ME Australia's response to the National Health and Medical Research Council on:

The Myalgic Encephalomyelitis (ME) and Chronic Fatigue Syndrome Advisory (CFS) Committee Draft Report - on the research and clinical guidance requirements for Australians with ME and CFS

Acknowledgments

This response has been developed by the ME Australia collaborative network, with assistance and advice from international and Australian scientific experts in ME and CFS. ME Australia would like to thank the carers of people with ME and people with ME who also took the time to provide input into this response.

Contents

Executive Summary

The establishment of an advisory committee to investigate ME and CFS by the NHMRC and the recommendations in this draft report are positive developments for people with Myalgic Encephalomyelitis (ME). ME Australia supports the report being finalised quickly to support agencies urgent consideration of the recommendations. We agree with the committee that once a final report is available, it will provide a starting point for consideration by relevant agencies.

Report recommendations

We strongly support the recommendation to issue a targeted call for research, providing funding is directed to biomedical research. The prevalence (100,000 to 250,000 Australians), burden of disease (1 in 4 people house or bed bound) and years of failing to fund needed biomedical research into ME and CFS, make a clear case for biomedical research funding[1]. It is recommended the NHMRC consider allocating $15 million to fund biomedical research into ME and CFS.

This amount of funding will bring forward diagnostic tests, and over time, treatment. It would be useful for the NHMRC to consider how collaboration can best be supported and how data from these funded studies can be made available.

The recommendation to establish new clinical guidelines is strongly supported. There is a clear need to improve the accuracy of diagnosis in Australia. Two in five people diagnosed as having ME or CFS by a primary health physician in Australia do not meet the CFS Fukuda criteria, only 32 per cent meet the International Consensus Criteria for ME[2]. There are also numerous examples of people going undiagnosed for decades. New guidelines will assist diagnosis, provide guidance on treatment/management of common symptoms and stop preventable worsening of the disease, due to misguided medical advice.

The RACP guidelines commissioned by the Government are contributing to misdiagnosis and misleading research findings (due to incorrect cohort selection). It is more than 16 years since the Australian Senate passed a resolution requesting the Guidelines be reviewed, noting[3]:

'The RACP guidelines are not representative of the consultation process, incorrectly concluded the illness was fundamentally psychological, produced treatment plans that were inadequate and calls for their immediate review.'

While less critical than biomedical research funding and new clinical guidelines, the recommendation to include ME and CFS in existing health policy tools and health service research is supported. Our view is that consideration of their inclusion, should occur once new clinical guidelines are established. While not disagreeing with conducting research into the economic impact of ME and CFS on the more than $1.8 trillion Australian annual GDP, this is considered a lower priority than other recommendations.

Overview of draft report

The willingness of committee members volunteering to look into ME and CFS is appreciated. Their efforts in providing a starting point for relevant agencies will benefit a large number of people over the medium to long term.

When building on this starting point, it is essential that agencies obtain the relevant scientific expertise. This includes scientific researchers with biomedical experience in ME and CFS. The lack of relevant scientific expertise in the committee has been raised directly with the NHMRC by scientists, stakeholders and members of the Australian Senate[4]. Agencies should consider how they will include this expertise, patients, carers and stakeholders in next steps.

We ask the NHMRC to note that while the report treats ME and CFS as indivisible and calls it ME/CFS, this is at odds with how the World Health Organization classifies these diseases[5]. It is also at odds with the Institute of Medicine report that describes ME/CFS as an umbrella term that includes both ME and CFS[6]. It is important for people with ME or CFS that both are taken seriously and not treated as identical diseases. It is also worth noting the term ME/CFS appears inconsistent with the revised terms of reference at Attachment G, which refers to ME and CFS.

Recommendations

Report

1. NHMRC should encourage the committee to finalise the report quickly, with minimal nuance and change

2. To inform their responses to the report, agencies should consult biomedical researchers with experience in ME and CFS, and stakeholders.

Research funding – the NHMRC should:

3. Consider issuing a targeted call for research above its standard $3m to $5m, providing $15m would bring promising research to scale

4. Restrict the targeted call for research to biomedical research into ME and CFS

5. Maximise the return on investment, by funding applicants with existing biomedical research experience in ME or CFS, or partner with those who have existing experience

6. Require commissioned research to use the ME: International Consensus Criteria (ICC) and

    a. Allow researchers to use other diagnostic criteria, providing these results are published independently alongside the ME: ICC results

    b. Allowed researchers to include people with comorbidities, providing these results are independently published alongside the ME: ICC results.

Guidelines

7. The NHMRC establish an expert panel of scientists with biomedical expertise in ME and/or CFS to guide the development of new clinical guidelines

8. Adopt an open and transparent process in developing the guidelines

9. Develop guidelines that recognise differences between ME and CFS

10. Avoids mistakes of the RACP Guidelines commissioned by the Government.

Advisory Committee process

11. The NHMRC should continue to consider how it can improve its advisory processes.

There is a clear need to finalise report

Recommendations one and two

1. NHMRC should encourage the committee to finalise the report quickly, with minimal nuance and change
2. To inform their responses to the report, agencies should consult biomedical researchers with experience in ME and CFS, and stakeholders.

We agree with the committee's view that their report, once finalised, is a starting point. It is our view there is an urgent need to fund biomedical research and to develop new clinical guidelines. Considering this, we recommend the report be finalised as quickly as possible. Delivering on these recommendations will benefit a large number of people over the medium to long term.

While appreciative of the generosity by committee members to volunteer their time, the composition of the committee suggests further effort spent trying to nuance and adjust the report is unlikely to be warranted. When weighed against the need to act, previous NHMRC commitments to act[7], there is a clear need to rapidly move to the next steps. We certainly, would not support the advisory committee being extended beyond April 2019.

It is our strong view that parts of the report are misleading. For example, the report treats ME and CFS as indivisible, and refers to these two diseases using an umbrella term ME/CFS[8]. It is important for people with ME or CFS that both are taken seriously and not treated as identical diseases. It is also worth noting the term ME/CFS appears inconsistent with the revised terms of reference at Attachment G, which refers to providing advice on ME and CFS.

Providing agencies obtain relevant scientific expertise prior to designing or implementing a response to recommendations, it is our view that flaws in the report can easily be overcome. The expertise should include scientific researchers with biomedical experience in ME and/or CFS. Agencies should also consider how they will include patients, carers and stakeholders in next steps. Appropriate engagement by agencies, can overcome the lack of relevant scientific expertise in the committee, which has been raised directly with the NHMRC by scientists, stakeholders and Australian Senators.

Response to recommendations

Research funding

Recommendations three and four

3. The NHMRC should consider issuing a targeted call for research above its standard $1m per year for three to five years; providing $15m would bring promising research to scale
4. Restrict the targeted call for research to biomedical research into ME and CFS

We consider there is a strong case for a targeted call for research, as Australian scientists have been seeking funding for biomedical research into ME and CFS for more than 25 years. For example, the majority of research applications to the NHMRC on ME and CFS received between 1992 and 2002 focused on biomedical aspects of these diseases[9]. Unfortunately, research focusing on the biomedical nature of ME and CFS has not been successful in receiving funds from Government through current funding processes[10].

We consider there is a case for a larger than normal targeted call for research of $1 million per annum. This is based on the prevalence (100,000 to 250,000 Australians) and burden of disease (1 in 4 people house or bed bound). It is also based on the promising state of Australian science, which includes the identification and patenting of biomarkers.

It is remarkable what Australian scientists have found with very limited funding. With additional funding to bring research to scale, we could see diagnostic tests developed and over time treatment. Examples, of the progress Australian scientists have made include:

- Identifying a specific mitochondrial defect and compensatory increases in mitochondrial proteins, cellular stress signalling pathways and energy metabolism in cultured ME cells
- Altered metabolite profiles in the serum of ME patient consistent with a shift in energy metabolism
- Altered gut/stool microbiomes in ME patients
- Genetic markers (SNPs) in genes involved in energy metabolism and mitochondrial function that are associated with ME.

From our discussion with Australian biomedical research scientists, funding of $15 million would see rapid progress with:

- The development of a new diagnostic protocol for ME combining data from clinical examination, urine and blood pathology, and cell culture
- Understanding the molecular pathophysiology of ME and thus potentially reveal treatment options
- Validating previous discoveries through the study of much larger cohorts
- Mechanistic molecular studies to understand cause-effect relationships in ME
- The discovery and development of new treatments, based on understanding ME mechanisms.

Recommendation five

5. Maximise the return on investment, by funding applicants with existing biomedical research experience in ME or CFS, or partner with those who have existing experience

Considering the long run scarcity of funding for biomedical research into ME and CFS, it is important to maximise the return on investment of a targeted call to research. The report's recommendation to establish an Australian collaborative research consortium is a potential option to do this.

The committee's consortium approach would ensure commissioned research includes existing Australian scientific expertise developed over the years. Although, there are considerable risks this approach would result in delays (e.g. if university boards need to sign off on being part of a consortium). We are not certain this approach is the most efficient way to support collaboration.

We ask the NHMRC to consider how collaboration can be fostered. This should include examining ways to ensure the needed expertise is included in any commissioned research. Our proposal is that research funding goes to scientists with existing biomedical research experience in ME and/or CFS, or to those who partner with scientists with this existing experience. We think another way to boost collaboration is to make it a requirement the data generated from the funding is made available to other scientists researching ME and CFS in Australia.

Recommendation six

6. Research commissioned should use the ME: International Consensus Criteria (ICC) and
    a. Be allowed to use other diagnostic criteria, providing these results are published independently alongside the ME: ICC results
    b. Be allowed to include people with comorbidities, providing these results are independently published alongside the ME: ICC results.

The World Health Organization classifies ME and CFS as separate diseases[11]. The Institute of Medicine report describes ME/CFS as an umbrella term that includes both ME and CFS[12]. The ME: ICC isolate people with ME from those with CFS. The report notes there are more than 20 diagnostic criteria used, which produces wide variance in population. Using standard diagnostic criteria is the most likely approach to support replication.

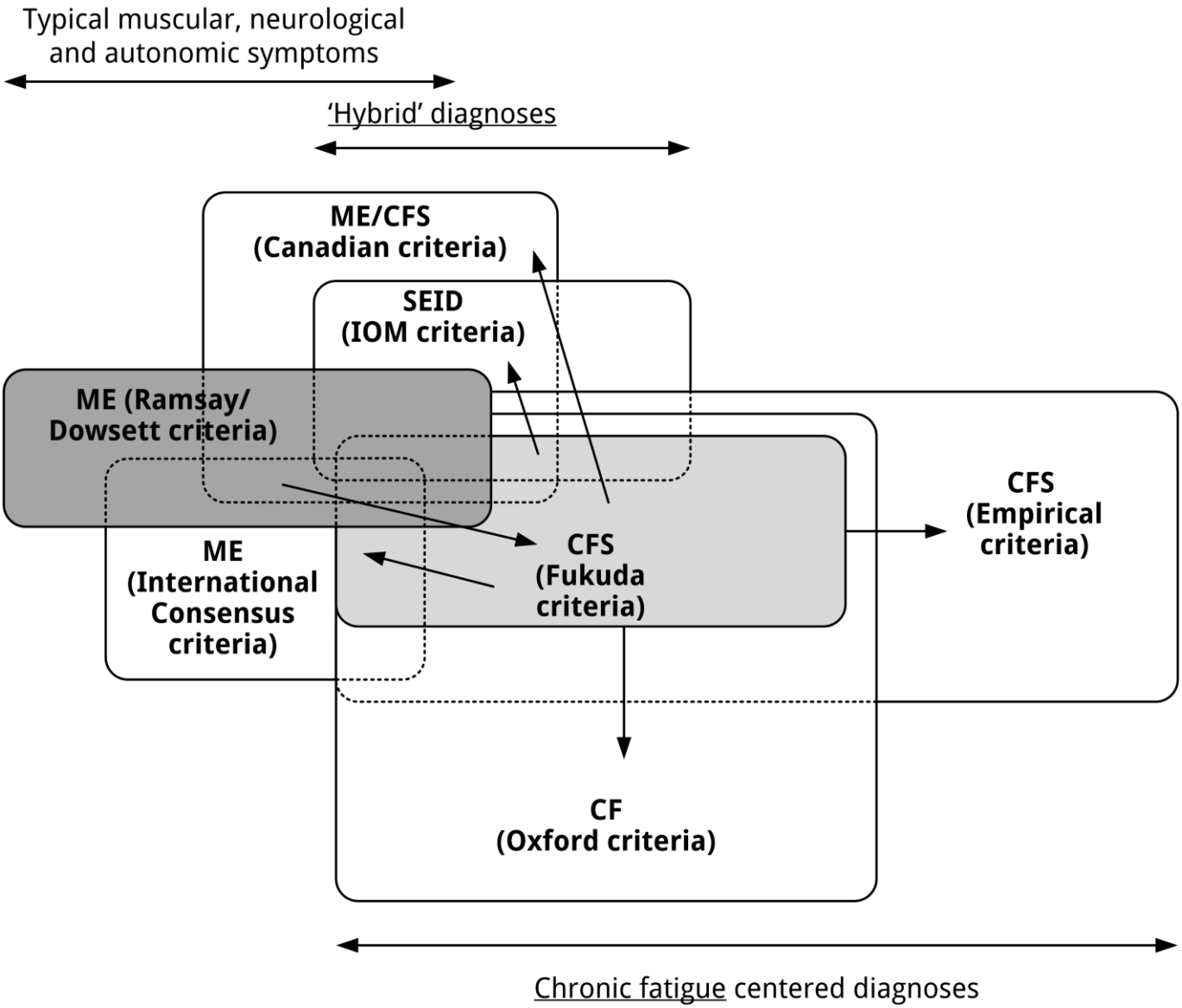
While the committee has recommended the Canadian Consensus Criteria (CCC), this is not supported. This is based on advice from international and Australian scientists. Their view is the CCC is the precursor to the ME: ICC, and the ME: ICC has replaced the CCC, and as such the CCC is considered obsolete and surpassed[13]. Again based on advice from scientists, at this stage we also do not support the committee's recommendation for pediatric primer, as advice suggests it is still in need of psychometric validation[14].

Studies have shown that patients with ME: ICC experience more bodily pain, have greater functional impairment and physical, mental and cognitive problems than patients who meet the Fukuda CFS criteria; but, not ME: ICC [15] (refer **Appendix A** for more information). Our view is there is benefit in determining the similarities and differences between people with ME and people with CFS (as defined by different criteria), and for people with comorbidities[16]. The key issue is to ensure the groups are kept separate in order to provide clear contrasts. Figure one (page 11) provides an example of how cohorts can differ depending on the criteria used.

The report suggests the use of different criteria can be mitigated by using the National Institute of Neurological Diseases and Stroke Common Data Elements. In our view this is not an optimal approach.

We consider commissioning research that specifically includes and measures findings for people diagnosed under the ME:ICC is warranted, considering how this population group differs from patients using other CFS criteria. We consider there is merit in applicants including other criteria or people with comorbidities providing the results for this group are published separately from those in the ME: ICC cohort.

Figure one: Overlap between different criteria for ME and CFS - Twisk[17]



New clinical guidelines

Recommendation seven and eight

7. The NHMRC establish an expert panel of scientists with biomedical expertise in ME and CFS to guide the development of new clinical guidelines
8. Ensure there is an open and transparent process in developing the guidelines

The recommendation to establish new clinical guidelines is strongly supported. Noting, the NHMRC have previously commissioned work on using the ME: ICC as the basis for their replacement. While this was due to be complete in 2014, unfortunately it was not delivered[18].

There is a clear need to improve the accuracy of diagnosis in Australia. Two in five people diagnosed as having ME or CFS by a primary health physician in Australia do not meet the CFS Fukuda criteria, only 32 per cent meet the ME: ICC. There are also example of people going undiagnosed for decades. New guidelines will assist diagnosis and provide guidance on treatment/management of common symptoms.

As previously noted, while the willingness of committee members volunteering to look into ME and CFS is appreciated, there is a strong need to ensure there is relevant scientific expertise guiding the development of the guidelines. The importance of this expertise has been raised directly with the NHMRC by scientists, stakeholders and members of the Australian Senate[19].

An expert committee overseeing the development of new guidelines will provide confidence in the process. For it to be considered an expert committee by patients and their carers, it will include a majority of scientific researchers with biomedical experience in ME and/or CFS.

It is also our view that confidence in a process to develop new guidelines will be significantly enhanced if people involved in the RACP Guidelines are not directly involved. The Australian Parliament expressed the view the RACP Guidelines were not representative of the consultation process, were wrong about the nature of the illness and called for their immediate review. Involving people who were part of a process whose results were not representative of the consultation process, nor correct about the nature of the illness, invites unnecessary risk.

Another issue raised directly with the NHMRC by the scientists, stakeholders and members of the Australian Senate is that the advisory committee process should have been more open and transparent[20]. In developing guidelines, it will be important to consider how patients, carers and stakeholders can be actively informed and engaged in the development of new clinical guidelines.

Recommendation nine

9. Developing guidelines that recognise differences between ME and CFS

As set out in recommendation six, ME and CFS are distinct diseases (WHO ICD-11 and IOM Report). The new guidelines should be developed recognising differences between ME and CFS. This is especially important considering differences in symptoms, an example of differences in symptoms is provided at **Appendix A**.

Recommendation 10

10. Avoids mistakes of the RACP Guidelines commissioned by the Government

As the report notes, the RACP Guidelines are still available for use by medical practitioners, which is concerning. It also notes the RACP Guidelines, which were funded by the Government and published 6 May 2002 has been subject to criticism. The draft report suggests the criticism be considered in the historical context they were developed; when not much was known about ME and CFS.

The view that not much was known about ME and CFS, appears inconsistent with studies that had been published prior to 2002. The view becomes even more questionable once the work of Ramsay and Hyde, the evidence used by the World Health Organization in its 1969 classification of ME as a neurological illness and the RACP Guidelines quoting more than 500 articles is considered[21]. This view is also inconsistent with the Australian Senate resolution on 16 May 2002, that urged the Government to call for

'an immediate review of the guidelines, with a view of replacing them with more comprehensive guidelines that reflect a more representative view of the analysis of ME/CFS'

We concur with the criticism mentioned in the report on the RACP guidelines and agree that comprehensive and more appropriate guidelines are required. As noted earlier, the NHMRC has previously supported a process based on the ME: ICC to replace them. The table below sets out how we would expect any future guidelines funded by Government to differ from the RACP Guidelines.

Table One: proposed differences between RACP Guidelines and future guidelines

Issue	RACP	Future
Should health professionals share their diagnosis with their patients?	Not always When they are younger, have less severe symptoms, shorter duration of illness a more non-committal diagnosis may be appropriate (s45)	Yes Patients have the right to be correctly diagnosed
Should patients be trusted to tell practitioners about their health?	No Whenever possible, an independent, corroborating history should be sought from a spouse, partner or family member (s35)	Yes As outlined in – the Medical Board of Australia's Good medical practice: a code of conduct for doctors in Australia (section three)[22]

Issue	RACP	Future
Does it overlap with nervous exhaustion?	Yes Extent of overlap with nervous exhaustion, anxiety and depression yet to be determined (s27-28)	No WHO ICD-11 ME and CFS are listed as neurological disease that occur following a viral infection (ME since 1969[23]) WHO didn't accept view put in 1970 that ME was mass hysteria (based on gender split) and suggestion it be called "myalgic nervosa"[24]
Does it overlap with mental illness?	Yes Obvious overlap of somatoform disorders and CFS (s29)	No A/A and IOM Report – many health care professionals mistake it for a mental health condition[25]
Do patients beliefs or attitudes stop them from recovering?	Yes Health practitioners should identify beliefs and attitudes that impair recovery (s40) Studies that incorporate a cognitive component produce more sustained improvements (s40)	No Scientist have identified dysfunction within cells, this is the issue[26] CDC advises no current cure or treatment, suggest focus on managing symptoms[27]
Does prescribing physical activity help cure a person?	Yes Physical activity and rehabilitation achieve good short-term results (s40)	No A/A and the AHRQ systematic review found no evidence exercise has any impact for people with ME or CFS – Fukuda criteria[28]

Issue	RACP	Future
Is it a distinct clinical illness or disease?	No CFS creates an artificial boundary within a continuum of fatigue (s45). List of symptoms not a disease (s23)	Yes ME and CFS diseases in WHO ICD 11 WHO listed ME as a disease since 1969
Focus on fatigue relate to exhaustion?	No If fatigue is >6 months, disabling and accompanied by neuropsychiatric conditions – diagnose CFS (s23)	Yes ME: ICC – people with ME have an adverse reaction to exertion ME: ICC – the use of 'fatigue' has been the most confusing and misused criterion
Distinguish between ME and CFS?	No	Yes WHO ICD -11 lists them separately IOM Report recognises ME and CFS are distinct conditions under umbrella ME/CFS. See also ME: ICC

Advisory committee process

Recommendation 11

11. The NHMRC should continue to consider how it can improve its advisory processes

We are very appreciative of the NHMRC establishing the advisory committee and support the Australian Senate's statement that it is a positive development[29]. Similar to the Australian Senate, we do think this process would have benefited from being run in a more open and transparent manner[30]. We also concur with senators and other stakeholders that the committee's report could have been improved if it had been more open to relevant scientific expertise.

In this regard, examples of more open consultative processes that operate in both the United States and the United Kingdom are worth considering for any future advisory committee process run by the NHMRC.

In the United States, the CFS advisory committee which reported to Assistant Secretary of Health and Human Services on issues relating to ME and CFS from 2001 to 2018, delivered an open and transparent process by[31]:

- Calling for voting members through an expression of interest process, setting out clear criteria they needed to meet (scientist were required to have recent biomedical research expertise in ME or CFS)
- Allowing members of the public to observe and even address the committee for one minute if desired
- Publishing an agenda ahead of the meeting, including papers and presentations
- Broadcasting the meeting on the web
- Providing transcripts, video footage and minutes of meetings on its website.

In the United Kingdom, the National Institute for Health and Care Excellence commitment to rigorous, open and transparent processes include[32]:

- Allowing members of the public and press to observe board meetings, advisory committee meetings and other meetings
- Publishing dates of scheduled meetings and locations well in advance
- Publish the agenda in advance
- Allowing people to register as a stakeholder to provide input
- Publishing minutes of meetings, rather than publishing a public summary of meeting.

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Appendix A

As recognised by the World Health Organization, the Institute of Medicine's report and the ME: ICC, ME is separate to CFS and the inclusion of it within overly inclusive groups is unhelpful. As can be seen in the tables in this appendix, there is significant difference in symptoms between people with ME and with CFS; but, also overlap.

Commissioning research using multiple diagnostic criteria and comparing them through the Neurological Diseases and Stroke Common Data Elements is likely to be misleading. As it risks mixing up people with ME, with people who have CFS or at times something else.

Table one: comparison of functioning CFS (Fukuda) vs ME: ICC

SF-36 Subscales (Higher score indicates **less** impairment)

	DePaul Sample			Newcastle Sample		
	CFS M (*SD*)	ME M (*SD*)	Sig.	CFS M (*SD*)	ME M (*SD*)	Sig.
Physical Functioning	34.1 (*17.5*)	26.9 (*18.6*)	**	41.9 (*30.8*)	29.3 (*23.3*)	
Role Physical	7.9 (*19.5*)	2.5 (*10.7*)	*	12.0 (*20.6*)	7.3 (*17.5*)	
Bodily Pain	50.0 (*23.8*)	35.6 (*19.9*)	***	40.0 (*26.2*)	29.5 (*21.4*)	
General Health	28.6 (*15.3*)	22.6 (*13.3*)	**	32.3 (*18.8*)	19.1 (*10.5*)	**
Social Functioning	21.2 (*21.7*)	19.5 (*18.7*)		31.0 (*24.4*)	26.5 (*19.9*)	
Mental Health	71.5 (*16.9*)	71.6 (*17.0*)		59.1 (*17.4*)	61.4 (*21.5*)	
Role Emotional	79.5 (*37.9*)	80.7 (*36.1*)		65.4 (*43.7*)	59.4 (*44.3*)	
Vitality	15.4 (*14.2*)	11.2 (*11.9*)	*	18.0 (*13.4*)	13.4 (*15.2*)	

*$p < 0.05$;
**$p < 0.01$;
***$p < 0.001$

Table two: comparison of symptoms CFS (Fukuda) vs ME: ICC

(high score indicates more impairment)

	DePaul Sample			Newcastle Sample		
	CFS M (*SD*)	**ME M (*SD*)**	**Sig.**	**CFS M (*SD*)**	**ME M (*SD*)**	**Sig.**
Fatigue	78.8 (*17.0*)	80.0 (*15.1*)		75.0 (*14.6*)	80.4 (*15.7*)	
Post-exertional malaise						
Dead, heavy feeling after starting to exercise	60.5 (*31.6*)	73.2 (*26.4*)	**	62.0 (*29.4*)	73.0 (*24.5*)	
Next-day soreness after non-strenuous activities	68.6 (*22.2*)	78.8 (*18.4*)	**	61.1 (*30.5*)	75.2 (*21.2*)	*
Mentally tired after slightest effort	55.9 (*27.3*)	68.2 (*21.8*)	**	63.0 (*29.0*)	68.8 (*23.1*)	
Minimum exercise makes you tired	66.6 (*27.0*)	81.7 (*18.4*)	***	60.6 (*28.0*)	75.0 (*20.0*)	*
Physically drained / sick after mild activity	65.2 (*27.5*)	76.7 (*20.2*)	**	56.7 (*34.0*)	69.3 (*22.2*)	
Sleep						
Unrefreshing sleep	73.5 (*24.3*)	81.8 (*18.1*)		79.3 (*16.9*)	84.3 (*16.6*)	
Need to nap during each day	53.2 (*31.2*)	51.1 (*30.4*)		46.2 (*35.3*)	54.1 (*32.5*)	
Problems falling asleep	56.3 (*34.6*)	62.0 (*30.1*)		51.4 (*29.6*)	52.1 (*34.5*)	
Problems staying asleep	56.3 (*30.6*)	65.9 (*29.6*)		43.5 (*27.5*)	53.0 (*34.3*)	
Waking up early in the morning	43.4 (*30.1*)	52.6 (*34.4*)		38.9 (*27.9*)	48.4 (*34.1*)	
Sleeping all day / staying awake all night	15.2 (*26.9*)	17.5 (*27.3*)		10.6 (*18.3*)	20.4 (*27.0*)	

Pain						
Muscle pain	50.4 (*27.4*)	68.6 (*23.3*)	***	64.8 (*21.9*)	75.9 (*24.1*)	*
Pain in multiple joints	35.8 (*34.0*)	59.7 (*29.5*)	***	57.4 (*32.9*)	71.1 (*25.8*)	*
Eye pain	25.0 (*27.1*)	38.0 (*28.7*)	**	32.4 (*28.9*)	43.3 (*26.5*)	
Chest pain	18.9 (*23.3*)	30.1 (*24.8*)	**	21.2 (*24.7*)	30.5 (*25.4*)	
Bloating	30.7 (*28.3*)	53.6 (*24.3*)	***	26.4 (*27.0*)	51.3 (*30.7*)	***
Abdomen / stomach pain	24.1 (*22.7*)	47.2 (*23.8*)	***	21.0 (*25.7*)	49.4 (*30.7*)	***
Headaches	41.7 (*24.7*)	53.9 (*24.4*)	**	48.6 (*25.1*)	65.5 (*22.4*)	**
Neurocognitive						
Muscle twitches	22.4 (*20.4*)	37.6 (*26.9*)	***	27.4 (*30.2*)	42.7 (*30.1*)	*
Muscle weakness	53.9 (*29.6*)	66.6 (*24.3*)	**	55.3 (*28.3*)	71.1 (*22.6*)	**
Sensitivity to noise	54.9 (*29.8*)	66.3 (*25.7*)	**	37.5 (*33.5*)	61.6 (*29.0*)	**
Sensitivity to bright lights	46.1 (*32.1*)	65.2 (*24.0*)	***	41.3 (*30.2*)	57.3 (*28.4*)	*
Problems remembering things	60.8 (*23.8*)	68.9 (*20.4*)	*	61.5 (*24.2*)	75.2 (*20.3*)	**
Difficulty paying attention for long periods of time	64.6 (*28.2*)	77.4 (*21.5*)	**	70.0 (*21.3*)	77.8 (*20.8*)	
Difficulty expressing thoughts	54.9 (*25.5*)	67.1 (*21.3*)	**	55.8 (*27.7*)	67.2 (*23.9*)	
Difficulty understanding things	37.3 (*22.7*)	54.1 (*21.2*)	***	51.9 (*28.2*)	57.9 (*27.2*)	
Can only focus on one thing at a time	60.6 (*31.5*)	74.9 (*22.8*)	***	63.0 (*24.9*)	68.4 (*25.7*)	
Unable to focus vision / attention	38.6 (*26.2*)	56.8 (*22.4*)	***	49.0 (*29.8*)	53.4 (*24.8*)	
Loss of depth perception	14.6 (*25.3*)	31.6 (*32.8*)	***	17.9 (*32.6*)	35.0 (*32.3*)	*

Slowness of thought	51.1 (*24.3*)	63.9 (*22.0*)	***	53.4 (*26.6*)	62.3 (*24.9*)	
Absent-mindedness	52.2 (*29.1*)	65.2 (*23.6*)	**	52.4 (*28.3*)	68.5 (*25.6*)	*
Autonomic						
Bladder problems	19.1 (*26.4*)	38.1 (*34.2*)	***	15.5 (*22.6*)	35.7 (*33.8*)	**
Irritable bowel problems	29.6 (*28.9*)	56.4 (*28.5*)	***	31.7 (*29.6*)	57.0 (*34.0*)	**
Nausea	22.1 (*20.3*)	38.3 (*24.1*)	***	24.5 (*19.5*)	43.3 (*26.2*)	**
Feeling unsteady on feet	28.8 (*20.5*)	50.2 (*26.5*)	***	34.6 (*24.6*)	52.6 (*28.0*)	**
Shortness of breath	29.3 (*26.1*)	44.0 (*25.2*)	***	21.5 (*19.3*)	42.8 (*27.8*)	***
Dizziness / fainting	29.5 (*24.5*)	44.5 (*24.0*)	***	38.5 (*25.5*)	48.1 (*30.1*)	
Irregular heart beats	20.2 (*22.9*)	38.3 (*27.0*)	***	24.5 (*27.3*)	40.0 (*32.4*)	*
Neuroendocrine						
Losing / gaining weight without trying	31.6 (*35.0*)	42.6 (*33.2*)	*	38.5 (*36.0*)	51.3 (*34.1*)	
No appetite	15.9 (*18.4*)	26.3 (*25.6*)	**	15.0 (*21.9*)	34.5 (*32.0*)	**
Sweating hands	8.6 (*19.1*)	14.5 (*23.1*)		9.5 (*18.1*)	28.1 (*32.6*)	**
Night sweats	26.6 (*29.2*)	40.0 (*30.9*)	**	26.0 (*28.4*)	38.4 (*30.2*)	
Cold limbs	44.8 (*30.5*)	56.9 (*29.7*)	**	36.5 (*29.3*)	58.6 (*33.0*)	**
Chills / shivers	25.0 (*25.3*)	41.4 (*27.9*)	***	22.6 (*23.7*)	42.5 (*30.7*)	**
Feeling hot / cold for no reason	40.9 (*28.3*)	58.3 (*27.5*)	***	44.0 (*27.7*)	59.9 (*28.2*)	*
Feeling like you have a high temperature	18.9 (*26.4*)	40.4 (*29.4*)	***	27.6 (*35.0*)	47.2 (*29.9*)	*
Feeling like you have a low temperature	18.9 (*26.7*)	34.0 (*29.5*)	***	10.9 (*22.5*)	29.6 (*30.9*)	**

Alcohol intolerancef	35.2 (*39.3*)	58.3 (*37.8*)	***	27.5 (*32.1*)	56.9 (*35.3*)	***
Immune						
Sore throat	29.8 (*25.1*)	39.6 (*22.5*)	**	24.0 (*22.5*)	50.2 (*28.3*)	***
Tender lymph nodes	29.4 (*26.0*)	50.6 (*28.1*)	***	20.0 (*21.0*)	46.7 (*29.3*)	***
Fever	8.1 (*15.1*)	18.9 (*21.8*)	***	11.5 (*20.4*)	27.2 (*26.8*)	*
Flu-like symptoms	36.6 (*22.7*)	63.9 (*23.5*)	***	36.5 (*30.0*)	62.5 (*21.8*)	***
Sensitivity to smells/foods/medications/chemicals	36.0 (*36.0*)	66.8 (*30.7*)	***	22.6 (*29.6*)	54.7 (*35.5*)	***

*$p < 0.05$;
**$p < 0.01$;
***$p < 0.001$