Concept Paper

Development of Epidemiological Research Guidelines for Myalgic Encephalomyelitis / Chronic Fatigue Syndrome in Canada

Enkhzaya Chuluunbaatar-Lussier , Travis Boulter , Sunita Vohra , Rahul Shetty , Sharon Houle , Riina Bray , Kathleen Kerr , Luis Nacul *

Posted Date: 23 May 2024

doi: 10.20944/preprints202405.1571.v1

Keywords: myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS), research guidelines, standardization of data collection, Canadian

Concept Paper

Development of Epidemiological Research Guidelines for Myalgic Encephalomyelitis / Chronic Fatigue Syndrome in Canada

Enkhzaya Chuluunbaatar-Lussier [1,2,†], Travis Boulter [1,3,†], Sunita Vohra [4], Rahul Shetty [5], Sharon Houle [6], Riina Bray [7], Kathleen Kerr [7,*], Luis Nacul [1,2,3,8,9,*]

1 Women's Health Research Institute, BC Women's Hospital, Vancouver, British Columbia, Canada
2 Department of Family Practice, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada
3 Provincial Health Service Authority, Vancouver, British Columbia, Canada
4 Departments of Pediatrics and Psychiatry, Faculty of Medicine & Dentistry, University of Alberta, Alberta, Canada
5 Institute for Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada
6 Integrated Chronic Care Service Nova Scotia Health Authority, Nova Scotia, Canada
7 Department of Family and Community Medicine, University of Toronto, Toronto, Canada
8 Complex Chronic Diseases Program, BC Women's Hospital, Vancouver, British Columbia, Canada
9 Department of Clinical Research, London School of Hygiene and Tropical Medicine, UK
† Joint first or last authors.
* Correspondence: luis.nacul@cw.bc.ca

Abstract: The Interdisciplinary Canadian Collaborative ME Research Network (ICanCME), established in 2019, aims to foster research in Canada and contribute to finding the causes and possible treatments for myalgic encephalomyelitis /chronic fatigue syndrome (ME/CFS), thereby reducing the impact of ME/CFS on the health of Canadians. The main objectives of this paper are to suggest standards for ME/CFS research for the collection of data from participants (Recommended Data Elements) and to consider other factors, such as design, language, cultural issues, equity, and diversity. Consensus of the relevant contents of this research guideline was reached during the ICanCME working group meetings and were based on existing guidelines. Members of the working group contributed to guideline development based on their respective expertise. The proposed research guidelines could improve research quality and advance knowledge in the field of ME/CFS, and ultimately benefit ME/CFS patients.

Keywords: myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS); research guidelines; standardization of data collection; Canadian

Introduction

ME/CFS is a complex, chronic, and multi-system disease characterized by disabling fatigue that lasts more than 6 months, characterized by intolerance to efforts, post-exertional malaise, and unrefreshing sleep [1]. Other symptoms include orthostatic intolerance, cognitive difficulties, and pain, including headaches, muscle and joint pain [2]. The etiology of ME/CFS is not fully understood, however determination is multi-causal, like in other chronic diseases. Viral infection has been shown to be the strongest risk factor for disease incidence [3,4]. ME/CFS affects all age, ethnicity, and socio-economic groups, however, at least two thirds of the affected people are women [5].

The prevalence of ME/CFS varies with estimates affected by factors such as how research methods, case ascertainment and definitions are applied, setting (e.g. primary care or population based) and geographical area. For example, data for 3 regions of England, based on primary care data yielded minimal prevalence rates of 0.1% – 0.2% , with a corresponding incidence rate of 0.015 new cases per 1000-year [6]. In Canada, there are no population based prevalence rates available, but

 doi:10.20944/preprints202405.1571.v1

survey data from 2017 suggested the prevalence of self-reported physician diagnosed ME/CFS as around 1.5%, or 561,500 people [7]. According to the 2015-2016 Canadian Health Survey on Seniors, 3.0% of women and 1.5% of men aged over 65 years old reported a diagnosis of ME/CFS, [7].

While the first epidemiological study on ME/CFS was conducted in 1930s [8], early research on ME/CFS was limited, but has been increasing since the 1990s, and the number of articles published in PubMed, as filtered through the term "myalgic encephalomyelitis chronic fatigue syndrome and/or ME/CFS" has increased considerably, 380 in 2010, 499 in 2020, then since 2021 with over 600 articles published yearly (https://pubmed.ncbi.nlm.nih.gov/?term=myalgic+encephalomyelitis+chronic+fatigue+syndrome&filter=simsearch3.fft&filter=dates.2010-2022) [9].

While the amount of research on ME/CFS has been increasing in the last decade, there are still gaps in our basic understanding of the disease. ME/CFS presents unique challenges to researchers and patients. For example, First, while ME/CFS carries a high disease burden, there are no specific biomarkers for diagnostic confirmation, no clinically approved treatments, or permanent cure [10]. Moreover, symptoms of ME/CFS largely affect activities of daily living and health-related quality of life that cause considerable burden to patients and their family members [11]. The economic burden of ME/CFS is high not only due to its chronic nature and long-term debilitating symptoms, but also has increased due to the recent significant incidence and prevalence increases resulting from the COVID-19 pandemic. The estimated 5-9 million new cases of post-acute sequalae of COVID (i.e. Long-COVID) in the United States, many of whom meet the diagnostic criteria for ME/CFS) has been suggested, in a preliminary estimate, to increase annual medical costs and lost income, with total annual economic impact of COVID-19 estimated in $140 billion to $600 billion in 2022 in that country [12].

The complexities of ME/CFS and the methodological challenges associated with its study indicate the need for a comprehensive, systematic, and integrated approach to the assessment, differential diagnosis, and research of individuals with ME/CFS. Approaches to case recognition and treatment have been reviewed recently, including through guidelines such as the NICE guidelines for the UK [13] and those from the European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (EUROMENE), which included clinicians and researchers from over 20 European countries (as of 2018) [14]. However, there is a need for recommendations on the conduct and reporting of epidemiological and clinical studies of people with ME/CFS in Canada. This could lead to better standardization and quality of research across the country.

The Interdisciplinary Canadian Collaborative ME Research Network (ICanCME) is a multidisciplinary network. ICanCME aims to create a patient-centered network building research capacity from discovery to implementation [15]. The ultimate goal of ICanCME is to find the cause(s) and possible treatments for myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS), thereby reducing the impact of ME/CFS on the health of Canadians. The network established working groups to support its strategic pillars and research priorities. Each working group included researchers, clinicians, health professionals, patient partners and/or caregivers, and trainees. Working Group Five: Epidemiology, Data Management and Study Design (WG5) had the purpose. The outcomes of WG5 to date are the development of two recommendations: Recommended Data Elements and current paper, and Recommendations on Epidemiological Research on ME/CFS, which would benefit researchers, clinicians and patients in terms of standardizing diagnostic criteria and efficient research in ME/CFS.

Therefore, in this research guideline, we propose a conceptual framework for epidemiological research focusing on ME/CFS in Canada, including the Recommended Data Elements (RDEs) for ME/CFS studies (Table 1).

 doi:10.20944/preprints202405.1571.v1

Table 1. Recommended Data Elements for ME/CFS Research. ICanCME Network.

Domain	Recommended Data Elements in ME/CFS	Supplementary Tools & Tests
Diagnosis of ME	Use one or more of the following: ▪ IOM (2015)[1] ▪ Canadian Consensus Criteria (2003)[2] ▪ NICE Criteria (2021)[3]	▪ Fibromyalgia (FM) criteria (2016) for those with widespread pain
Symptoms and Clinical Assessments	▪ Symptoms Assessment Questionnaire (SAQ)	▪ De Paul Questionnaire DPQ (Full)
Disease Severity and Quality of Life	▪ RAND SF-36 (V.1) ▪ Phenotyping Questionnaire Short Form (PQ-Symp 12) or DPQ-short form ▪ Hours of Upright Activity (Good Day, Bad Day Questionnaire)	▪ UKMEB PPQ (full) ▪ Fibromyalgia Impact Questionnaire (FIQ) for those with FM
Fatigue and PEM	▪ Fatigue Visual Analogue Scale ▪ Fatigue severity scale ▪ DePaul Symptom Questionnaire PEM section (DSQ)	▪ Multidimensional Fatigue Index (MFI)20 ▪ 4-questions on fatigue and energy from RAND SF-36 (Question numbers: 23, 27, 29, 31)
Pain	▪ Pain Visual Analog Scale (from MPQ-SF21)** ▪ Pain score from RAND SF-36	▪ Brief Pain Inventory SF (if studying pain specifically) ▪ Short Form McGill Pain Questionnaire21 (for general use and FM)
Sleep and autonomic symptoms	▪ Pittsburgh Sleep Quality Index ▪ Sleep Quality Visual Analogue Scale ▪ Compass-31	▪ Autonomic questions from PPQ (7 Q's) and PPQ sleep questions (3 Q's) ▪ Orthostatic Intolerance Questionnaire (OIQ)
Psychological Morbidity and Cognition	▪ GAD-2** (move to GAD-7 if positive) ▪ PHQ-2** (move to PHQ-9 if positive) ▪ Neuro-QoL Cognitive short form	▪ Mental Summary Score from SF-36 ▪ Cognitive failures questionnaire ▪ Neuro-QoL Depression Short Form ▪ Neuro-QoL Anxiety Short Form
Physical Exam Measures	▪ NASA 10 minute lean test OR 10 minute passive standing test ▪ Weight and Height ▪ Hand-grip strength ▪ Beighton Score ▪ Serum CK	▪ Romberg test ▪ Tandem gait ▪ Average number of steps per day (accelerometer) ▪ Heart rate variability

 doi:10.20944/preprints202405.1571.v1

Demographics	▪ CCDP** Demographics form v2.0	▪ Stats Canada Demographics
Laboratory tests	*Usage Guidelines:* It is recommended to look at blood tests that are common to the three diagnostic guidelines listed above and report on these (at minimum). ME/CFS criteria blood tests common to all Clinical Consensus Criteria: ▪ HBAIC or Fasting Glucose ▪ CBC ▪ CPK ▪ ESR or CRP ▪ U + Electrolytes (Na, K Ca, P04) ▪ GFR/Creatinine ▪ ALT, BiL, ALP, Albumin ▪ B12 ▪ TSH ▪ Ferritin ▪ Celiac screening ▪ Urinalysis for protein, blood, & glucose	Note: These tests are used in support the identification of alternative diagnoses or co-morbidities. Some tests are recommended routinely, other tests (not shown) may be recommended according to clinical needs

**SF stands for Short Form; MPQ-SF – McGill Pain Questionnaire Short Form; GAD – General Anxiety Disorder; PHQ – Patient Health Questionnaire, CCDP – Complex Chronic Diseases Program at British Columbia Women's Hospital, Canada

Source:

1. Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; Board on the Health of Select Populations; Institute of Medicine. *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness*. Washington (DC): National Academies Press (US); February 10, 2015
2. Carruthers BM, et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Journal Of Chronic Fatigue Syndrome. 2003;11(1)
3. *Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management*. London: National Institute for Health and Care Excellence (NICE); October 29, 2021

The goals of this research guideline (in line with the RDEs goals) are to:

- Disseminate standards for collection of data from participants enrolled in ME/CFS studies that is, a set of recommended data elements (RDEs).
- Consider language and cultural issues, as well as equity, diversity and concerns on inclusion criteria such as design and methods.
- Improve data quality and research on ME/CFS for benefiting patients and practitioners.

 doi:10.20944/preprints202405.1571.v1

Development Process

This project was first proposed by the members of the Working Group 5 ICanCME network in 2020 (co-chairs: Nacul and Kerr). We invited group members and patients with ME/CFS to join in the development of the research guidelines, where the participants would contribute specific knowledge and viewpoints according to their specialties, areas of interest, and experience.

We did not systematically review the evidence related to case definitions or diagnostic criteria because this has been done in other studies [1,16]. Nevertheless, we did consult similar epidemiological research guidelines published by others, such as from the EUROMENE network [17]. In this guideline, we have incorporated the standardization of data elements and instruments from the RDEs developed by the ICanCME sub-group. This was a comprehensive process in which researchers, physicians and other health professionals, patients and patient carers discussed existing practices in Canada and internationally and referred to existing guidelines for data elements for ME/CFS such as the NINDS Common Data Elements of 2018 [18] and those recommended for epidemiological studies from EUROMENE [19].

Data Collection Standardization

In Canada, clinicians and researchers generally use Canadian Consensus Criteria (2003) [20], and Institute of Medicine (2015) [21] criteria for diagnosis for ME/CFS, however, variation in case definition and guidelines have been problematic, as have the way different researchers apply chosen criteria [22] . Misclassification in selecting individuals for research has been an important source of "bias" in many studies [23]. Use of case definitions with poor specificity and non-random recruitment of participants are examples of issues that are commonly encountered. Moreover, the collected data from individual researchers often have inadequate definitions and use different instruments. This often presents a challenge to compare study results, sharing their data to combine, or harmonization for large-scale analyses, which could save time and costs.

As recommended in the RDEs, four main areas of information can be gathered: a) core general information on participants, b) provisional diagnosis, c) clinical assessment, and d) symptom profiling (Figure 1). While the RDEs represent data elements recommended for all quantitative studies in ME/CFS, further relevant data can be collected by individual researchers, based on the research questions, study design, and area of interest,

 doi:10.20944/preprints202405.1571.v1

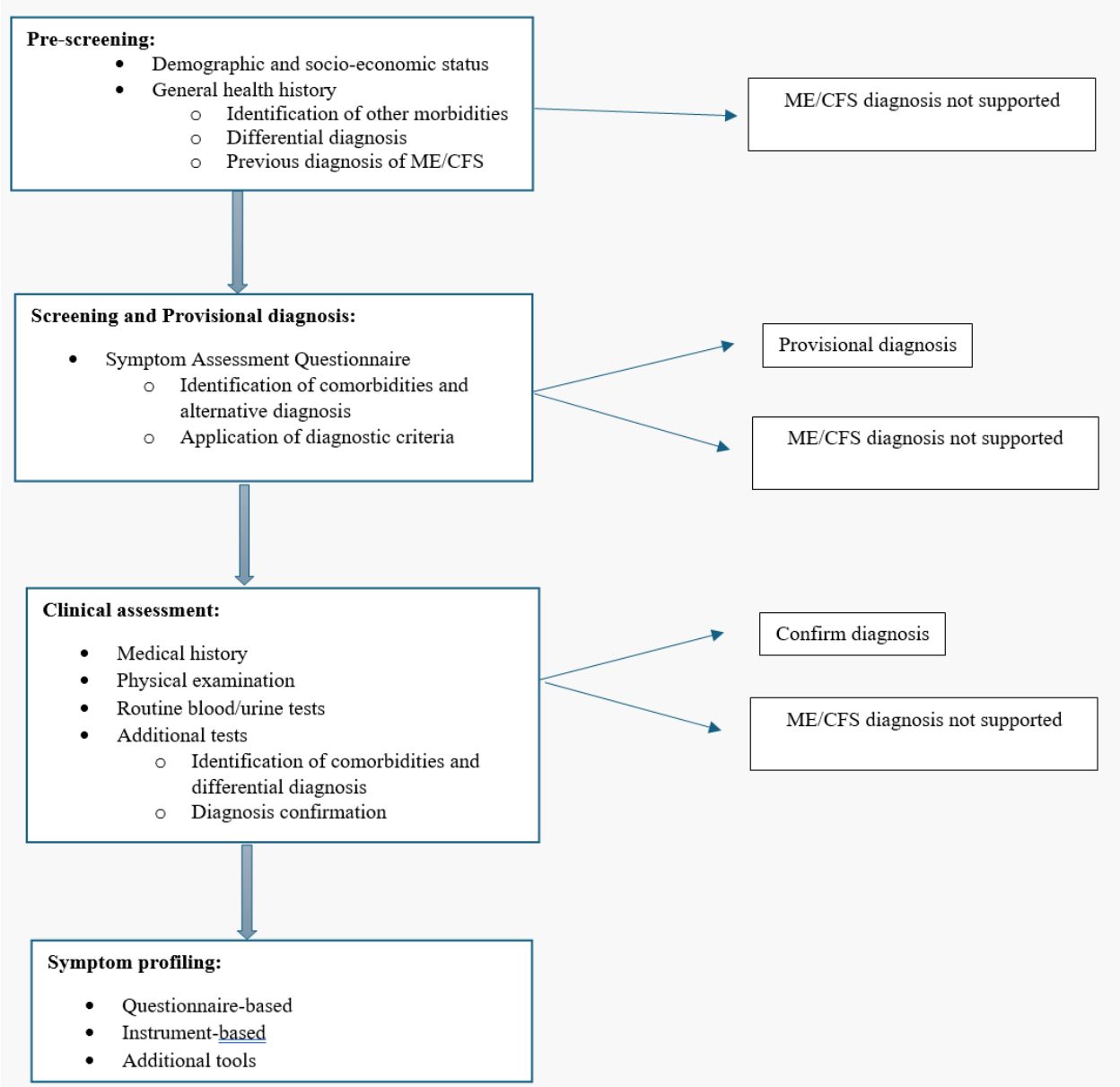

Figure 1. ME/CFS Diagnostic Flowchart. *Source*: Adapted from the Recommendations for Epidemiological Research in ME/CFS from the EUROMENE Epidemiology Working Group preprint 30 Sept 2020 [19].

(a) ***Core General Information***

Core general information consists of data related to demographic and socio-economic characteristics, and general health history of the research participants. For demographic data, RDEs recommend collecting the information of date of birth, sex at birth, gender identity, ethnicity, and marital status. Socio-economic characteristics consist of level of education, occupation and employment, family income before tax, and living conditions. These data can be collected in any database but have been specifically designed for use in the Research Electronic Data Capture (REDCap) application.

(b) ***Provisional diagnosis***

Provisional diagnosis can be determined by the responses to self- reported questionnaires (e.g. Symptoms Assessment Questionnaire). However, diagnosis confirmation will require further assessment and/or confirmation by a health professional (e.g. physician with experience in the

 doi:10.20944/preprints202405.1571.v1

diagnosis of ME/CFS or family physician, which is preferably done through face-to-face visits and/or online consultations), as per case definition criteria.

(c) ***Clinical assessment and d) symptom profiling (diagnosis confirmation)*** (reference: MDE's by ICanCME WG5)

For the diagnosis of ME/CFS the Institute of Medicine 2015 [21], NICE 2021 [13], and 2003 Canadian Consensus Criteria [24] were selected. These diagnostic criteria are widely recommended internationally. The working group agreed that it was necessary to help guide researchers by recommending approved diagnostic criteria for ME/CFS. Furthermore, WG5 recommends researchers be explicit in their manuscripts about the diagnostic criteria used and how they were applied.

Clinical-related information comes from standard questionnaires, such as the United Kingdom ME Biobank (UKMEB) Symptoms Assessment Questionnaire (SAQ), which facilitates diagnosis according to clinical criteria, and ideally is followed by a full clinical assessment including detailed history by a professional with experience in ME/CFS diagnosis. Symptom profiling can be based on questionnaires (self-report or proxy assisted). The SAQ is in use in British Columbia, and Ontario is planning to start using it because it enables researchers to assess if a research participant is likely to meet any of the clinical criteria prior to meeting a clinician. Additionally, the SAQ has been recommended by the EUROMENE Epidemiology Group as part of their Common Data Elements. Lastly, the instrument supports having comprehensive datasets in a single instrument. Other items recommended for assessments of ME/CFS patients included, measures of fatigue, pain, sleep disturbance, as well as recommended blood and urine tests are described in Table 1.

Sub-grouping of patients may include strata such as sex, age-group, type of onset (acute or insidious), post-infectious or otherwise, etiology if known of triggering infection, e.g. SARS-CoV-2, Epstein-Barr, etc. Disease severity can be ascertained clinically or with the help of standard questionnaires such as the Patient Phenotyping Questionnaire or an equivalent, including questionnaire short forms, e.g. Patient Phenotyping Questionnaire (PPQ-12), DePaul -Short questionnaire.

Day-to-day fluctuation in symptoms needs to be considered, as limited information on single time points may not be reliable, with substantially different results possible on a good day compared to a bad day. Symptoms may also be very different during periods of "crashes". The need for rest before prolonged or physically demanding testing is a consideration for research participants.

Additional Considerations on ME/CFS Research

1. **Comorbidities and their identification in ME/CFS**

Comorbidity can play an important role in different types of research. Comorbidities are co-existing conditions can be related or unrelated to the primary disease [25]. It is also possible that the primary disease and comorbid conditions share the same risk factors or pathophysiological mechanism. Research should describe comorbid conditions as ME/CFS can be associated with various syndromes, diseases, or comorbidities such as fibromyalgia, mast cell activation, postural orthostatic tachycardia, and small fiber neuropathy [26] Table 2 summarizes examples of co-morbidities, based on suggested entities as in the European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome [14] and Canadian Consensus Criteria (2003) [24]. Approximately 75% of ME/CFS patients also meet criteria for fibromyalgia [27]. Castro-Marrero et al conducted a nation-wide population-based cohort study in Spain, found that 80% of patients with ME/CFS had co-morbidities, which they classified into five subgroups. Among these, pain related conditions such as fibromyalgia, myofascial pain, shoulder tendinopathy, and epicondylitis were the most prevalent comorbid conditions [28]. Moreover, the Institute of Medicine (IOM) 2015 noted that comorbid conditions can be used to stratify cases as ME/CFS + fibromyalgia; ME/CFS + postural orthostatic tachycardia syndrome; ME/CFS + depression; ME/CFS + anxiety [21]. Infections such as EBV or other herpesvirus, COVID-19, and borreliosis seem to represent important triggers of

 doi:10.20944/preprints202405.1571.v1

ME/CFS, however the role as comorbid condition in the form of persistent infection by these or other agents require further investigations.

According to de Groot et al., there are four important reasons for measuring comorbidity in research: 1) to be able to control for confounding factors, 2) to identify effect modification, 3) to use comorbidity as a predictor of study outcome, 4) to measure co-occurring conditions [25]. A number of co-morbidity indexes have been used in other diseases studies [25], such as the Charlson Comorbidity Index (CCI) [29], the Cumulative Illness Rating Scale [30], and the Index of Coexisting Disease [31]. However, the applicability of a comorbidity index for studies on However, the applicability of a comorbidity index for studies on ME/CFS is still an area that needs to be developed further, and which would need to consider comorbidity alongside with differential diagnosis and exclusionary conditions.

Table 2. Comorbid conditions of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.

Comorbidities suggested in clinical guidelines	
Both Canadian Consensus Criteria[1] and EUROMENE[2]	**Conditions in one of the guidelines**
Fibromyalgia	Restless leg syndrome, periodic limb disorder[1]
Myofascial pain syndrome	Hypermobility Ehlers-Danlos syndrome[1]
Irritable bowel syndrome	Chronic pelvic pain, endometriosis
Migraine	Interstitial cystitis[1]
Mild depression	Mast cell activation disorder, eosinophilic esophagitis[1]
Mild anxiety	Multiple chemical sensitivities[2]
Allergy and food intolerances and atopic conditions	Raynaud's phenomenon[2]
Postural orthostatic tachycardia syndrome	Temporomandibular joint syndrome[2]
Neuro-mediated hypotension	Prolapsed mitral valve[2]
Hashimoto thyroiditis	
Sicca syndrome	

Sources: 1. Carruthers et al, 2003 (see reference No.[24]); 2. Nacul et al , 2021 (see reference No. [14]);

2. Long-COVID and ME/CFS

Since COVID-19 pandemic, there is increasing recognition that a significant proportion of Long-COVID cases develop a clinical presentation indistinguishable from ME/CFS [32,33]. A growing body of evidence suggests that the symptomatology of Long-COVID and ME/CFS overlap in a substantial subset of cases when ME/CFS is assessed according to multiple case definitions [32]. Long-COVID may be identified in persons with persistent symptoms following probable or confirmed SARS-CoV-2 infection, present at 3 months from the acute infection and which cannot be explained by an alternative diagnosis [34]. Long-COVID is characterized by persistent disabling fatigue and other

 doi:10.20944/preprints202405.1571.v1

symptoms, such as cognitive problems, headaches, disrupted sleep, myalgias and arthralgias, post-exertional malaise, orthostatic intolerance, tachyarrhythmias and gastrointestinal complaints, all of which greatly interfere with an individual's ability to function at home and at work [33]. Thus, recently, many studies focusing on Long-COVID and ME/CFS suggest some Long-COVID cases fit well as a sub-type of ME/CFS cases. A systematic review conducted in 2021 stated that 25 out of 29 ME/CFS symptoms were reported in at least one selected Long-COVID study [32,33]. The prevalence of Long-COVID amongst those infected with COVID-19 varies widely based on definition and measurement differences, and estimates range from 9-42% [35–38].

3. Concerns of bias in epidemiological studies

In an epidemiological study, during the designing and interpretation of results phases, researchers take into consideration the external and internal validity of the study. The external validity includes generalization of the study to wider populations [39]. Internal validity considers whether the sample is biologically and statistically representative of the study population. Statistical generalization is important in survey sampling in which the sample must be statistically representative of the target population [40].

The internal validity can be affected by selection or information bias, and confounding or random error. Bias has been defined as "any systematic error in the design, conduct or analysis of a study that results in a mistaken estimate of an exposure's effect on the risk of disease" [39]. In other words, bias is any deviation in the collection, analysis, interpretation and publication of data leading to conclusions that systematically underestimate or overestimate the true relationship between a given exposure and a specific disease or any other outcome [41]. Selection bias can result from the way study participants are selected for and participate in studies. Types of selection bias include 1) non-response bias; 2) incidence-prevalence bias (or survival bias); 3) loss-to-follow -up bias; and 4) volunteer bias. Information bias occurs during data collection. Misclassification is the most common type of information bias [39] and it can be non-differential or differential, depending on whether it affects different study groups, equally or not. The lack of biomarkers for diagnosis and the application of imperfect methods for diagnosis have been main barriers to progress in ME/CFS.

Researchers can minimize bias through the appropriate selection of the study design, careful choice of procedures of data collection on exposures and co-variables and disease-related outcomes. Identification and adequate measurement of confounding variables allow for their control in analysis or stratification. Large sample sizes will increase study power and reduce probability of random errors. Statistical power is typically set at least 80% or 0.8, and alpha-1 error at 5% or 0.05 [42].

4. Equity Diversity and Inclusion (EDI) Considerations

The Tri-agencies which are the Canadian Institute of Health Research (CIHR), the Natural Sciences and Engineering Research Council of Canada (NSERC), and the Social Science and Humanities Research Council of Canada (SSHRC), are the source or research policies and guidelines in Canada. These agencies suggest that equitable, diverse, and inclusive Canadian research is essential to creating the excellent, innovative and impactful research necessary to advance knowledge and understanding, and respond to local, national and global challenges.

For term definitions, please see the Equity and Inclusion Office at the University of British Columbia (available at https://equity.ubc.ca/resources/equity-inclusion-glossary-of-terms/). Detailed information on EDI in research team can be found in Canada Research Chairs website, https://www.chairs-chaires.gc.ca/program-programme/equity-equite/best_practices-pratiques_examplaires-eng.aspx .

In the field of ME/CFS, consideration of equity, diversity, and inclusion is essential with regards to research conduct, sample selection and recruitment, as well as interpretation of results.

Research in the field has mainly focused on white individuals, less in ethnic minorities [6], and typically those with better access to care and services [43]. In particular, the severely affected have been often left out of research studies [44].

Selection bias has also resulted from non-random selection of patients or selection of volunteers, or those with unconfirmed diagnosis by a competent health professional. Self-report of CFS has been found to over-represent the true number of people who would meet specific diagnostic criteria [45] .

 doi:10.20944/preprints202405.1571.v1

The nature of the disease requires some adaptation of methods to enable participation. For example, use of short forms whenever possible, allowance for pauses/ breaks during data collection and other research procedures, as well as consideration of timing and mode of data collection are important. Home visits may be the only option for some assessments of patients who are more severely affected, with online assessment also an option in some cases, and may facilitate inclusion of persons with more severe disabilities and those living distant from the assessment centers.

5. **Language and Culture Considerations**

In line with EDI considerations, the assessment of the health and healthcare needs of minorities including indigenous and immigrant populations are acknowledged to potentially differ in health and social sciences. Specifically, self-reported health and risk factor status differs in ethnic variations because of cultural and language differences [46]. Canada has two official languages: English and French. It is also a home for many different ethnic groups including indigenous populations. Many of the self-report questionnaires in ME/CFS, used for case definitions are only available in English. According to Hunt and Bhogal, the most sophisticated translation techniques are applied in the field of patient assessed outcomes, where methods have evolved to a prolonged process of item selection, testing, and retesting and consultations with people monolingual in the target language(s) [46]. Bradley also identified guidelines for translation of questionnaires [47].

Indigenous people including First Nations, Inuit and Métis comprise around 5% (n=1,807,250) of total population of Canada [48]. Table 2 shows the number and percentage of Indigenous people in different provinces. Over 70 indigenous languages are spoken and among them 188,900 people with an Indigenous mother tongue in Canada [48], and language and cultural barriers add to other factors involved in health care access by this population. In terms of health care, indigenous health is in federal, provincial, and territorial legislation and policy [48,49]. Despite the availability of resources, the narrative review conducted by Nguyen et al., suggested there are three categories of barriers to access to healthcare: proximal, intermediate, and distal barriers [50]. The ME/CFS epidemiological study conducted by Nacul et al., in British Columbia based on the BC Generations Project (BCGP) cohort (https://www.bcgenerationsproject.ca/) found less than 4% (while 2.2% in BCGP cohort in 2016) were indigenous participants [51], indicating, this population is under-represented in this large based population study in that Province (the study is currently in press). Engagement of Indigenous populations (and other under-represented ethnic groups), in research participation planning, conduct, analysis and dissemination of studies, as well as in their participation as study subjects.

Conclusions

This initial research guideline provides a framework for ME/CFS research in Canadian settings. We refer to existing guidelines, such as the European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome [19], NINDS common data elements [18] as well as to current practices at ME/CFS clinics in Canada. Guidance on research methods is beyond the aims of this guideline, as these are widely covered in various references from epidemiology and research methods. We also aimed to emphasize how common drawbacks in research can be addressed, and in particular taking into account particularities of the disease and the Canadian context. We propose the standardization of diagnostic criteria and data collection, as guidance for consideration in this field of research. While this is aimed to facilitate better comparison of research studies and meta-analyses, the choice of specific research methods are expected to be determined by individual research groups. This is a field of research that evolves rapidly, not least considering new etiologies, such as cases following COVID-19, as research needs to adapt to new knowledge and challenges. This report aimed to list some important points for consideration, however, we recognize the scope for further work toward a deeper understanding of many of the aspects covered here.

Acknowledgments: The authors would like to gratefully acknowledge the participation and support of members of the Working Group Five of the ICanCME research network, patient-partners and their families. Especially

 doi:10.20944/preprints202405.1571.v1

Cathy and John Prescott for their reviews and comments on this paper. Dr. Nacul would like to acknowledge the Pacific Public Health Foundation (previously known as the BCCDC Foundation for Public Health) and BC Women's Health Foundation for their sponsorship of his protected research time. Dr. Nacul and Dr. Chuluunbaatar would also like to acknowledge the ICanCME and BCWHF for funding research and their contribution to the postdoctoral research fellow program. The ICanCME research network is funded by the Canadian Institute of Health Research (CIHR).

References

1. Lim E-J, Son C-G. Review of case definitions for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Journal of Translational Medicine. 2020;18(1):289.
2. Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, et al. Myalgic encephalomyelitis: International Consensus Criteria. Journal of Internal Medicine. 2011;270(4):327-38.
3. Bansal AS, Bradley AS, Bishop KN, Kiani-Alikhan S, Ford B. Chronic fatigue syndrome, the immune system and viral infection. Brain, Behavior, and Immunity. 2012;26(1):24-31.
4. Lacerda EM, Geraghty K, Kingdon CC, Palla L, Nacul L. A logistic regression analysis of risk factors in ME/CFS pathogenesis. BMC Neurol. 2019;19(1):275.
5. Nacul L, O'Boyle S, Palla L, Nacul FE, Mudie K, Kingdon CC, et al. How Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Progresses: The Natural History of ME/CFS. Frontiers in Neurology. 2020;11.
6. Nacul LC, Lacerda EM, Pheby D, Campion P, Molokhia M, Fayyaz S, et al. Prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in three regions of England: a repeated cross-sectional study in primary care. BMC Medicine. 2011;9(1):91.
7. Statistics C. CCHS_Ann_2015-16_stata_dta.zip. In: Statistics C, editor. Canadian Community Health Survey: Public Use Microdata File, 2015/2016. V1 ed: Abacus Data Network; 2018.
8. Schäfer ML. [On the history of the concept neurasthenia and its modern variants chronic-fatigue-syndrome, fibromyalgia and multiple chemical sensitivities]. Fortschr Neurol Psychiatr. 2002;70(11):570-82.
9. PubMed. Number of articles published in myalgic encephalomyelitis/chronic fatigue syndrome 2023 [cited 2024 January 28]. Available from: https://pubmed.ncbi.nlm.nih.gov/?term=myalgic+encephalomyelitis+chronic+fatigue+syndrome&filter=simsearch3.fft&filter=dates.2010-2022.
10. Jason LA, Sunnquist M, Brown A, Evans M, Vernon SD, Furst J, et al. Examining case definition criteria for chronic fatigue syndrome and myalgic encephalomyelitis. Fatigue. 2014;2(1):40-56.
11. Nacul LC, Lacerda EM, Campion P, Pheby D, Drachler MdL, Leite JC, et al. The functional status and well being of people with myalgic encephalomyelitis/chronic fatigue syndrome and their carers. BMC Public Health. 2011;11(1):402.
12. Mirin AA. A preliminary estimate of the economic impact of long COVID in the United States. Fatigue: Biomedicine, Health & Behavior. 2022;10(4):190-9.
13. Excellence NIfHaC. Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management. NICE Guideline, No.206. London: National Institutes for Health and Care Excellence (NICE); 2021.
14. Nacul L, Authier FJ, Scheibenbogen C, Lorusso L, Helland IB, Martin JA, et al. European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (EUROMENE): Expert Consensus on the Diagnosis, Service Provision, and Care of People with ME/CFS in Europe. Medicina (Kaunas). 2021;57(5).
15. ICAnCME. What is ICanCME? : The Interdisciplinary Canadian Collaborative ME Research Network; [Available from: https://www.icancme.ca/.
16. Haney E SB, McDonaugh M. Diagnostic Methods for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. Annals of Internal Medicine. 2015;162(12):834-40.
17. Estévez-López F, Mudie K, Wang-Steverding X, Bakken IJ, Ivanovs A, Castro-Marrero J, et al. Systematic Review of the Epidemiological Burden of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Across Europe: Current Evidence and EUROMENE Research Recommendations for Epidemiology. J Clin Med. 2020;9(5).
18. NINDS Common Data Elements - Myalgic Encephalomyelitis/Chronic Fatigue Syndrome [Internet]. National Institute for Neurological Disorders and Stroke. 2020 [cited 03/02/2024]. Available from: https://www.commondataelements.ninds.nih.gov/sites/nindscde/files/Doc/MECFS/CDEStartupResource_MECFS.pdf.
19. Mudie K, Estévez-López F, Sekulic S, Ivanovs A, Sepulveda N, Zalewski P, et al. Recommendations for Epidemiological Research in ME/CFS from the EUROMENE Epidemiology Working Group. Preprints: Preprints; 2020.

 doi:10.20944/preprints202405.1571.v1

20. Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, Lerner AM, et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Journal Of Chronic Fatigue Syndrome. 2003;11(1):7-115.
21. IOM. Institute of Medicine, Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Mil Med. 2015;180(7):721-3.
22. Strand EB, Nacul L, Mengshoel AM, Helland IB, Grabowski P, Krumina A, et al. Myalgic encephalomyelitis/chronic fatigue Syndrome (ME/CFS): Investigating care practices pointed out to disparities in diagnosis and treatment across European Union. PLoS One. 2019;14(12):e0225995.
23. Nacul L, Lacerda EM, Kingdon CC, Curran H, Bowman EW. How have selection bias and disease misclassification undermined the validity of myalgic encephalomyelitis/chronic fatigue syndrome studies? J Health Psychol. 2019;24(12):1765-9.
24. Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, Lerner AM, et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Journal Of Chronic Fatigue Syndrome. 2003;11(1):7-115.
25. de Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity. a critical review of available methods. J Clin Epidemiol. 2003;56(3):221-9.
26. Guralnik JM. Assessing the impact of comorbidity in the older population. Ann Epidemiol. 1996;6(5):376-80.
27. Wirth KJ, Löhn M. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Comorbidities: Linked by Vascular Pathomechanisms and Vasoactive Mediators? Medicina (Kaunas). 2023;59(5).
28. Castro-Marrero J, Faro M, Aliste L, Sáez-Francàs N, Calvo N, Martínez-Martínez A, et al. Comorbidity in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: A Nationwide Population-Based Cohort Study. Psychosomatics. 2017;58(5):533-43.
29. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
30. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc. 1968;16(5):622-6.
31. Miskulin DC, Athienites NV, Yan G, Martin AA, Ornt DB, Kusek JW, et al. Comorbidity assessment using the Index of Coexistent Diseases in a multicenter clinical trial. Kidney Int. 2001;60(4):1498-510.
32. Wong TL, Weitzer DJ. Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)—A Systemic Review and Comparison of Clinical Presentation and Symptomatology. Medicina. 2021;57(5):418.
33. Komaroff AL, Lipkin WI. ME/CFS and Long COVID share similar symptoms and biological abnormalities: road map to the literature. Front Med (Lausanne). 2023;10:1187163.
34. Soriano JB MS, Marshall JC, RFelan P, Diaz JV. A clinical case definition of post-COVID-19 condition by a Delphi consensus. The Lancet Infectious Diseases. 2022;22(4):E102-E7.
35. Woodrow M, Carey C, Ziauddeen N, Thomas R, Akrami A, Lutje V, et al. Systematic Review of the Prevalence of Long COVID. Open Forum Infectious Diseases. 2023;10(7).
36. Kozak R, Armstrong SM, Salvant E, Ritzker C, Feld J, Biondi MJ, et al. Recognition of Long-COVID-19 Patients in a Canadian Tertiary Hospital Setting: A Retrospective Analysis of Their Clinical and Laboratory Characteristics. Pathogens. 2021;10(10):1246.
37. Shepherd C. Long-Covid and ME/CFS - Are they the same condition? 2023 [Available from: https://meassociation.org.uk/wp-content/uploads/LONG-COVID-AND-MECFS-ARE-THEY-THE-SAME-CONDITION-MAY-2023.pdf.
38. UK GUCC-it. Coronavirus cases in England: GOV.UK 2023 [updated Thursday 14 December 2023. Available from: https://coronavirus.data.gov.uk/details/cases?areaType=nation&areaName=England.
39. Gordis L. Bias, Confounding, and Interaction. Epidemiology: Saunders Elsevier; 2008. p. 247-56.
40. Rothman KJ. Epidemiology. An Introduction. Epidemiology An Introduction. 1st ed. New York: Oxford University Press; 2002. p. 20-1.
41. Last J. A Dictionary of Epidemiology. 5th ed. Oxford: Oxford University Press; 2009.
42. Baguley T. Understanding statistical power in the context of applied research. Applied Ergonomics. 2004;35(2):73-80.
43. Almeida APSC, Nunes BP, Duro SMS, Facchini LA. Socioeconomic determinants of access to health services among older adults: a systematic review. Revista de Saúde Pública. 2017;51.
44. Kingdon C, Giotas D, Nacul L, Lacerda E. Health Care Responsibility and Compassion-Visiting the Housebound Patient Severely Affected by ME/CFS. Healthcare. 2020;8(3):197.
45. Chuluunbaatar E TM, Nacul L. Epidemiology of Myalgic Encephalomyelitis among individuals with self-reported Chronic Fatigue Syndrome and their health-related quality of life in Canada. International Association of Chronic Fatigue Syndrome Myalgic Encephalomyelitis (IACFSME) 2023; New York, New York, USA2023.
46. Hunt SM, Bhopal R. Self report in clinical and epidemiological studies with non-English speakers: the challenge of language and culture. Journal of Epidemiology and Community Health. 2004;58(7):618.

 doi:10.20944/preprints202405.1571.v1

47. Bradley C. Translation of Questionnaires for Use in Different Languages and Cultures. Handbook of Psychology and Diabetes: Routledge; 1994. p. 13.
48. Statistics Canada GoC. Indigenousidentity by Registered or Treaty Indian Status: Canada, provinces and territories, census metropolitan areas and census agglomerations with parts 2021 [Available from: https://www12.statcan.gc.ca/.
49. Canada Go. Indigenous health care in Canada [Available from: https://www.sac-isc.gc.ca/eng/1626810177053/1626810219482.
50. Nguyen NH, Subhan FB, Williams K, Chan CB. Barriers and Mitigating Strategies to Healthcare Access in Indigenous Communities of Canada: A Narrative Review. Healthcare. 2020;8(2):112.
51. Project BG. Our Participants: BC Generations Project; 2023 [Available from: https://www.bcgenerationsproject.ca/about/our-participants/