6 months duration, accompanied only by cognitive or short term memory impairment. This was subsequently estimated to cost AUD59 million annually in both direct health care costs and indirect costs regarding lost productivity (Lloyd and Pender, 1992). In contrast to current case definitions, this study described cognitive disturbance as the hallmark of the illness. On the contrary, the Fukuda and more recent International case definitions emphasise the role of post-exertional malaise and describe a multisystem disorder. As a result the attributes described in the Richmond Valley study may be

representative of a significantly different clinical profile. Hence, studies that characterise Australian samples are not available and the Royal Australasian College of Physicians guidelines for clinical practice includes limited evidence from Australian based cohorts (Working Group of the Royal Australasian College of Physicians, 2002a).

The aim of this study was to summarise socio-demographic and illness characteristics in those reporting CFS/ME symptoms according to current case definitions in Australia. A better understanding of the above is important for detecting potential risk factors and predictors associated with CFS/ME, and for health care provision. These findings are presented according to guidelines for strengthening the reporting of observational studies in epidemiology (Vandenbroucke et al., 2007).

7.3 Methods

Participants in this study were enrolled in a voluntary research database for CFS/ME managed by the National Centre for Neuroimmunology and Emerging Diseases (NCNED) within Griffith University. It commenced following approval from Griffith University Human Research Ethics Committee (HREC reference number MSC0413) and utilised responses from a cross-sectional survey of participants during a 2 year period from April 2013 to April 2015.

Recruitment was based on self-identification. Upon contacting the research centre, those interested in the study received an information pack and consent form by agreeing to terms and conditions disclosed online or by hardcopy sent in the mail. Once consent was provided, the study questionnaire was made available through an online link or by hardcopy in the mail. Items in the study questionnaire were developed by the authors and participants were asked to disclose sociodemographic details, medical history, and complete a 60 item checklist on their fatigue and concurrent symptoms. To be included in this study, participants were required to (i) report receiving a diagnosis of CFS/ME by their primary physician (ii) were between 18 and 65 years of age and (iii) were a resident of Australia.

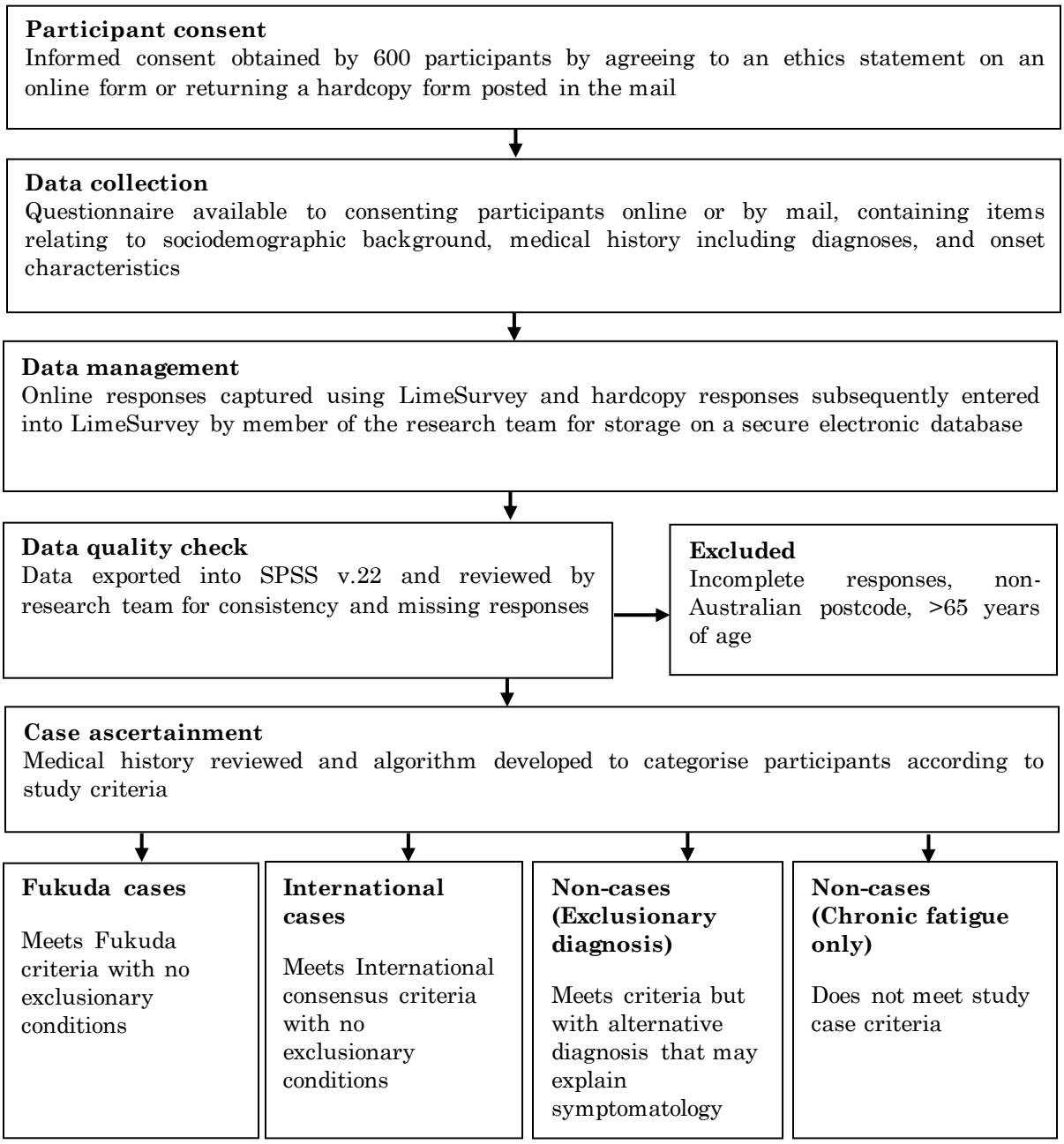

Figure 7.1: Flow chart of case ascertainment

The method of case ascertainment is summarised in Figure 7.1. Responses to the study questionnaire were collected using an online survey application known as LimeSurvey (Schmitz, 2012), and stored on a secure server hosted by Griffith University. Data from hardcopy versions of the study questionnaire returned to the research centre by mail were subsequently entered into the LimeSurvey application by a member of the research team to consolidate all responses. All personal data was encrypted to remove the identity of participants.

Disclosed medical histories were reviewed to exclude any potential diagnoses or conditions that may be an alternative explanation for symptoms. This included, but was not limited to major heart disease, neurological disorders such as multiple sclerosis, autoimmune disease such as rheumatoid arthritis and diabetes, and thyroid disorders. If present, these participants were classified as non-cases.

An algorithm was designed to ascertain whether participants met the Fukuda and International case definitions. To be reported as a case, reported symptoms were required to meet at least one of the above criteria with no exclusionary conditions. Accordingly, cases were reported as either Fukuda vs. International defined cases. Those that reported chronic fatigue for at least 6 months but did not meet any study criteria due to lack of accompanying symptoms were considered atypical and were reported in this study as cases of chronic fatigue (CF). Hence, the primary outcome of interest included the frequency of Fukuda vs. International defined cases, chronic fatigue, and non-cases.

Socio-demographic data included location, age, sex, ethnicity, education and employment. Postcodes were used to verify Australian residency and were classified according to the Australian Bureau of Statistics (ABS) Australian Standard Geographical Classification definition for urban and rural areas (Australian Bureau of Statistics, 2012). This classifies populations of 100,000 or more as major urban areas, 1,000 – 99,999 as other urban, and remaining postcodes as rural. BMI was classified according to the World Health Organisation (2006) global database on body mass index. Accordingly, underweight was considered <18.50, normal 18.50 – 24.99, overweight 25.00 – 29.99, and obese ≥ 30.00. With regards to ethnicity, participants were classified according the ABS Australian classification for cultural and ethnic groups (Australian Bureau of Statistics, 2011). This included Non-indigenous Australian, Indigenous Australian, Oceanian (New Zealand, Melanesian, Papuan, Micronesian, and Polynesian), North West European, Southern and Eastern European, North African and Middle Eastern, South East Asian, North East Asian, Southern and Central Asian, People of the Americas, and Sub-

Saharan African. Participant education was categorised according to highest level of education completed. In terms of employment, full time hours were defined as 35 hours per week or more and part time hours were considered less than 35 hours per week in accordance with the ABS Labour Force Survey (Australian Bureau of Statistics, 2013). Participants were further classified as those on disability pension, retired, and unemployed.

Illness characteristics outcomes of interest included age of onset (time since first experiences symptoms), age of diagnosis by a primary care physician, duration of illness (time elapsed since onset of illness). Furthermore, participants were asked to identify location of onset by state within Australia and by country if overseas. The study further surveyed triggers and exposures that participants associated with prior to their illness suggested by the International Consensus Primer for Medical Practitioners (Carruthers et al., 2012c).

With regards to symptomatology, fatigue was defined as persistent or recurrent for at least 6 months that was not due to ongoing exertion and significantly interfered with activities of daily life. Post-exertional neuroimmune exhaustion was defined according to the Carruthers et al. 2011 definition that describes a marked, rapid physical or cognitive fatigue in response to exertion; post-exertional symptom exacerbation; the post-exertional fatigue maybe immediate or delayed; a prolonged recovery period; and a substantial reduction in pre-illness activities. Post-exertional malaise was defined as significant worsening of symptoms following physical and mental exertion. Further, participants were also asked to only nominate symptoms that had persisted or recurred concurrently with fatigue and did not appear prior to the onset of fatigue.

The study includes descriptive statistics of the above characteristics. Analysis of variance (ANOVA) was used to analyse difference among mean age, as well as Pearson's chi-squared analysis to compare the frequency of symptoms between Fukuda and International defined cases using SPSS v.22 (IBM Corporation, 2013).

7.4 Results

Of 600 respondents, a total of 535 participants met the inclusion criteria. The location of participants in this study are summarised in Figure 7.2. The majority of participants were from Queensland, followed by New South Wales, and Victoria and 91.89% had postcodes corresponding to major urban regions of Australia.

Figure 2: Frequency of participants in the CFS/ME registry by state
QLD, Queensland; NSW, New South Wales; ACT, Australian Capital Territory; VIC, Victoria; TAS, Tasmania; SA, South Australia; NT, Northern Territory; WA, Western Australia

Of 535 individuals assessed, CFS/ME as characterised by the Fukuda definition was evident in 30.28%%. A further 31.96 % also met the International definition. 23.18% were classified as CF, as they met criteria for chronic fatigue but did not report sufficient symptoms to meet the Fukuda or International definitions. The remaining 14.58% reported an alternative physical or psychological diagnosis that accounted for their symptom profile and were thus classified as non-cases.

The sociodemographic of characteristic of Fukuda cases, International cases, chronic fatigue, and non-cases are summarised in Table 7.1. In total, the

highest proportion of participants were non-Indigenous Australian (total 74.39%), female (total 78.61%), with a mean age of 46.41 (SD 11.97). A total of 47.48% of participants were within a normal range for BMI. A higher proportion of individuals had completed either undergraduate (27.85%) or postgraduate (18.13%) university degrees. The majority of participants were on disability (34.21%) or unemployed (26.73%), while the lowest proportion maintained full time roles (9.72%). The distribution of the above characteristics was similar between study groups.

Table 7.2 summarises the onset characteristics of Fukuda, International and CF cases. The mean age of illness onset for Fukuda ($p=0.030$) and International ($p<0.001$) defined cases were significantly younger in comparison to CF. Across all groups, the highest proportion of cases originated in Queensland. More than 5% of cases across all groups originated overseas. The most common reported infectious triggers were cold and flu, upper respiratory infections, and gastrointestinal illness. Furthermore, the most common non-infectious trigger reported was periods of undue stress.

Reported symptoms of Fukuda, International, and CF cases are reported in Table 7.3. The most common symptoms reported by more than two thirds of both Fukuda and International defined cases included fatigue; cognitive overload; difficulty making decisions; short term memory problems; headaches; muscle pain; joint pain; unrefreshed sleep; sensitivities to light, noise, vibration, odours, taste and/touch; light headedness; and intolerances to extremes of temperature.

Table 7.1: Sample demographic characteristics

	Fukuda	International	CF	Non-cases	Total
N (%)	162 (30.28%)	171 (31.96 %)	78 (14.58%)	124 (23.18%)	535 (100%)
Age in years mean (SD)	46.7 (11.76)	44.02 (11.72)	48.52 (14.63)	48.63 (11.17)	46.41 (11.97)
Female n (%)	117 (72.22%)	132 (77.19%)	62 (79.49%)	108 (87.10%)	417 (78.61%)
BMI					
	9 (5.56%)	11 (6.43%)	11 (14.10%)	4 (3.23%)	35 (6.54%)
	78 (48.15%)	86 (50.29%)	28 (35.89%)	62 (50.00%)	254 (47.48%)
	62 (38.27%)	37 (21.63%)	22 (28.21%)	28 (22.58%)	149 (27.85%)
	13 (8.02%)	37 (21.63%)	17 (21.79%)	30 (24.19%)	97 (18.13%)
Ethnicity					
Non-indigenous Australian	125 (77.16%)	122 (71.35%)	60 (76.92%)	91 (73.39%)	398 (74.39%)
Indigenous Australian	1 (0.62%)	2 (1.17%)	1 (1.28%)	4 (3.23%)	8 (1.50%)
Oceanian	4 (2.47%)	10 (5.85%)		6 (4.84%)	20 (3.74%)
NW European	33 (20.37%)	49 (28.65%)	13 (16.67%)	36 (29.03%)	131 (24.49%)
SE European	8 (4.94%)	4 (2.34%)	3 (3.85%)	6 (4.84%)	21 (3.93%)
NA & ME	1 (0.62%)	1 (0.58%)			2 (0.37%)
SE Asian	1 (0.62%)			1 (0.81%)	2 (0.37%)
SC Asian	1 (0.62%)	1 (0.58%)		1 (0.81%)	3 (0.56%)
Americas	1 (0.62%)				1 (0.19%)
Sub Saharan African	2 (1.23%)	1 (0.58%)	1 (1.28%)	1 (0.81%)	5 (0.93%)
Education n (%)					
Primary school	1 (0.61%)	1 (0.01%)			2 (3.74%)
High school	40 (24.69%)	42 (24.56%)	8 (10.64%)	23 (18.55%)	113 (21.12%)
Professional[ii]	34 (20.98%)	40 (23.39%)	15 (19.15%)	33 (26.61%)	122 (22.80%)
Undergraduate	49 (30.25%)	53 (30.99%)	38 (48.94%)	43 (34.68%)	183 (34.21%)
Postgraduate	38 (23.46%)	35 (20.47%)	17 (21.28%)	25 (20.16%)	115 (21.50%)
Employment n (%)					
Full time	20 (12.35%)	17 (9.84%)	6 (7.69%)	9 (7.26%)	52 (9.72%)
Park time	45 (27.78%)	48 (27.98%)	11 (14.10%)	22 (17.74%)	126 (23.55%)
Disability	49 (30.25%)	59 (34.72%)	31 (39.74%)	44 (35.48%)	183 (34.21%)
Retired	3 (1.85%)	4 (2.07%)	15 (19.23%)	9 (7.26%)	31 (5.79%)
Unemployed	45 (27.78%)	43 (25.39%)	15 (19.23%)	40 (32.26%)	143 (26.73%)

[i]Percentage exceeds 100 as participants may be more than one ethnicity; NW, North West; SE, South East; NA, North African; ME, Middle Eastern; SC, South or Central

[ii]Professional training denotes a non-university qualification

[iii]Recipient of a disability pension

Table 7.2: Sample onset characteristics for CFS/ME and CF cases

	Fukuda	International	CF
Age of onset mean (SD)	30.84 (12.64)	28.33 (11.35)	35.16 (13.05)
Age of diagnosis mean (SD)	34.71 (11.97)	32.82 (10.93)	38.24 (10.67)
Duration of illness mean (SD)	14.54 (10.07)	14.74 (11.46)	13.96 (11.15)
Onset within Australia (by state)			
Queensland	67 (41.36%)	57 (33.33%)	19 (24.36%)
New South Wales	41 (25.31%)	41 (23.98%)	17 (21.79%)
Victoria	23 (14.20%)	32 (18.71%)	19 (24.36%)
South Australia	7 (4.32%)	8 (4.68%)	14 (17.95%)
Western Australia	7 (4.32%)	5 (2.92%)	2 (2.56%)
Northern Territory	2 (1.23%)		
Tasmania		4 (2.34%)	
Australian Capital Territory	2 (1.23%)	7 (4.09%)	2 (2.56%)
Subtotal	151 (93.21%)	154 (90.06%)	74 (94.87%)
Overseas onset (by country)			
Belgium	1 (0.62%)		
Canada		1 (0.58%)	
Ethiopia	1 (0.62%)		
Fiji		1 (0.58%)	
France		1 (0.58%)	
India	1 (0.62%)		
Indonesia		1 (0.58%)	
Japan			1 (1.28%)
Nepal			1 (1.28%)
New Zealand	1 (0.62%)	5 (2.92%)	
Papua New Guinea		1 (0.58%)	
South Africa	2 (1.23%)	1 (0.58%)	1 (0.58%)
United Kingdom	4 (2.47%)	4 (2.34%)	1 (1.28%)
United States	1 (0.62%)	1 (0.58%)	
Vietnam		1 (0.58%)	
Subtotal	11 (6.79%)	17 (9.94%)	4 (5.13%)
Infectious triggers[i]			
Cold or flu	60 (37.04%)	65 (38.01%)	15 (19.23%)
Immunisation	14 (8.64%)	19 (11.11%)	3 (3.85%)
Upper respiratory infection	33 (20.37%)	57 (33.33%)	8 (10.26%)
Sinusitis	22 (13.58%)	25 (14.62%)	4 (5.13%)
Pneumonia	5 (3.09%)	7 (4.09%)	0 (0.00%)
Gastrointestinal illness	25 (15.43%)	49 (28.65%)	11 (14.10%)
Dental infection	7 (4.32%)	5 (2.92%)	1 (1.28%)
Urinary tract infection	3 (1.85%)	8 (4.68%)	1 (1.28%)
Blood transfusion	0 (0.00%)	1 (0.58%)	0 (0.00%)
Unfamiliar sickness when travelling	11 (6.79%)	19 (11.11%)	5 (6.41%)
Contaminated water	3 (1.85%)		
Poor recycled air	10 (6.17%)	6 (3.51%)	4 (5.13%)
Non-infectious triggers[i]			
Post-chemical toxins	17 (10.49%)	21 (12.28%)	6 (7.69%)
Heavy metals	6 (3.70%)	8 (4.68%)	1 (1.28%)
Moulds	10 (6.17%)	16 (9.36%)	0 (0.00%)
Severe physical trauma	22 (13.58%)	21 (12.28%)	2 (2.56%)
Anaesthetic	12 (7.41%)	17 (9.94%)	1 (1.28%)
Undue stress	78 (48.15%)	79 (46.20%)	16 (20.51%)
Steroid[ii]	0 (0.00%)	5 (2.92%)	0 (0.00%)

[i]Percentage does not add to 100 with participants reporting more than one trigger
[ii]Prescription due to acute respiratory illness

Table 7.3: Frequency of reported symptoms for CFS/ME and CF cases

Symptom	Fukuda	International	CF	Fukuda vs. International[a]	
				r	P
Fatigue					
Fatigue[i]	162 (100.00%)	171 (100.00%)	78 (100.00%)	.	.
Post-exertional neuroimmune exhaustion[ii]	8 (4.94%)	171 (100.00%)	3 (3.85%)	0.557	0.000**
Post-exertional malaise	62 (38.27%)	171 (100.00%)	9 (11.54%)	0.432	0.000**
Cognition					
Confusion	100 (61.73%)	125 (73.10%)	4 (5.13%)	0.131	0.018*
Disorientation	52 (32.10%)	91 (53.22%)	3 (3.85%)	0.222	0.000**
Cognitive overload	119 (73.46%)	146 (85.38%)	12 (15.38%)	0.166	0.003*
Difficulty making decisions	117 (72.22%)	137 (80.12%)	10 (12.82%)	0.104	0.062
Slowed speech	58 (35.80%)	91 (53.22%)	6 (7.69%)	0.183	0.001**
Dyslexia	32 (19.75%)	52 (30.41%)	0 (0.00%)	0.127	0.023*
Short term memory	117 (72.22%)	131 (76.61%)	6 (7.69%)	0.058	0.058
Pain					
Headaches	116 (71.60%)	139 (81.29%)	6 (7.69%)	0.128	0.022*
Muscle pain	132 (81.48%)	154 (90.06%)	6 (7.69%)	0.147	0.008
Joint pain	113 (69.75%)	122 (71.35%)	3 (3.85%)	0.022	0.691
Abdomen pain	61 (37.65%)	99 (57.89%)	1 (1.28%)	0.211	0.000**
Chest pain	50 (30.86%)	73 (42.69%)	5 (6.41%)	0.128	0.022
Sleep disturbances					
Insomnia	74 (45.68%)	106 (61.99%)	4 (5.13%)	0.172	0.002*
Prolonged sleep	69 (42.59%)	73 (42.69%)	6 (7.69%)	0.003	0.003*
Reverse sleep	13 (8.02%)	41 (23.98%)	2 (2.56%)	0.222	0.000**
Frequent awakenings	80 (49.38%)	112 (65.50%)	5 (6.41%)	0.172	0.002*
Awakening earlier than expected	46 (28.40%)	77 (45.03%)	6 (7.69%)	0.179	0.001*
Vivid dreams or nightmares	58 (35.80%)	98 (57.31%)	6 (7.69%)	0.225	0.000**
Unrefreshed sleep	143 (88.27%)	157 (91.81%)	14 (17.95%)	0.81	0.081
Sensory, perceptual and motor disturbances					
Inability to focus vision	75 (46.30%)	106 (61.99%)	5 (6.41%)	0.166	0.003*
Sensitivities[iii]	117 (72.22%)	151 (88.30%)	10 (12.82%)	0.227	0.000**
Poor depth perception	24 (14.81%)	56 (32.75%)	1 (1.28%)	0.216	0.000**
Muscle weakness	123 (75.93%)	144 (84.21%)	7 (8.97%)	0.119	0.033*
Twitching	61 (37.65%)	89 (52.05%)	4 (5.13%)	0.151	0.007*
Poor coordination	78 (48.15%)	100 (58.48%)	6 (7.69%)	0.110	0.049*
Feeling unsteady on feet	79 (48.77%)	123 (71.93%)	8 (10.26%)	0.250	0.000**

Symptom	Fukuda	International	CF	Fukuda vs. International[a]	
				r	P
Immune					
Sore throat	71 (43.83%)	108 (63.16%)	3 (3.85%)	0.204	0.000**
Tender lymph nodes	66 (40.74%)	98 (57.31%)	0 (0.00%)	0.174	0.002*
Sinusitis	56 (34.57%)	82 (47.95%)	1 (1.28%)	0.142	0.011*
Recurrent or persistent infections	41 (25.31%)	63 (36.84%)		0.129	0.021*
Gastrointestinal and genitourinary					
Nausea	66 (40.74%)	102 (59.65%)	3 (3.85%)	0.198	0.000*
Abdominal pain	60 (37.04%)	103 (60.23%)	5 (6.41%)	0.242	0.000*
Bloating	95 (58.64%)	119 (69.59%)	4 (5.13%)	0.123	0.027*
Irritable bowel	73 (45.06%)	101 (59.06%)	6 (7.69%)	0.148	0.008*
Food intolerance[iv]	95 (58.64%)	139 (81.29%)	10 (12.82%)	0.266	0.000**
Urinary urgency or frequency	75 (46.30%)	113 (66.08%)	7 (8.97%)	0.210	0.000**
Cardiovascular					
Orthostatic intolerance[v]	32 (19.75%)	53 (30.99%)	3 (3.85%)	0.133	0.017*
Neurally mediated hypotension[v]	9 (5.56%)	15 (8.77%)	1 (1.28%)	0.064	0.251
Postural orthostatic tachycardia syndrome[v]	18 (11.11%)	27 (15.79%)	1 (1.28%)	0.071	0.205
Ataxia[v]	2 (1.23%)	10 (5.85%)	1 (1.28%)	0.126	0.023*
Heart palpitations	64 (39.51%)	95 (55.56%)	6 (7.69%)	0.168	0.003*
Light headedness	107 (66.05%)	144 (84.21%)	8 (10.26%)	0.231	0.000**
Respiratory					
Air hunger	47 (29.01%)	65 (38.01%)	4 (5.13%)	0.099	0.075
Laboured breathing	47 (29.01%)	70 (40.94%)	3 (3.85%)	0.130	0.020*
Fatigue of chest muscles	55 (33.95%)	69 (40.35%)	3 (3.85%)	0.070	0.211
Autonomic					
Abnormal body temperature	56 (34.57%)	88 (51.46%)	4 (5.13%)	0.178	0.001**
Fluctuating body temperature	61 (37.65%)	81 (47.37%)	2 (2.56%)	0.103	0.064
Sweating episodes	68 (41.98%)	94 (54.97%)	4 (5.13%)	0.137	0.014*
Recurrent feverishness	50 (30.86%)	82 (47.95%)		0.181	0.001**
Cold extremities	78 (48.15%)	121 (70.76%)	6 (7.69%)	0.243	0.000**
Intolerance of extremes temperature	109 (67.28%)	139 (81.29%)	7 (8.97%)	0.176	0.002*

[a]Pearson correlation *Correlation is significant at the 0.05 level; **Correlation is significant at the 0.001 level

[i]Fatigue as defined by Fukuda et al. (1994) criteria that is fatigue not due to ongoing exertion and significantly interferes with daily activities and work; [ii]PENE as defined by Carruthers et al. (2011) that includes post-exertional fatigue, post-exertional symptom exacerbation, prolonged recovery period of 24 hours of longer and lack of stamina; [iii]Sensitivity to light, noise, vibration, odour, taste and/or touch; [iv]Intolerance to food, medications, odors or chemicals; [v]Conditions diagnosed by a clinician

At the $p<0.001$ level, a significantly higher proportion of International defined cases reported post-exertional neuroimmune exhaustion, post-exertional malaise, disorientation, slowed speech, abdominal pain, reversed sleep cycles, vivid dreams or nightmares, sensitivities to light, noise, vibration, odours, taste and/or touch, depth perception, feeling unsteady on their feet, sore throat, food intolerances, urinary disturbances, light headedness, abnormal body temperature, recurrent feverishness, and cold extremities.

7.5 Discussion

This study was performed to review the socio-demographic and illness characteristics of CFS/ME patients within Australia. The key findings of this study include (i) the frequency of Fukuda, International and CF defined cases (ii) socio-demographic characteristics that have not been previously reported in an Australian sample according to current definitions of CFS/ME (iii) the average age of onset, diagnosis and common infectious and non-infectious triggers and events (iv) a high frequency of varied symptoms experienced by patients and significant differences between Fukuda and International defined patient sets.

7.5.1 Case ascertainment

In this study, a significant proportion of Fukuda defined cases further fulfilled the International definition. This supports previous findings that International defined cases represent a subgroup within the broad spectrum of Fukuda defined CFS/ME (Brown et al., 2013b, Johnston et al., 2014b). Accordingly, it has been demonstrated that International defined cases have reported decreased physical and social functioning in comparison to Fukuda defined cases (Brown et al., 2013b, Johnston et al., 2014b). A significant proportion (24.1%) of participants in this study reporting a diagnosis of CFS/ME were not considered cases due to concurrent conditions that would explain their symptoms. This finding is highly consistent with the UK prevalence study, in which 24% of GP diagnosed cases did not fulfil their

study criteria for CFS/ME using similar methods of case ascertainment (Nacul et al., 2011).

In the absence of a reliable biological test, CFS/ME remains a challenging diagnosis and illness to identify. General practitioners' attitudes towards CFS/ME are diverse regarding their opinions and management of CFS/ME (Steven et al., 2000, Bowen et al., 2005, Raine et al., 2004). Indeed, the significant variability found between case definitions for CFS/ME is an immediate cause of confusion for clinicians and researchers alike (Johnston et al., 2014d). Further reasons include limited knowledge, lack of recognition for the disorder, and limited contact with CFS/ME patients that do not access care due to the severity of their condition as well as their low expectations for receiving adequate care and support (Drachler et al., 2009).

7.5.2 Socio-demographic characteristics

The findings of our study suggest the CFS/ME predominantly affects those between 45 and 55 years, however the range in our cohort extended from 18 to 65 and thus CFS/ME was not exclusive to any age set. The profile of patients in this study, are similar to early US studies on the primary care prevalence on CFS/ME lead by the Centres for Disease Control and Prevention (CDC) in that the majority of participants were Caucasian females and highly educated (Reyes et al., 1997). A higher ratio of females is commonly reported within CFS/ME (Jason et al., 1999, Lawrie and Pelosi, 1995, Lloyd et al., 1990), however several studies have suggested that women are more likely to access all levels of health services than men (Galdas et al., 2005). While the majority of participants in this study identified as non-indigenous Australians, community based studies in the US suggest that the prevalence of CFS/ME may actually be higher among their minority populations for example, rates have been reported as higher amongst African Americans and Latinos in comparison to Caucasians (Jason et al., 1999).

As a cross-sectional study, it cannot be determined whether weight and obesity were significant predictors for CFS/ME or the reverse. However

a high proportion of participants were overweight and obese. In a Dutch survey, CFS participants were more likely to be obese (OR = 0.5) in comparison non-fatigued participants (van't Leven et al., 2010). This could be associated with the debilitating and chronic nature of the illness that may result in significantly decreased mobility as severe cases are often housebound or bedridden. Accordingly, overweight and obese individuals with CFS/ME have demonstrated significantly poorer physical functioning than controls of similar weight (Flores et al., 2013b).

The functional impact of the illness is also evident in the significantly high proportion of individuals that are unemployed, on disability pension, or maintain part-time roles. This is of particular concern considering many are still in the most economically and socially productive years of their lives and thus, represents significant economic losses at both the population and patient level. This reduced economic position adds further to the stress, anxiety or depression that may develop with a chronic condition, particularly in those patients that are bedridden or housebound for protracted periods of time and receive limited support.

7.5.3 Illness characteristics

The peak onset of CFS/ME was relatively young in this sample, between the ages of 25 and 35 years. A relatively large proportion identified infectious triggers such as cold, flu and upper respiratory infections, and gastrointestinal illness. Further, a considerable number of cases began overseas as a result of an unknown infection. Though this study did not identify specific infections, an Australian prospective cohort study found that 11% of those that acquired an acute infection of either Epstein-Barr virus (glandular fever), Coxiella burnetii (Q fever), or Ross River virus (epidemic polyarthritis) went on to fulfil Fukuda et al. (1994) symptom criteria (Hickie et al., 2006). Many patients reporting an infection also reported significant periods of undue stress. This does align with the proposed pathophysiology that CFS/ME presents as a multisystem disorder involving interactions between the immune and central nervous system, and

that stress may potentially reactivate or replicate a latent virus such as Epstein-Barr developing symptoms of CFS/ME (Glaser and Kiecolt-Glaser, 1998).

This study identified the most common symptoms reported by patients representing Fukuda and International defined cases. Cognitive issues, muscle pain and weakness, sleep disturbances, and sensory disturbances in particular were the most common issues reported. Food intolerances, urinary disturbances and intolerance of extreme temperature were highly prevalent among International defined cases (more than two thirds) and could be considered distinguishing features in comparison to Fukuda defined cases.

7.5.4 Limitations and recommendations

The results of this study may not be representative of all CFS/ME patients in the general population given that the sample was not from a community-based survey. A significant proportion of the patients reported are from the state of Queensland due to proximity to the research centre and their participation in further biological studies on CFS/ME. Hence, community based sampling across Australian states would be recommended to confirm whether geographical differences were apparent. The most common findings of this study however, provide an indication of what should be screened if a community based study commenced. A limitation is reliance on reported symptoms for case ascertainment however the methods of this study remain important as an initial screening tool to identify cases of CFS/ME. Methods such as the recruitment of patients from GP databases may not have been as successful as self-identification of a largely unrecognised and misdiagnosed condition. Furthermore, in contrary to typical patterns of chronic disease where the most severe cases present to primary care, severe cases of CFS/ME may be less likely to present to primary care due to being bedridden. Further, a consultation with a primary care professional is limited as and there currently remains no successful therapy for the illness.

This information is intended to guide decision makers and clinicians on what patient and illness characteristics may be expected when potential cases of CFS/ME arise. To improve understanding on the prognosis of CFS/ME, future directions aim to follow up those patients recruited in this study longitudinally as a prospective cohort. This will capture not only changes in employment status, but also the pattern of symptomatology. Symptom severity and the functional impact of the illness will also be monitored. The alignment of this clinical severity with laboratory findings will be particularly valuable for identifying potential biological markers and the aetiology or pathomechanism behind this illness.

7.6 Conclusions

This study has identified a significant cohort of Australians that fulfil CFS/ME definitions that have substantially low rates of full-time employment and are in high need of improved health care support. Upper respiratory infections and gastrointestinal illness, as well as stressful life events were common events prior to the onset of their illness. Those meeting the International definition further appear to represent a distinct clinical group with distinguishing symptoms. The improved characterisation of Australian CFS/ME will help guide decisions in diagnosis, management and health service provision.

Competing interests

The authors declare no competing interests for this study.

Author contributions

SCJ, DRS and SMM were responsible for study design and revisions of this manuscript. SCJ was responsible for data management, analysis, drafting and revisions.

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Chapter 8: Management of Chronic Fatigue Syndrome: Current Approaches and Future Directions

Statement of Co-authorship

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My contribution to the paper involved the design of the study, provision of data, analysis, and preparation of the resulting manuscript.

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8.1 Introduction

Chronic Fatigue Syndrome (CFS) is a complex, debilitating illness that continues to attract controversy. There has long been considerable debate between the disciplines about its potential aetiology, case definition, diagnosis, and management. This also includes the nomenclature and overlap of this illness with Myalgic Encephalomyelitis (ME). To encompass the range of literature that refers to either, this chapter utilizes the joint acronym CFS/ME to review several management strategies and future directions.

Prior to discussing proposed interventions for CFS/ME, it is important to acknowledge that there are several case definitions available for CFS/ME, which vary significantly in their inclusion of specific symptoms and exclusion of concurrent conditions (Johnston et al., 2013e). The most common criteria adopted worldwide (Johnston et al., 2013f) are the Fukuda criteria (Fukuda et al., 1994), which requires the presence of debilitating fatigue that is not due to ongoing exertion for at least 6 months. This is accompanied by at least 4 of the following: post-exertional malaise, impairment of short term memory or concentration, unrefreshing sleep, headaches, muscle pain, joint pain, tender lymph nodes, and sore throat. Other commonly used criteria, include the Oxford criteria (Sharpe et al., 1991) that describe a severe, disabling physical and mental fatigue, which has been present at least 50% of the time during the past 6 months and has a definite onset. These criteria suggest that other symptoms may be present, in particular pain, mood and sleep disturbance, but are primarily based on a model of unexplained fatigue. These criteria do not mention the relationship between fatigue and post-exertional malaise, which is often described as a distinguishing feature of CFS/ME by other definitions.

More recently devised criteria include the Canadian consensus criteria (Carruthers et al., 2003) and the International consensus criteria (Carruthers et al., 2011), which suggest the illness is associated with several systems of the body. Rather than a nominal list, patients must meet a

required number of symptoms from categories relating to impairment of the neurological, autonomic, endocrine, and immunological systems. According to the Canadian consensus, patients must experience ongoing or relapsing problems with fatigue, post-exertional malaise, and pain, two neurocognitive symptoms, at least one symptom from two of the following categories: autonomic, neuroendocrine, immune for at least 6 months (Carruthers et al., 2003).

The International consensus criteria introduced further requirements for what constitutes fatigue and post-exertional malaise, which is referred to as post-exertional neuroimmune exhaustion (PENE). Accordingly, in response to exertion patients should exhibit a marked, rapid physical and/or cognitive fatigue; exacerbation of other symptoms; immediate or delayed exhaustion; prolonged recovery time; and a lack of stamina that results in a substantial reduction in premorbid activity levels. Many symptoms previously suggested in the Canadian criteria were placed into three categories: neurological; immune, gastrointestinal and genitourinary; and metabolic issues (Carruthers et al., 2011). As a result, CFS/ME can indeed encompass patients that exhibit very different profiles of illness according to the different definitions.

Although the above physiological disturbances have been associated with CFS/ME (Barnden et al., 2011, Brenu et al., 2012, Chen et al., 2008a, de Lange et al., 2005, Lorusso et al., 2009, Maes and Twisk, 2009, Meeus et al., 2008, Myhill et al., 2009, Tirelli et al., 1998, VanNess et al., 2007, Cho et al., 2006), further evidence is required to understand their exact role and how they may interact in the illness. Patients' symptoms may be global in nature, while others could experience predominate issues relating to a particular system (Carruthers et al., 2012c). Thus, CFS/ME may resemble other diseases and disorders, and screening can potentially be a long and expensive process. The range of symptoms can also vary in frequency and severity, and some patients may not show immediate, visible signs while others may be bedridden for prolonged periods, and unable to care for their

needs (Baker and Shaw, 2007, Carruthers et al., 2011). These factors make CFS/ME a particularly challenging illness to manage, and clinical guidelines vary significantly in their attention to certain aspects of the disorder.

8.2 Proposed Management Strategies

There are no definitive therapeutic drugs for CFS/ME therefore the major focus is on the development of effective management regimes. This chapter reviews and appraises several non-pharmacological interventions that have been proposed for CFS/ME patients. This includes management of sleep, proposed rehabilitation therapies, and models of specialised medical care for CFS/ME and the individual requirements of this patient group.

8.2.1 Sleep management

Unrefreshing sleep, despite sufficient or extended periods of rest is a common symptom of CFS/ME (Nisenbaum et al., 2003a, Unger et al., 2004) According to large population based studies, it is considered the most prevalent of the 8 accompanying symptoms in the Fukuda criteria, reported in up to 95% of cases (Jason et al., 1999). Many primary sleep disorders such as sleep apnoea and narcolepsy however, present similar symptoms associated with fatigue as CFS/ME. In a comparison between Fukuda defined CFS/ME patients with and without a primary sleep disorder, the two groups could not be distinguished based on symptoms alone (Le Bon et al., 2000). It is further suggested that primary sleep disorders may occur at the same frequency in CFS/ME as the general population (Jackson and Bruck, 2012, Reeves et al., 2006). Though the relationship between sleep abnormalities and CFS/ME remains unclear (Le Bon et al., 2000), it is important to differentiate primary sleep disorders from CFS/ME, as patients may respond well to available therapy.

In addition to identifying treatable sleep disorders, introducing better sleep practices or sleep hygiene is often recommended (Carruthers et al., 2012a, Craig and Kakumanu, 2002, Friedberg et al., 2012b). This includes

reducing stimuli and relaxing prior to bed time, establishing regular sleep and wake times, and creating a suitable sleep environment. Careful consideration however, needs to be made with managing severe patients and the further risks of declining physical and psychological health associated with being bedbound for prolonged periods of time (Baker and Shaw, 2007). This can includes monitoring for postural hypotension, deep venous thrombosis, osteoporosis, pressure sores, deconditioning, and depression due to social isolation. There are no specific studies however, on its direct benefit to reducing the impact of fatigue in CFS/ME, and is generally considered a good practice across many chronic illnesses and among healthy individuals.

8.2.2 Rehabilitative therapies

There are three main models of rehabilitative therapy that have been proposed for CFS/ME. These are cognitive behavioural therapy (CBT) with a clinical psychologist, graded exercise therapy (GET) with a physiotherapist, and adaptive pacing therapy (APT) assisted by occupational therapists. These have been the largest trialled therapies proposed for CFS/ME, and a particular focus of investigations originating in the United Kingdom known as the PACE trial (White et al., 2013, White et al., 2011). Their effectiveness remains a sizeable topic of debate (Baker and Shaw, 2007), with reports of improved outcomes from CBT and GET (Knoop et al., 2007, White et al., 2013), against arguments claiming harmful outcomes and in favour of models of specialised health care (Maes and Twisk, 2010, Twisk and Maes, 2008).

CBT has been the most largely proposed intervention for CFS/ME, and is based on a psychological theory that cognitive and behavioural responses such as fear of symptoms and avoidance of activity that may perpetuate physiological symptoms and disability (Sharpe et al., 1996, White et al., 2013, White et al., 2011, Surawy et al., 1995). The goal is to identify and address these behaviours in a behavioural experiment, which establish a baseline of activity, rest, and sleep patterns and then introduce

gradual increases in physical and mental activity. Additional problem solving activities for emotional or social issues are also introduced (White et al., 2007).

GET is based on a theory of deconditioning and exercise intolerance, in which patients experience a physical decline in function due to ongoing inactivity, or bed rest. It is believed such deconditioning is accompanied by increased perceptions of effort, contributing to further inactivity(Fulcher and White, 1998). The goal of therapy is to reverse this process and return patients to regular physical activities. A baseline of achievable exercise or physical activity is established, followed by incremental increases in duration of time, with target heart rate ranges. The aim was to achieve 30 minutes of light exercise five times a week. Once achieved, the intensity of the exercise was gradually increased usually from walking. Overall, both CBT and GET consider CFS/ME to be a reversible condition and that patients health can be restored through behavioural changes (White et al., 2007).

The outcomes of the PACE trial recommended that either CBT or GET were effective treatment for CFS/ME when added to specialist medical care, compared to APT or specialist medical care alone (White et al., 2011). Patients from this trial were recruited from six specialist clinics in the UK, and went through two phases of screening. This involved initial assessment by a medical doctor for alternative diagnoses and secondary screening of psychiatric disorders by a structured clinical interview according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) for exclusionary mood and anxiety disorders. The patient set of these trials were based on the Oxford criteria, which as discussed previously are solely based on a model of persistent fatigue. The reported improvements are also modest, with only 40-50% reporting reduced fatigue, compared to 20-30% that only received specialist care. An important consideration is that positive outcomes for CBT and GET reported in these trials are primarily based on subjective, self-reporting measures from a subset of patients that

do not necessarily exhibit problems with post-exertional malaise, or other accompanying symptoms. Further to this, reported outcomes of CBT and GET to date do not represent severe patients that are bedridden and unable to participate. This remains a fundamental flaw in the rationale for the use of CBT and GET.

In significant contrast to CBT and GET, APT regards CFS/ME has an underlying physiological process that is not reversible by changes in behaviour and that restoration to full pre-morbid health status and functioning is intermittent (Cairns and Hotopf, 2005). It is based on a theory that CFS/ME results in reduced or limited amounts of available energy, which is often referred to as a patient's energy budget or bank (Jason et al., 2008a, Pesek et al., 2000). The aim of therapy is to help patients adapt to these limitations and facilitate optimal use of energy through self-management techniques that balance periods of activity and rest, within ones limits (Baker and Shaw, 2007). Strategies include daily activity diaries, learning to identify early signs of over exertion, limiting demands and stress, regular planning of rest and relaxation, and alternating between different types of activities. Increases in activity are only encouraged if it did not exacerbate symptoms (White et al., 2007).

Post-exertional malaise is considered a cardinal feature of CFS/ME by many of the various definitions (Carruthers et al., 2003, Carruthers et al., 2011, Fukuda et al., 1994). The physiological response to exertion has been examined in Fukuda et al. defined CFS/ME patients through cardiopulmonary exercise stress testing. This measures cardiovascular, pulmonary, and metabolic functioning and no difference was detected on initial day of testing. However during the second day, CFS/ME patients have been shown to have a 22% drop in maximal oxygen update (VO_2 max) and a 27% drop in anaerobic threshold (VanNess et al., 2007). This consecutive testing has demonstrated a significant characteristic that may distinguish CFS/ME from other fatigue related conditions, including depression. However, in addition to these atypical physiological responses,

prolonged recovery periods have also been described (Carruthers et al., 2003, Carruthers et al., 2011, Fukuda et al., 1994). Thus, conducting such a test routinely to confirm and quantify the presence of post-exertional malaise could be inappropriate in the context of management, as it could contribute to substantial worsening of a patient's condition.

CBT and GET propose that patients should return to regular functioning by overcoming psychological barriers. These models however, are unable to be reconciled with growing immunological, neurological, and cardiovascular evidence that implicate that several pathomechanisms may be involved in this condition. GET for example, is a state that is most often associated with hospitalization of the elderly (Gillis and MacDonald, 2005), which does not reflect the complex nature of CFS/ME symptomatology. APT aims to reduce the frequency and severity of adverse responses by encouraging patients to address both too little and too much exertion in their daily activities and work within these limitations.

CBT and GET on the other hand, introduce physical benchmarks for patients to meet. A significant concern therefore, is the effects of these therapies on disability and quality of life in over time, given the chronic nature of CFS/ME. Some studies have suggested that initial gains diminish with time, where health-related quality of life did not improve with CBT and GET, compared to those receiving specialist medical care alone. Moreover, SF-36 scores for physical functioning and bodily pain were worse in those receiving these interventions (Núñez et al., 2011). A further study concluded that in terms of disability, neither intervention restored health, which was defined as the ability to return to full time work (Ross et al., 2004). This suggests that the outcomes of CBT and GET from randomised control setting are not necessarily appropriate for application in long-term clinic settings, with diverse patient sets.

Altogether, poor long-term outcomes of CBT and GET contradict its psychological basis that CFS/ME is a reversible condition. Thus returning a patient to pre-morbid health levels should not be the major goal of

managing CFS/ME. Further, these psychological models do not explain the growing evidence of decreased neurological, immunological, gastrointestinal, cardiovascular and autonomic responses in patients. Due to the disputed efficacy of CBT and GET, APT may offer a more realistic approach considering the various physiological impairments that have been reported in patients, as its primary goal is to reduce the overall functional impact of CFS/ME.

8.2.3 Specialised medical care

As there are significant limitations in therapeutic treatments available for CFS/ME, and diverse pathophysiologies have been associated with the disorder, an individualised, tailored approach may be a more rational approach to its management. CFS/ME patients most often present in a primary health care setting (Brown, 2014). General practitioners however, are often reluctant to make a conclusive diagnosis, and resources for its clinical management are not readily available or in general use (Johnston et al., 2014a). Hence, it is assumed that cases CFS/ME are largely underdiagnosed, and further misdiagnosed as other conditions (Griffith and Zarrouf, 2008, Reyes et al., 2003a, Solomon and Reeves, 2004). Though physiological abnormalities are increasingly being reported in CFS/ME (Carruthers et al., 2011), currently there is no specific test available so diagnosis relies largely on the exclusion of other conditions. This requires a thorough physical and mental health examination and detailed medical history, as well as a series of laboratory and further specialist tests if needed, to investigate any causes of symptoms.

There is no universal pharmaceutical intervention to alleviate CFS/ME hence traditional medications are administered to target specific symptoms and unique pathology of each patient. Across clinical guidelines, it is generally recommended that patients' start with reduced doses and to increase slowly as patients often report sensitivities (Baker and Shaw, 2007, Carruthers et al., 2012c, Friedberg et al., 2012b). CFS/ME are also known to trial a wide range of over the counter and complementary medicines to try

and manage their illness, however there are no specific trials, or evidence to demonstrate their effectiveness in CFS/ME (Kreijkamp-Kaspers et al., 2011). Patients for example, have been known to take a number of both prescription and over the counter medications known to cause sleep disturbances (Jones et al., 2003). Due to patient's sensitivities and such treatment seeking behaviour, it is important to include a review of patient's medications, as these could also potentially contribute to their symptoms. Pain management in particular, can often be complex and challenging in CFS/ME patients (Meeus and Nijs, 2007), which may require close monitoring for use of various analgesics.

The main principal is that patient's primary symptoms need to be distinguished from other illness, secondary aggravators or environmental stressors. Once any other conditions are identified and adequately treated, a diagnosis of CFS/ME can be considered if the patient's symptoms meet available symptom criteria (Carruthers et al., 2003, Carruthers et al., 2011, Fukuda et al., 1994). Establishing a formal diagnosis is important not only to proceed with management of the illness for the clinician, but for the patient's wellbeing, through acknowledgement of the illness and providing assurance of care. As there is substantial difference between the criteria, it is important to specify how the case of CFS/ME was defined. A crucial issue is that CFS/ME is a broad diagnosis that encompasses a wide range of patients that each present their own unique problems in addition to debilitating fatigue. Clearly defining patient sets could help identify candidates with a similar symptom profile (Jason et al., 2005), and subsequently those that may be more suitable for particular interventions.

One of the premises of the Canadian consensus and International consensus criteria is that it facilitates an investigation of symptoms according to different bodily systems, which can help reveal patients most disabling issues. Cardiovascular abnormalities in particular, have long been associated with CFS/ME and it is often recommended to perform a tilt table test to confirm the presence of orthostatic intolerance (Streeten et al., 2000).

Other conditions include neutrally mediated hypotension (NMH), and postural orthostatic tachycardia syndrome (POTS), which require referral to a cardiologist for overnight monitoring of cardiac output. These issues have been strongly associated with the functional impact of CFS/ME so its detection could lead to significant improvements in a patient's condition (Streeten et al., 2000, Karas et al., 2000).

In a systematic review of the clinical outcomes of CFS/ME, full recovery was rare however improved conditions have been reported across the literature. In general, less symptom severity and long term service leave are seen as a predictor of improved prognosis (Cairns and Hotopf, 2005). As a chronic illness, patients often exhibit periods of remission and relapse throughout the course of CFS/ME and shorter periods of illness were associated with longer periods of remission (Nisenbaum et al., 2003b). Thus, early recognition of signs and symptoms of CFS/ME may reduce the long term impact of CFS/ME.

As a multifaceted illness, patients may require help from a variety of specialists. In addition to identifying exclusionary conditions, it is common for CFS/ME patients to present with a range of comorbidities (Johnston et al., 2014a). As a general rule, any medical condition that has been treated and controlled or physical abnormality that is not sufficient for an alternative diagnosis can be considered as a co-morbid condition. Most commonly noted comorbidities are Fibromyalgia (Buchwald and Garrity, 1994a, Aaron et al., 2000, Jason et al., 2000), and Irritable Bowel Syndrome (Gomborone et al., 1995, Carruthers et al., 2012c, Friedberg et al., 2012b). As the physiological basis for this condition becomes better understood, many of the accompanying signs of anxiety and depression in patients could be explained by uncertainty about longer term recovery and long periods of physical disability that are endured by many.

Accordingly, the role of psychiatry in particular has also evolved from a primary diagnosis to one of support in management of this condition. Psychiatrists have at least two important obligations in ME/CFS

management. First, they should be aware of the evidence base in ME/CFS pathology and understand the complex immunological, neurological and cardiovascular presentations of these patients and ensure that referrals to them are not mislabelled a primary psychiatric disorder. Second, psychiatrists have a role in understanding the often disabling nature of the condition and the profound experience of unwellness that may accompany it. Patients may be bed-bound for extremely long periods and may even require assistance for personal care and hygiene. Social interaction is extremely impaired in some, which poses further risks of suicide through isolation and despair.

Overall, a key aspect in management is to establish strong communication and a therapeutic relationship that recognises key risk features of the patient's condition and promotes patient-centred management (Horton et al., 2010). A multidisciplinary approach in which specialists provide advice to a patient's general practitioner, together with the patients input for an individualised treatment program that best meets the patient's needs.

8.3 Conclusions

CFS/ME is a heterogeneous disorder and while sharing many common features, patients often present with unique pathological features. The review presented in this chapter is based on evidence on adult cases and should not be applied to paediatric cases, which have many further considerations. There remains no universal therapy available for CFS/ME, and outcomes of current trials indicate that there is a vital need for research to clearly define the characteristics of patients who would benefit from specific interventions. Given the diversity that is found among CFS/ME patients, an individualised tailored approach to treatment and care is recommended with attention to several characteristics specific to this patient group. Patients need to build a good awareness of their health and notify doctor of any change to treatment strategies as many over the counter medications could result in adverse effects. Further, patients should closely

monitor their own progress and appearance of new symptoms as these patients may be at particular risk of developing new primary diagnoses, but attributing symptoms as part of their experience with CFS/ME.

From a practitioner's perspective, expecting a patient to return to usual daily activities and full-time work should not be the immediate goal of management, as restoration to full pre-morbid health status and functioning is rare and patients can be at risk of severe relapses from overexertion. Patients are at risk of developing secondary psychiatric issues as a chronic illness, however primary psychiatric theories surrounding CFS/ME are in significant contrast to the body of evidence on immunological, neurological and cardiovascular presentations of patients. By defining patients according to their most severe perturbations, targeted treatment and pharmacotherapy can be introduced that may result in a positive response. Hence, the potential of individualized management in CFS/ME should receive greater attention and lead further investigations.

Chapter 9: Conclusions

9.1 Summary of findings

The main findings of this thesis are summarised as follows:

Chapter 2: Review of clinical guidelines published for CFS/ME identified significant differences in required symptoms, and in their suggestion of comorbid disorders. There is also no specification on how symptoms should be measured, altogether contributing to the significant variability found in CFS/ME studies.

Chapter 3: Systematic review of prevalence studies on CFS/ME demonstrated the Fukuda definition as the most common. The International definition was not adopted. Furthermore, paediatric studies were reliant on Fukuda definition for CFS/ME, which was primarily designed for adult cases, highlighting the importance of paediatric considerations.

Chapter 4: In the absence of prevalence estimate for CFS/ME in Australia, the expected prevalence of CFS/ME was estimated 3.28% (95% CI: 2.24–4.33) for self-reported cases and 0.76% (95% CI: 0.23–1.29) for clinically assessed cases.

Chapter 5: A pilot study suggested that International defined cases represent a distinct subgroup found within Fukuda defined patient sets, with greater functional impairment according to SF-36 scales for physical functioning, physical role, bodily pain and social functioning, and all WHO DAS 2.0 scales.

Chapter 6: In a sample of 515 patients reporting a diagnosis of CFS/ME, 24.7% fulfilled the Fukuda definition, and a further 31.8% met the International definition. However, a significant proportion of cases was considered chronic fatigue only or had an exclusionary condition. Within Fukuda and International defined cases, secondary insomnia, irritable

bowel syndrome, sinusitis, and orthostatic intolerance were highly common (>20%).

Chapter 7: A total of 535 patients diagnosed with CFS/ME by a primary care physician were identified. The mean age of all patients was 46.41 years (SD 11.97) and majority female (78.61%), The most common triggers included cold or flu, gastrointestinal illness, and periods of undue stress. Of 54 symptoms surveyed, fatigue, cognitive and short term memory symptoms, headaches, muscle and joint pain, unrefreshed sleep, sensory disturbances, muscle weakness, and intolerance to extremes of temperature were the most commonly occurring symptoms. Significant differences in symptom occurrence between Fukuda and International defined cases were also identified.

Chapter 8: Outcomes of current trials indicate that there is a vital need for research to clearly define the characteristics of patients who would benefit from specific interventions.

Altogether, this thesis has identified a significant cohort of Australians that fulfil CFS/ME definitions that have substantially low rates of full-time employment and are in high need of improved health care support. Upper respiratory infections and gastrointestinal illness, as well as stressful life events were common events prior to the onset of their illness. Those meeting the International definition further appear to represent a distinct clinical group with distinguishing symptoms and significantly worse functional status.

9.2 Limitations

In addition to specific limitations discussed within each publication, comprehensive identification of CFS/ME cases in Australia was not considered feasible at this stage. Rather, the results of this review revealed that efforts must be made towards improving its recognition and diagnosis by using the clinical definitions that are available. The primary aim was to establish a baseline for identifying cases of CFS/ME by developing a

database eligible for those who report a diagnosis of CFS/ME by their primary care practitioner. Thus, this is considered the first stage of screening for cases of CFS/ME in the Australian population.

9.3 Recommendations and future directions:

A significant outcome of this study is that it has established a cohort that may be available for longitudinal follow-up vital for monitoring the prognosis of CFS/ME. It further provides an invaluable patient source for the advancement of clinical and biological research on CFS/ME. The results presented in this thesis serve as a pilot study for further expansion as a nationwide surveillance system for CFS/ME if increased engagement is made with Australian general practitioner networks. As this thesis is based on self-reported medical history by patients, the next stage of screening should be to further validate medical records and introduce examination of physical and mental health by a physician. Future directions aim to collate the following data:

1. Population health data: geographical distribution, age, sex, ethnicity, education, occupation, health service use
2. Clinical data: medical history including comorbidities, medications, severity, and impairment to physical and mental health, BMI, and vitals such as heart rate and blood pressure
3. Biological data: results from investigations supported by other research grants including immunological and genomic profiling, and general pathology tests

The development of a robust and diverse repository for CFS/ME will identify key attributes of the illness and significant predictors and risk factors. This is expected to have a substantial impact across several areas:

Public health policy: The findings will help guide decision makers in health service provision on how to adequately care and support patients with CFS/ME. This may lead to improved services for patients with CFS/ME reducing the health and economic burden of CFS/ME.

Clinical practice: Currently, diagnosis of CFS/ME is an exhaustive process based on exclusion of other disease and early detection is central to improving management of this illness. Australian guidelines may consider the sociodemographic and illness characteristics reported in this study as common indicators of CFS/ME.

Medical research: The systematic approach adopted by this project and future development of an improved case definition will improve the quality of CFS/ME research and detection of specific biological markers. This may pave the way for more appropriate and better targeted treatments.

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Appendix 1: Participant consent form

Protocol number: MSC/01/13/HREC

What does participation involve?

Participation involves an online questionnaire that requires at least an hour. You may require more time, but you are able to save your progress and resume when suitable. If you would prefer a hard copy of this questionnaire in the mail please contact: smantha.johnston3@griffithuni.edu.au.
It contains sections according to:
1. Consent
2. Demographics
3. History of illness
4. Your daily activities

At times, you may encounter questions that may not seem directly related to your condition. Embedded are two questionnaires known as the Short Form Health Survey and World Health Organisation Disability Adjustment Schedule. These are generic instruments designed to measure quality of life and disability in chronic conditions and we aim to represent CFS/ME on these scales.

What happens to my information?

The contact details you provide are strictly for administration and verification purposes only. In accordance with the Queensland Information Standard 42, Griffith University is committed to protecting your privacy. The conduct of this research involves the collection, access and/or use of your identified personal information. The information collected however, is confidential and will not be disclosed to third parties without your consent, except to meet government, legal or other regulatory authority requirements. A de-identified copy of this data may be used for other research purposes. However, your anonymity will at all times be safeguarded. For further information consult the University's Privacy Plan at http://www.griffith.edu.au/privacy-plan or telephone (07) 3735 4375.

Participation is voluntary

Participation in the registry is voluntary, and you are free to withdraw at anytime with no comment or penalty to Griffith University.

Further questions?

If you should require further information about the study, please contact:
National Centre for Neuroimmunology and Emerging Diseases
MHIQ, Griffith University, Southport QLD, 4215
Phone: 07 5678 9283 Email: ncned@griffith.edu.au

Ethical conduct

Griffith University conducts research in accordance with the *National Statement on Ethical Conduct in Human Research* (2007). If you have any concerns or complaints about the ethical conduct of the research project please contact the Manager, Research ethics by phone (07) 3735 4375 or email research-ethics@griffith.edu.au.

Informed consent

Protocol number: MSC/01/13/HREC

Chief investigator: Professor Sonya Marshall-Gradisnik

Co-investigator: Professor Donald Staines

Student researcher: Ms Samantha Johnston

Centre: Griffith University National Centre for Neuroimmunology and Emerging Diseases

- I understand that I participation involves an online questionnaire
- I have had any questions answered to my satisfaction
- I understand the risks involved
- I understand that there will be no direct benefit to me from my participation in this research
- I understand that my participation in this research is voluntary
- I understand that I am free to withdraw at any time, without comment or penalty
- I understand that if I have any additional questions I can contact the research team
- I understand that I can contact the Manager, Research Ethics, at Griffith University Human Research Ethics Committee if I have any concerns about the ethical conduct of the project
- I agree to participate in the project.

Name: …… (please print)

Signature: …….. Date: ……..

Mailing address: ……

Email: ……

Phone: ……..……..

Appendix 2: Participant questionnaire

Protocol number: MSC/01/13/HREC

SECTION A: BACKGROUND

1. Date of birth (dd/mm/yy) _____ Age (years) ___

2. Your Sex □ Female □ Male

3. Your height _____ cm weight _____ kg

4. Your **highest** level of education obtained?

   □ Primary school
   □ Secondary (high) school
   □ Professional training (not university)
   □ Undergraduate
   □ Post graduate/Doctoral

5. Your **current** employment status?

   □ Employed full time
   □ Employed part time/casual
   □ On disability pension
   □ Retired
   □ Unemployed
   □ Studying full time
   □ Studying part time

6. Please indicate whether you are volunteering as any of the following?

   □ CFS/ME participant
   □ Multiple Sclerosis participant
   □ Rheumatoid Arthritis participant
   □ MDS participant
   □ A "healthy" volunteer
   □ Other (please specify) _____

7. Do you have a family member/relative that has or has had ME/CFS?

   □ Yes □ No If yes, how are you related? (e.g. brother)_____

8. Have you received a diagnosis of Myalgic Encephalomyelitis or Chronic Fatigue Syndrome by a GP? □ Yes □ No

9. Are you currently diagnosed with any other chronic illness/disease? □ Yes □ No

   If yes, please specify _____

10. Are you currently on any prescription medication? □ Yes □ No

    If yes, what prescription/s are you taking? _____

    _____

11. Are you currently a smoker? □ Yes □ No

SECTION B: SYMPTOMS

12. Have you experienced ongoing problems with severe fatigue ie. fatigue interferes with daily activity/responsibilities?
    □ Yes □ No (please continue to Section C)

13. How old were you when the fatigue began to interfere? ___ years

14. Have you experienced periods of recovery and relapse from this fatigue? □ Yes □ No

15. If yes, how long ago was your last relapse? ____ months ago

16. Do you notice any of the following physical activity or mental exertion?
    - □ My fatigue gets worse
    - □ Other symptoms get worse
    - □ My fatigue usually occurs immediately
    - □ My fatigue is usually delayed (I "pay for it" later)
    - □ My recovery period is unusually long
    - □ I have low stamina (I substantially reduce what is required of me)

To the best of your knowledge, please select whether any of the following symptoms have **persisted or recurred during the past 6 months or more**? Please select those symptoms that only appeared with or after the fatigue.

17. Any of the following cognitive symptoms?

    - □ Slowed thought
    - □ Impaired concentration
    - □ Confusion
    - □ Disorientation
    - □ Cognitive overload
    - □ Difficulty making decisions
    - □ Slowed speech
    - □ Dyslexia
    - □ Short term memory loss

18. Do you experience any of the following pain symptoms?

- Headache or migraine
- Muscle pain
- Joint pain (without redness or swelling)
- Abdomen pain
- Chest pain

19. Do you experience any of the following sleep disturbances?

- Insomnia
- Prolonged sleep including naps
- Sleeping most of day and awake at night
- Frequent awakenings
- Awaking earlier than before illness started
- Vivid dreams/nightmares
- Unrefreshed sleep

20. Do you have any of the following sensory, perceptual or motor disturbances?

- Inability to focus vision
- Sensitivity to light, noise, vibration, odour, taste and touch
- Impaired depth perception
- Muscle weakness
- Twitching
- Poor coordination
- Feeling unsteady on feet

21. Do you experience any of the following immune, gastrointestinal, urinary problems?

- Tender lymph nodes
- Sore throat
- Other flu-like symptoms
- Viral infections with prolonged recovery periods
- Nausea, abdominal pain, bloating or irritable bowel syndrome
- Urinary urgency, frequency, or the need to wake up at night to urinate
- Sensitivities to food, medications, odours or chemicals

22. Do you experience any of the following symptoms?

- Heart palpitations
- Light-headedness or dizziness
- Respiratory issues such as air hunger or difficulty breathing
- Abnormal body temperature
- Sweating episodes
- Recurrent feelings of feverishness
- Cold hands and feet
- Intolerance of extreme temperature

23. Have you been diagnosed with any of the following conditions?

- Orthostatic intolerance
- Neurally mediated hypotension
- Postural orthostatic tachycardia syndrome
- Ataxia

SECTION D: SF-36 SCALE

The following questions regard your general health **during the past month.**

24. In general, would you say your health is:

- ☐ Excellent
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor

25. Compared to one year ago, how would you rate your health in general now?

- ☐ Much better now than a year ago
- ☐ Somewhat better now than a year ago
- ☐ About the same as one year ago
- ☐ Somewhat worse now than one year ago
- ☐ Much worse now than one year ago

26. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.	☐	☐	☐
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?	☐	☐	☐
c. Lifting or carrying groceries.	☐	☐	☐
d. Climbing several flights of stairs.	☐	☐	☐
e. Climbing one flight of stairs.	☐	☐	☐
f. Bending, kneeling or stooping.	☐	☐	☐
g. Walking more than one kilometre.	☐	☐	☐
h. Walking several blocks	☐	☐	☐
i. Walking one block	☐	☐	☐
j. Bathing or dressing yourself	☐	☐	☐

27. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

a. Cut down the amount of time you spent on work or other activities?

□ Yes □ No

b. Accomplished less than you would like? □ Yes □ No

c. Were limited in the kind of work or other activities? □ Yes □ No

d. Had difficulty performing the work or other activities □ Yes □ No

28. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

a. Cut down the amount of time you spent on work or other activities?

□ Yes □ No

b. Accomplished less than you would like? □ Yes □ No

c. Didn't do work or other activities as carefully as usual □ Yes □ No

29. During the past 4 weeks…

	Not at all	Slightly	Moderately	Quite a bit	Extremely
a. To what extent has your physical health, or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?	□	□	□	□	□
b. How much bodily pain have you had?	□	□	□	□	□
c. How much did pain interfere with your normal work (including both work outside the home and housework)?	□	□	□	□	□

30. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4weeks…

	All the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of pep?	□	□	□	□	□	□
b. Have you been a very nervous person?	□	□	□	□	□	□
c. Have you felt so down in the dumps nothing could cheer you up?	□	□	□	□	□	□
d. Have you felt calm and peaceful?	□	□	□	□	□	□
e. Did you have a lot of energy?	□	□	□	□	□	□
f. Have you felt downhearted and blue?	□	□	□	□	□	□
g. Did you feel worn out?	□	□	□	□	□	□
h. Have you been a happy person?	□	□	□	□	□	□
i. Did you feel tired?	□	□	□	□	□	□
j. How much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	□	□	□	□	□	□

31. How TRUE or FALSE is each of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	□	□	□	□	□
b. I am as healthy as anybody I know	□	□	□	□	□
c. I expect my health to get worse	□	□	□	□	□
d. My health is excellent	□	□	□	□	□

SECTION E: WHO DAS 2.0

Think back over the month and answer these questions, thinking about how much difficulty you had doing the following activities. For each question, please indicate only one response.

In the past 30 days, how much difficulty did you have had in:

	None	Mild	Moderate	Severe	Extreme or cannot do
27a. Concentrating on doing something for ten minutes?	☐	☐	☐	☐	☐
b. Remembering to do important things?	☐	☐	☐	☐	☐
c. Analysing and finding solutions to problems in day to day life?	☐	☐	☐	☐	☐
d. Learning a new task, for example, learning how to get to a new place?	☐	☐	☐	☐	☐
e. Generally understanding what people say?	☐	☐	☐	☐	☐
f. Starting and maintaining a conversation	☐	☐	☐	☐	☐
28a. Standing for long periods such as 30 minutes?	☐	☐	☐	☐	☐
b. Standing up from sitting down?	☐	☐	☐	☐	☐
c. Moving around inside your home?	☐	☐	☐	☐	☐
d. Getting out of your home?	☐	☐	☐	☐	☐
e. Walking a long distance such as a kilometre (or equivalent)?	☐	☐	☐	☐	☐
29a. Washing your whole body	☐	☐	☐	☐	☐
b. Getting dressed?	☐	☐	☐	☐	☐
c. Eating?	☐	☐	☐	☐	☐
d. Staying by yourself for a few days?	☐	☐	☐	☐	☐
30a. Dealing with people you do not know	☐	☐	☐	☐	☐

	None	Mild	Moderate	Severe	Extreme or cannot do
b. Maintaining a friendship	☐	☐	☐	☐	☐
c. Getting along with people who are close to you?	☐	☐	☐	☐	☐
d. Making new friends	☐	☐	☐	☐	☐
e. Sexual activities	☐	☐	☐	☐	☐
31a. Taking care of your household responsibilities	☐	☐	☐	☐	☐
b. Doing most important household tasks well?	☐	☐	☐	☐	☐
c. Getting all the household work done that you needed to do?	☐	☐	☐	☐	☐
d. Getting your household work done as quickly as needed?	☐	☐	☐	☐	☐
e. Your day-to-day work/school?	☐	☐	☐	☐	☐
f. Doing your most important work/school tasks well?	☐	☐	☐	☐	☐
g. Getting all the work done that you need to do?	☐	☐	☐	☐	☐
h. Getting your work done as quickly as needed?	☐	☐	☐	☐	☐
32a. How much of a problem did you have in joining in community activities (for example, festivities, religious or other activities) in the same way as anyone else can?	☐	☐	☐	☐	☐
b. How much of a problem did you have because of barriers or hindrances in the world around you?	☐	☐	☐	☐	☐

	None	Mild	Moderate	Severe	Extreme or cannot do
c. How much of a problem did you have living with dignity because of the attitudes and actions of others?	☐	☐	☐	☐	☐
d. How much time did you spend on your health condition, or its consequences?	☐	☐	☐	☐	☐
e. How much have you been emotionally affected by your health condition?	☐	☐	☐	☐	☐
f. How much has your health been a drain on the financial resources of you or your family?	☐	☐	☐	☐	☐
g. How much of a problem did your family have because of your health problems?	☐	☐	☐	☐	☐
h. How much of a problem did you have in doing things by yourself for relaxation or pleasure?	☐	☐	☐	☐	☐
33. In the past 30 days, how many days were difficulties present	Number of days _____				
34. In the past 30 days, for how many days were you **totally unable** to carry out your usual activities or work because of any health condition?	Number of days _____				
35. In the past 30 days, how many days did you reduce your usual activities or work because of any health condition	Number of days _____				

This concludes the survey, thank you for your participation

Appendix 3: CFS/ME definitions

Summary of definitions for CFS/ME

Definition	Fukuda criteria	Canadian consensus criteria (CCC)	International consensus criteria (ICC)
Fatigue	• At least 6 months • New or definite onset • Not due to ongoing exertion • Not alleviated by rest • Substantial reduction in daily activities • Not due to other medical conditions associated with fatigue	• At least 6 months • New onset • Not due to ongoing exertion • Substantial reduction in daily activities • Not due to other medical conditions associated with fatigue	• PENE[ii] (All 5 required) • Marked, rapid fatigue in response to minimal physical and/or mental activity • Fatigue can be immediate or delayed • Symptoms significantly worsen after minimal physical and/or mental activity • Prolonged recovery period • Substantial reduction to daily activities
Additional[i]	At least 4 of the following: • Post-exertional malaise lasting more than 24 hours • Unrefreshing sleep • Short term memory and/or concentration difficulties • Muscle pain • Joint pain without swelling/redness • Headaches of new type • Tender lymph nodes • Sore throat	• Post-exertional malaise and/or fatigue • Sleep dysfunction • Pain • Neurological/cognitive (Two or more symptoms) At least one symptom from two of the following subcategories Autonomic • Orthostatic intolerance • Irritable bowel syndrome • Urinary frequency and bladder dysfunction • Palpitations	Neurological (At least one symptom from all four subcategories): • Cognitive difficulties • Pain • Sleep disturbances • Sensory, perceptual and motor disturbances Immune, Gastro-intestinal & Genitourinary (At least one symptom from three subcategories): • Flu-like symptoms • Susceptibility to viral

	• Exertional dyspnoea Neuroendocrine manifestations • Loss of thermostatic stability • Subnormal body temperature and marked diurnal fluctuation • Sweating episodes • Feverishness and cold extremities • Intolerance of extremes of temperature • Marked weight change Immune • Tender lymph nodes • Sore throat • Flu-like symptoms • General malaise • Sensitivities to food, medications and/or chemicals	infections • Gastro-intestinal tract disturbances • Genitourinary disturbances • Sensitivities to food, medications, odours and/or chemicals Energy production/transportation impairments (At least one symptom from any subcategory): • Cardiovascular • Respiratory • Loss of thermostatic stability • Intolerance of extremes of temperature

[ii]Symptoms accompanying fatigue should not have preceded onset of fatigue and be persistent or recurring

[iii]Fatigue described as post-exertional neuroimmune exhaustion (PENE)

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