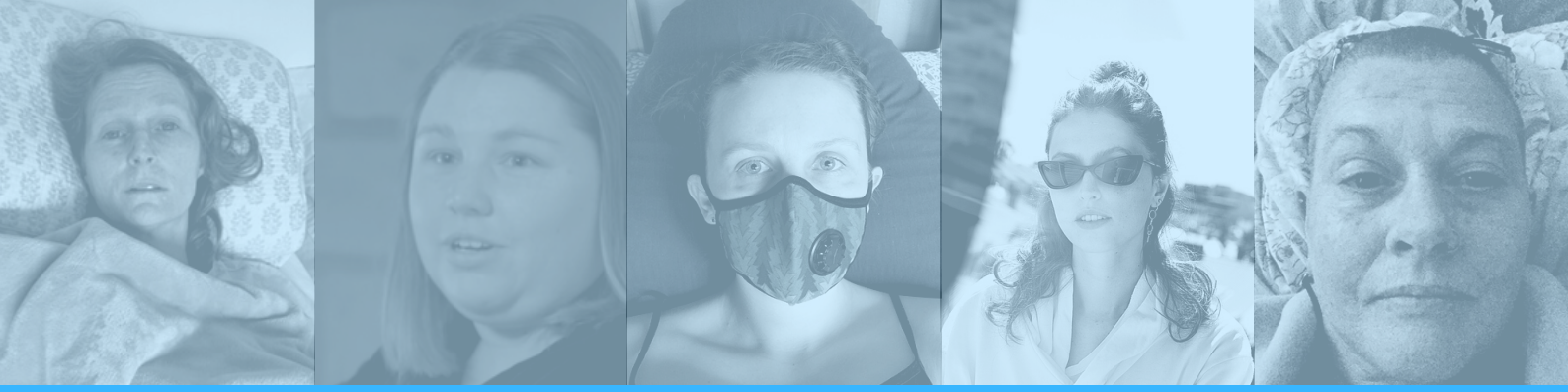

State of the Nation

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), Long COVID and post-infection diseases

Because people with ME/CFS matter

emerge australia

November 2022

Foreword

Long COVID and ME/CFS: a unique opportunity

All of us are no doubt hoping that we are in the final phase of the COVID-19 pandemic and that life will soon return to normal. But many also understand that this may not be true for everyone, with some continuing to experience the persistent symptoms of Long COVID (LC) stemming from causes that medical specialists are as yet unable to identify.

LC looks very similar to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) that has long been a distressing and confusing condition for both patients and their physicians. With LC, both due to the precise diagnostic test for the triggering virus infection that has been used and the numbers involved, we have substantial, well-defined clinical cohorts with a known virus trigger that are available for continuing analysis with the best that modern molecular and imaging technology has to offer. This provides a unique opportunity to break open the whole LC/ME/CFS story in ways that will potentially lead to better treatments and full recovery.

With sophisticated clinical and research expertise, and an excellent public health system, Australia is in a unique position to make major contributions in this complex and difficult area.

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22 March 2022

Executive Summary

Australia is experiencing a tsunami of post-infection disease. This tsunami started with the first wave of COVID-19 infections in early 2020 and continues to grow. But those with Long COVID are not the only people living with post-infection disease.

Up to 250,000 Australians live with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a complex, debilitating, multisystem disease. For a majority of patients, ME/CFS develops after contracting a viral or bacterial infection. Once fit, healthy and active, people with ME/CFS live with a range of debilitating symptoms including post-exertional malaise, cognitive impairment, reduced energy and an inability to function at pre-illness levels.

Striking links have already been made between ME/CFS and Long COVID, suggesting they are very similar diseases.[1] Recent research suggests up to 45% of people with Long COVID meet the diagnostic criteria for ME/CFS.[2]

Researchers, government and healthcare providers do not need to reinvent the wheel: Emerge Australia already knows how best to support this tsunami of Long COVID patients because of our knowledge of ME/CFS. Emerge Australia can also anticipate the challenges people with Long COVID will face in navigating and accessing the health care system and social support and care.[3] Action must be taken now to improve awareness, knowledge and reduce barriers to accessing appropriate and timely care.

The burden of disease for ME/CFS is significant because the disease is so disabling and prevalent. People living with ME/CFS have just as poor or poorer employment, social and physical health outcomes than many other well-known diseases such as multiple sclerosis, HIV/AIDS, cancer and depression.[4,5,6] It is estimated ME/CFS costs the economy $14.8 billion annually.[7] Long COVID will only add to this burden, with predictions forecasting between 40,000 and 325,000 Australians might develop Long COVID in coming months.[8]

[1] S. Marshall-Gradisnik & N. Eaton-Fitch. 'Understanding myalgic encephalomyelitis' *Science*, 377:6611, (2022).
[2] C. Kedor, et al. 'A prospective observational study of post-COVID-19 chronic fatigue syndrome following the first pandemic wave in Germany and biomarkers associated with symptom severity'. *Nature communications*, 13:1 (2022).
[3] N. Goldberg, et al. 'A new clinical challenge: supporting patients coping with the long-term effects of COVID-19,' *Fatigue: Biomedicine, Health & Behavior*, (2022) DOI: 10.1080/21641846.2022.2128576.
[4] C. Kingdon, et al. 'Functional Status and Well-Being in People with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Compared with People with Multiple Sclerosis and Healthy Controls' *Pharmaco Economics – Open,* 2 (2018).
[5] L. Nacul, et al. 'The functional status and well being of people with myalgic encephalomyelitis/chronic fatigue syndrome and their carers' *BMC Public Health,* 11 (2011).
[6] M. Núñez, et al. 'Health-related quality of life in chronic fatigue syndrome versus rheumatoid arthritis as control group' *Journal of Chronic Fatigue Syndrome,* 14 (2008).
[7] S. Close, et al. 'The Economic Impacts of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome in an Australian Cohort' *Frontiers in Public Health*, 8 (2020).
[8] M. Henscher and MR Angeles 'Potential scale of Long COVID cases from the Omicron wave in Australia: Summer 2021-2022' *Institute for Health Transformation*, Deakin University, Melbourne, (2021). Available at: https://iht.deakin.edu.au/wp-content/uploads/sites/153/2022/02/Long-COVID-Omicron-briefing-paper-IHT-02-2022.pdf.

To reduce the impact of this burden, a number of systems and policies need to change. This change must bring proper recognition, research and support to the large cohort of people with ME/CFS and Long COVID. Emerge Australia has identified the following priority actions to increase support for people living with ME/CFS, Long COVID and post-infection disease:

1. GP education

Educate doctors to diagnose ME/CFS and Long COVID and provide evidence-based support to people with these diseases.

2. Coordination of care and allied health support services

Create an Optimal Care Referral Pathway placing people with ME/CFS at the centre of care decisions.

3. Funding for collaborative translational research

Ensure knowledge from ME/CFS research and the emerging field of Long COVID is shared and integrated.

4. Australian Clinical Guidelines

Update Australia's clinical guidelines to increase safety and quality of care and establish shared care.

5. Recommendations for policy change

Changes to policy are required to:

a) create two new strategies to create sector wide focus and collaboration on Long COVID, ME/CFS and other related post-infection diseases, with the creation of:
   i. Post-infection Disease National Health Priority Area; and
   ii. National Post-infection Disease Strategy.

b) expand access to telehealth and provide equitable access to government support for people with ME/CFS, Long COVID and post-infection diseases. This includes MBS funding and specific item numbers for dedicated ME/CFS and Long COVID chronic disease management plans that incorporate clinically indicated adequate home visits and telehealth consultations for house-bound patients.

The needs of people with ME/CFS have been overlooked for too long. The emergence of Long COVID has finally shone a spotlight on the limited understanding and long-term pervasive nature of ME/CFS and post-infection diseases.

Greater understanding, education and access to services and research funding will change the current, bleak outlook that people with ME/CFS, Long COVID and post-infection diseases face. Tailored and appropriate health care and support will enable individuals to achieve a better quality of life, and for some to potentially return to work, study and social activities.

Contents

Introduction

People with ME/CFS have long been overlooked by research, government and healthcare organisations. This report describes ME/CFS, its significant burden and the priority actions that must be taken to reduce disease burden, especially for those who live with its debilitating effects. As the number of people with Long COVID continues to rise, so will the burden of ME/CFS in Australia.

Long COVID presents an important opportunity for ME/CFS, and patients living with the disease, to experience the change required so they can finally receive equitable funding, research and support. Patients with ME/CFS have been fighting for decades to have their symptoms and experiences acknowledged and to gain access to necessary health and social care. Government and the healthcare system must learn from this history of neglect to ensure thousands of Long COVID patients and new ME/CFS patients do not experience the same indifference. For the thousands of Australians with ME/CFS who have already lost years of their lives to this disease, trust in health and social care systems must be rebuilt so they are seen, understood and supported.

This document is divided into three sections. Section *1. ME/CFS, Long COVID and post-infection diseases* introduces the critical challenge of ME/CFS: lack of recognition and inadequate biomedical understanding. While ME/CFS has been described in research for over 200 years, it has been largely overlooked globally by the medical community and governments. As a result, ME/CFS research has been severely underfunded, which has led to a limited understanding of the underlying pathophysiology of the disease. This section presents what is known about ME/CFS, including current biomedical knowledge and gaps, estimates regarding prevalence, prognosis and mortality, and the relationship with Long COVID.

Section *2. State of the Nation: Burden of ME/CFS* describes the lived experience of Australian ME/CFS patients in 2022 in relation to disability and wellbeing, economic outcomes, and access to appropriate care. For a person with ME/CFS, every aspect of life is impacted by their symptoms. Even those who are moderately unwell are often socially isolated, unable to work and often require assistance with activities of daily living. This has significant implications for the Australian economy and for the individual, with many ME/CFS patients living below the poverty line. Despite the severity and prevalence of ME/CFS, the lack of biomedical understanding of the disease, as described at section 1., has contributed to an entrenched misunderstanding and disbelief of the disease and patients by medical practitioners. Implications for the availability of safe, appropriate care are also described.

Finally, section *3. Priority actions to improve outcomes for people living with ME/CFS and Long COVID* draws on the previous two sections to outline actions to help people with ME/CFS and post-infection diseases, including Long COVID. Changes are required across our health and social care systems. General practitioners urgently need updated clinical guidelines to speed up diagnosis and implementation of safe management techniques and they need to be educated about how to use these guidelines in clinic. Greater funding for non-clinical services and allied health professionals through an Optimal Care Referral Pathway will help people with ME/CFS access a range of health care practitioners who can help them adapt to life with chronic illness. In addition to more research into ME/CFS, researchers should use the knowledge gained from ME/CFS to inform Long COVID research. Finally, recommendations are made for policy changes so individuals have equitable access to the NDIS, Disability Support Pension and telehealth. Current barriers to access need to be addressed as a matter of urgency, to ease the burden of daily living with this chronic and disabling disease.

1. ME/CFS, Long COVID and post-infection diseases

This section describes existing knowledge about ME/CFS. Subsection 1.1 explains the symptoms of ME/CFS and recommended diagnostic criteria. Subsection 1.2 discusses what is known about the prevalence and mortality of the disease. The existing, limited biomedical understanding of ME/CFS is included in subsection 1.3, and reasons for such limited understanding are explained in subsection 1.4. Finally, known links between Long COVID, ME/CFS and post-infection diseases are explained in subsection 1.5.

1.1. What is ME/CFS?

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a multisystemic, highly disabling disease characterised by post-exertional malaise (PEM). PEM is a worsening of symptoms such as fatigue, pain and cognitive impairment following physical or mental effort. Other common symptoms of ME/CFS include problems with sleep, thinking and concentrating, orthostatic intolerance, dizziness and hypersensitivity to light and sound.

ME/CFS is classified as a neurological disorder by the World Health Organization. It is a complex, multisystem disease that affects many parts of the body such as the brain, muscles, digestive, immune and cardiac systems. While research is yet to confirm the cause of ME/CFS, a majority of people with ME/CFS can attribute onset of symptoms after viral infection.[9] Other triggers of ME/CFS may include bacterial infection, physical trauma, environmental toxins and physical, mental or emotional stress, while genetic factors may contribute to an individual's susceptibility to these triggers.

The US National Academy of Medicine (NAM) estimates 90% of people living with ME/CFS are undiagnosed.[10] The NAM developed diagnostic criteria in 2015 to make it easier for doctors to diagnose ME/CFS. Emerge Australia recommends the US National Academy of Medicine (NAM) criteria for clinical diagnosis of ME/CFS. The symptoms included in the NAM criteria are not the only symptoms that people with ME/CFS experience, nor are they the only common symptoms. They are the minimum symptoms required to meet the diagnosis of ME/CFS using the NAM criteria.

[9] H. Naess, et al. 'Postinfectious and chronic fatigue syndromes: clinical experience from a tertiary-referral centre in Norway' *Vivo*, 24:2 (2010).
[10] 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' *National Academies Press (US)* (2015).

Symptoms required for a diagnosis of ME/CFS using the NAM criteria[11]

- **substantial reduction** in the ability to engage in pre-illness activity. This must have persisted for six months or more, and be accompanied by profound fatigue that isn't substantially improved with rest
- **post-exertional malaise (PEM)**, which is the worsening of symptoms following physical or mental exertion
- **unrefreshing sleep**

Plus, either:

- **cognitive impairment** (problems with memory, thinking or concentration)
- **orthostatic intolerance** (problems with sitting or standing, that may include dizziness, sweating, nausea and reduce or resolve when lying down)

1.2. Prevalence, prognosis and mortality

The lack of funding over many decades for ME/CFS research means there are large gaps in our understanding of prevalence, prognosis and mortality. Prevalence provides an overall picture of how many people have a particular disease, which informs disease burden. Long COVID means the prevalence of ME/CFS is expected to rise.

Prevalence

Accepted prevalence estimates vary from 0.4 to 1% of people living with ME/CFS.[12,13] Based on these numbers it is estimated up to 250,000 people live with ME/CFS in Australia. However, this is most likely an underestimate due to underdiagnosis and inaccurate records. Up to 90% of people may be undiagnosed or misdiagnosed.[14, 15, 16] Additionally, when patients visit their health care provider, it is likely ME/CFS is not reliably coded, which contributes to inaccuracies in the reported prevalence.[17]

While ME/CFS can affect anyone of any age, gender or socio-economic or cultural background, there are some noteworthy patterns:

- Women are three times more likely to be affected than men[18]
- The two most common ages of onset occur between the ages of 10 to 19 years and 30 to 39 years. The average age of onset is 33 years[19, 20]

[11] Centers for Disease Control and Prevention. 'CDC: IOM 2015 Diagnostic Criteria' (2015). Available at: https://www.cdc.gov/me-cfs/healthcare-providers/diagnosis/iom-2015-diagnostic-criteria.html.
[12] L. Jason, et al. 'A community-based study of Chronic Fatigue Syndrome' *Arch Int Med,* 159 (1999).
[13] L. Lorusso, et al. 'Immunological aspects of chronic fatigue syndrome' *Autoimmun Rev,* 8 (2009).
[14] Committee on the Diagnostic Criteria for ME/CFS. 'Beyond Myalgic Encephalomyelitis'.
[15] M. Reyes, et al. 'Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas' *Arch Intern Med,* (2003).
[16] Jason. 'A community-based study of chronic fatigue syndrome'.
[17] Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Advisory Committee. 'Report to the NHMRC Chief Executive Officer' *Australian Government*, (2019), p. 10.
[18] Committee on the Diagnostic Criteria for ME/CFS. 'Beyond Myalgic Encephalomyelitis'.
[19] P. Rowe, et al. 'Myalgic encephalomyelitis/chronic fatigue syndrome diagnosis and management in young people: a primer' *Front Pediatr*, 5 (2017), p. 121.
[20] I. Bakken, et al. 'Two age peaks in the incidence of chronic fatigue syndrome/myalgic encephalomyelitis: a population-based registry study from Norway 2008-2012' *BMC Med*, 12:1 (2014), p. 167.

- Approximately 25% of people experience severe symptoms, leaving them housebound or bedbound.[21] (see 2.1 Disability and wellbeing).

Despite the "Yuppie Flu" myth that ME/CFS is a disease of middle-class white people, research shows that people from minority groups and lower socio-economic status have as high, or higher, prevalence rates, than middle class white people.[22] Despite this, research studies continue to largely include only white people.

Prognosis

Long term prognosis of ME/CFS is difficult to predict. While some patients improve over time, full recovery, defined as a return to pre-illness functioning, is not common.[23, 24, 25] Recovery rates are estimated to be just 5-10%.[26, 27] Prognosis is better for young people (children and adolescents) and those with mild forms of the disease than it is for those middle-aged and older, and for those who are more severely unwell.[28]

ME/CFS can take a relapsing/remitting course, like multiple sclerosis.[29, 30, 31] This makes it difficult to determine whether cases of recovery are more accurately in remission, and at risk of relapse in the future. In up to 20% of cases the disease worsens over time.[32]

Mortality

It is similarly unclear whether ME/CFS increases risk for earlier mortality. Some studies suggest an elevated risk of suicide and earlier mortality compared to national norms.[33] However, this is another area where more research is required.

[21] Committee on the Diagnostic Criteria for ME/CFS. 'Beyond Myalgic Encephalomyelitis'.
[22] S. Kamaldeep, et al. 'Chronic fatigue syndrome in an ethnically diverse population: the influence of psychosocial adversity and physical inactivity' *BMC Medicine*, 9:26 (2011).
[23] International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. 'Chronic Fatigue Syndrome Myalgic Encephalomyelitis Primer for Clinical Practitioners' (2014) available at https://www.massmecfs.org/images/pdf/Primer_2014.pdf.
[24] J. Baraniuk. 'Chronic Fatigue Syndrome: BMJ Best Practice guideline' *BMJ* (2017).
[25] L. Jason, et al. 'A natural history study of chronic fatigue syndrome' *Rehabilitation Psychology,* 56:1 (2011).
[26] Baraniuk. 'Chronic Fatigue Syndrome: BMJ Best Practice guideline'.
[27] R. Nisenbaum, et al. 'A population-based study of the clinical course of chronic fatigue syndrome' *Health and Quality of Life Outcomes*, 1:1 (2003).
[28] International Association for CFS/ME. 'Chronic fatigue syndrome/myalgic encephalomyelitis: Primer for clinical practitioners'.
[29] International Association for CFS/ME. 'Chronic fatigue syndrome/myalgic encephalomyelitis: Primer for clinical practitioners'.
[30] G. Morris, and M. Maes. 'Myalgic encephalomyelitis/chronic fatigue syndrome and encephalomyelitis disseminata/multiple sclerosis show remarkable levels of similarity in phenomenology and neuroimmune characteristics' *BMC Medicine*, 11:1 (2005).
[31] L. Jason, S. Torres-Harding, and M. Njoku. 'The face of CFS in the US' *CFIDS Chronicle*, (2006).
[32] International Association for CFS/ME. 'Chronic fatigue syndrome/myalgic encephalomyelitis: Primer for clinical practitioners'.
[33] S. McManimen, et al. 'Mortality in Patients with Myalgic Encephalomyelitis and Chronic Fatigue Syndrome. Fatigue: biomedicine, health & behavior' 4:4, (2016).

1.3. Biomedical understanding of ME/CFS

Persistent underfunding of research into ME/CFS has led to poor understanding of its pathophysiology. Another limitation is the lack of a consensual study protocol, making comparison with other findings difficult. However, some gains have been made identifying body systems affected by the disease. A sample of these systems and their features is provided in Table 1, demonstrating the biological and wide-ranging impact of the disease.

System	**Tissue/Cell**	**Feature**
Metabolomics and mitochondria	Amino acid metabolism	Abnormalities in cellular energy production by mitochondria, including an increased use of amino acids over sugars.[34, 35, 36, 37]
	Slowed cellular metabolism	Significant decreases in metabolites indicating slowed metabolism overall. Changes in important cell membrane compounds, like sphingolipids and cholesterol.[38, 39, 40]
	Fatty acid processing	Dysregulation of fatty acid metabolism. [14] metabolites significantly altered in people with ME, including high heme levels; low cAMP (an important second messenger necessary to activate many proteins in cells); and several molecules associated with ketosis, the breakdown of fats in place of sugars.[41, 42]
Autonomic Nervous System		Measurable alterations in the functions of the cardiovascular system and autonomic nervous system have been observed in people with ME. Reduced blood volume and blood flow, issues with regulating heart rate and blood pressure, a lower VO2 max during exercise testing, and an inability to replicate levels of exertion on successive days have been found in multiple studies.[43]
Central Nervous System	Neuron	The symptomatology is related to a variety of sources of chronic neurological disturbance and associated distortions and chronicity in noxious sensory signalling and neuroimmune activation.[44]
	Glial cells	There is a significant blood–brain barrier permeability, microglia activation through toll-like receptors (TLR) signalling, secretion of IL-1B, upregulation of 5-HTT in astrocytes, reduced extracellular 5-HT levels, and hence a reduced activation of 5-HT receptors.[45]

[34] D. Missailidis, et al. 'An isolated Complex V inefficiency and dysregulated mitochondrial function in immortalized lymphocytes from ME/CFS patients' *Int. J. Mol. Sci.* 21:3 (2020).
[35] D. Missailidis, et al. 'Dysregulated Provision of Oxidisable Substrates to the Mitochondria in ME/CFS Lymphoblasts' *Int. J. Mol. Sci*, 22 (2021).
[36] Ø. Fluge, et al. 'Metabolic profiling indicates impaired pyruvate dehydrogenase function in myalgic encephalopathy/chronic fatigue syndrome' *JCI Insight,* 22:1:21 (2016).
[37] C. Armstrong, et al. 'Metabolic profiling reveals anomalous energy metabolism and oxidative stress pathways in chronic fatigue syndrome patients' *Metabolomics* 11, (2015).
[38] Naviaux et al. 'Metabolic features of chronic fatigue syndrome' *PNAS*, (2016).
[39] C. Armstrong, et al. 'The association of fecal microbiota and fecal, blood serum and urine metabolites in myalgic encephalomyelitis/chronic fatigue syndrome' *Metabolomics* 13:8 (2017).
[40] D. Nagy-Szakal, et al. 'Insights into myalgic encephalomyelitis/chronic fatigue syndrome phenotypes through comprehensive metabolomics' *Sci Rep* 8:10056 (2018).
[41] A. Germain, et al. 'Metabolic profiling of a myalgic encephalomyelitis/chronic fatigue syndrome discovery cohort reveals disturbances in fatty acid and lipid metabolism' *Mol Biosyst*., 31:13:2 (2017).
[42] D. Nagy-Szakal, et al. 'Fecal metagenomic profiles in subgroups of patients with myalgic encephalomyelitis/chronic fatigue syndrome' *Microbiome*. 26:5(1):44 (2017).
[43] For a list of studies, see #ME Action, 'ME Research Summary' (2019), available at: http://www.meaction.net/wp-content/uploads/2019/06/19_MEA_Revised_2019_Research_Summary_190610.pdf, pp 2-4.
[44] L. Komaroff. 'Advances in Understanding the Pathophysiology of Chronic Fatigue Syndrome' *JAMA* (2019).
[45] M. Noda, et al. 'T. Glial Activation and Expression of the Serotonin Transporter in Chronic Fatigue Syndrome' *Front. Psychiatry.* 9:589 (2018).

Central nervous system (cont.)	Neuroimaging	There is currently no neuroimaging finding or specific laboratory test to diagnose ME/CFS. There have been changes reported in brain volume[46, 47, 48], cerebral blood flow[49, 50, 51], anatomy[52, 53] and functional connectivity[54, 55, 56] but their meaning is yet to be determined.
Immune System	Lymphocytes Th1/Th2	Significant bias toward Th2 immune responses in ME/CFS patients leading to an effector memory cell bias toward type 2 responsiveness.[57]
	NK cells	Reduction of cytotoxic activity in ME/CFS, leading to a higher susceptibility of infection.[58]
	B cells	Studies have highlighted B cell response appears dysregulated in ME/CFS, suggesting the ME/CFS immune system is dysfunctional.[59, 60]
Neuroendocrine System	Hypothalamus–pituitary–adrenal (HPA) axis	Dysfunction of the hypothalamus-pituitary adrenal-axis (HPA) has been proposed as a contributing factor of ME/CFS. In a proportion of ME/CFS patients, mild hypocortisolism[61, 62], reduced ACTH responses[63] and enhanced negative feedback responses to glucocorticoids (GCs) have been reported[64, 65].

Table 1: A sample of body systems affected by myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Adapted from [66, 67]

[46] A. Finkelmeyer, et al. 'Grey and white matter differences in Chronic Fatigue Syndrome – A voxel-based morphometry study' *NeuroImage: Clinical,* 17 (2018).
[47] L. Barnden, et al. 'Hyperintense sensorimotor T1 spin echo MRI is associated with brainstem abnormality in chronic fatigue syndrome' *NeuroImage: Clinical,* 20 (2018).
[48] Z. Shan, et al. 'Progressive brain changes in patients with chronic fatigue syndrome: A longitudinal MRI study' *Journal of Magnetic Resonance Imaging,* 44 (2016).
[49] B. Natelson, et al. 'Multimodal and simultaneous assessments of brain and spinal fluid abnormalities in chronic fatigue syndrome and the effects of psychiatric comorbidity' *Journal of the Neurological Sciences,* 375 (2017).
[50] J. He, et al. 'Cerebral vascular control is associated with skeletal muscle pH in chronic fatigue syndrome patients both at rest and during dynamic stimulation' *NeuroImage: Clinical,* 2 (2013).
[51] B. Biswal, P. Kunwar and B. Natelson. 'Cerebral blood flow is reduced in chronic fatigue syndrome as assessed by arterial spin labeling' *Journal of the Neurological Sciences,* 301 (2011).
[52] M. Zeineh, et al. 'Right arcuate fasciculus abnormality in chronic fatigue syndrome' *Radiology,* 274 (2015).
[53] L. Barnden, et al. 'Evidence in chronic fatigue syndrome for severity-dependent upregulation of prefrontal myelination that is independent of anxiety and depression' *NMR Biomedicine* 28:3 (2015).
[54] X. Caseras, et al. 'Probing the working memory system in chronic fatigue syndrome: A functional magnetic resonance imaging study using the n-back task' *Psychosomatic Medicine,* 68 (2006).
[55] C. Gay, et al. 'Abnormal Resting-State Functional Connectivity in Patients with Chronic Fatigue Syndrome: Results of Seed and Data-Driven Analyses' *Brain Connectivity,* 6 (2016).
[56] Z. Shan, et al. 'Brain function characteristics of chronic fatigue syndrome: A task fMRI study' *NeuroImage: Clinical,* 19 (2018).
[57] A. Skowera, A. Cleare and D. Blair. 'High levels of type 2 cytokine-producing cells in chronic fatigue syndrome' *Clin. Exp. Immunol,* 135 (2004).
[58] J. Rivas, et al. 'Association of T and NK Cell Phenotype with the Diagnosis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)' *Front. Immunol*., 9:1028 (2018).
[59] A. Bradley, B. Ford and A. Bansal. 'Altered functional B cell subset populations in patients with chronic fatigue syndrome compared to healthy controls' *Clin. Exp. Immunol.,* 172 (2013).
[60] H. Ono, et al. 'Dysregulation of T and B cells in myalgic encephalomyelitis/chronic fatigue syndrome' *J Neuro Sci*, 381 (2017).
[61] F. van den Eede, et al. 'Hypothalamic-pituitary-adrenal axis function in chronic fatigue syndrome' *Neuropsychobiology* 55 (2007).
[62] L. Tak, et al. 'Meta-analysis and meta-regression of hypothalamic-pituitary-adrenal axis activity in functional somatic disorders' *Biological Psychology* 87 (2011).
[63] M. Demitrack, et al. 'Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome' *Journal of Clinical Endocrinology and Metabolism* 73 (1991).
[64] Van den Eade, 'Hypothalamic-pitutary-adrenal axis function'.
[65] J. Visser, et al. 'Increased sensitivity to glucocorticoids in peripheral blood mononuclear cells of chronic fatigue syndrome patients, without evidence for altered density or affinity of glucocorticoid receptors' *Journal of Investigative Medicine* 49 (2001).
[66] M. Cortes Rivera, et al. 'Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Comprehensive Review' *Diagnostics,* 9:3, 91 (2019).
[67] #ME Action, 'ME Research Summary'.

1.4. Gaps in biomedical understanding of ME/CFS

Despite ME/CFS impacting up to 1% of the population, biomedical research into ME/CFS and post-infection diseases has been critically underfunded for decades in Australia and overseas. For example, the United States National Institutes of Health also does not fund research into ME/CFS reflective of disease burden.[68]

In Australia, most research funding comes from philanthropy.[69] In 2019, NHMRC allocated $4.2m in funding for biomedical research into ME/CFS. This was after more than a decade of no funding. This $4.2 million has been distributed through four research teams to investigate metabolic and biological indicators. These projects are in progress and outcomes reports will not be available for some time.

In addition to being underfunded, the complex nature of ME/CFS creates a challenge for researchers. The diagnosis and treatment of ME/CFS for individuals is confounded by the extensive range, disparity and dissimilarity of presenting symptoms. This contributes to inconsistent use of diagnostic criteria in research and other methodological issues such as small sample sizes, largely due to lack of funding, have hampered progress. As a result, research to date has failed to identify a cause, clinically applicable diagnostic biomarker, effective treatments or a cure.

There has been widespread acknowledgement that more research is urgently needed to fill gaps in our biomedical understanding of the disease, its etiology, pathophysiology, diagnosis and treatment.[70,71,72] *Section 3.3 Funding for collaborative translational research*, expands on priority areas for research funding.

1.5. Relationship with Long COVID

While COVID-19 is a new illness, post-acute sequelae of SARS-CoV-2 infection, referred to as Long COVID[73] in this document, is most likely the latest post-infection disease in a long history. Post-infectious illness consistent with the symptoms of ME/CFS has been described in the scientific literature for over 200 years.[74] Post-infectious illness can be triggered by many different pathogens, such as Epstein Barr virus,[75,76] Ross River virus,[77] Human Herpes Virus 6 (HHV6)[78] and even Ebola virus.[79] The acute symptoms of these illnesses, and the organ damage they cause, can be very

[68] A. Mirin, M Dimmock and L. Jason. 'Research Update: The Relation Between ME/CFS Disease Burden and Research Funding in the USA'. *Work* 66:2 (2020).
[69] ME/CFS Advisory Committee, 'Report to the NHMRC', p. 3.
[70] Committee on the Diagnostic Criteria for ME/CFS. 'Beyond Myalgic Encephalomyelitis', p 225.
[71] Ø. Fluge, K. Tronstad and O. Mella. 'Pathomechanisms and possible interventions in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)', *The Journal of Clinical Investigation*, 131:14 (2021).
[72] ME/CFS Advisory Committee, 'Report to the NHMRC', pp. 16-17.
[73] N. Nabavi. 'Long covid: How to define it and how to manage it' *BMJ (Clinical research ed.),* 370 (2020).
[74] L. Komaroff & W. Lipkin. 'Insights from myalgic encephalomyelitis/chronic fatigue syndrome may help unravel the pathogenesis of postacute COVID-19 syndrome' *Trends in molecular medicine*, 27:9 (2021).
[75] J. Jones, et al. 'Evidence for active Epstein-Barr virus infection in patients with persistent, unexplained illnesses: elevated anti-early antigen antibodies' *Ann Intern Med,* 102 (1985).
[76] P. White, et al. 'Incidence, risk and prognosis of acute and chronic fatigue syndromes and psychiatric disorders after glandular fever' *Br J Psychiatry,* 173 (1998).
[77] I. Hickie, et al. 'Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study' *BMJ,* 333 (2006).
[78] A. Komaroff. 'Is human herpesvirus-6 a trigger for chronic fatigue syndrome?' *J Clin Virol.,* 37 (2006).
[79] L. Epstein, et al. 'Post-Ebola signs and symptoms in U.S. survivors' *N Engl J Med,* 373 (2015).

different. However, the lingering illness following each infection appears to be quite similar, both in symptomatology and underlying biology.[80,81,82]

Current estimates suggest 3% to 11.7% of people who have had COVID-19 will still be experiencing symptoms after 12 weeks[83], and can therefore be classified as having Long COVID.[84] The development of illness post-infection suggests an abnormal immune response is involved in Long COVID and ME/CFS.[85] Redox imbalance, inflammation and problems with energy production at a cellular level may explain the shared symptoms between the two diseases.[86,87]

One recent study found that 25 out of the 29 most commonly reported ME/CFS symptoms were also reported in at least one of the surveyed Long COVID studies. Three of the major symptoms of ME/CFS, fatigue, reduced daily activity and post-exertional malaise, were reported in several of the Long COVID studies. These findings indicate significant overlap between ME/CFS and Long COVID.[88]

It is unsurprising that research is showing up to 45% of Long COVID patients meet the diagnostic criteria for ME/CFS.[89] Despite this, rates of diagnosis of ME/CFS in Long COVID patients are currently low. One of the largest studies to date, which surveyed 3762 people from 56 countries 7 months post COVID infection, found that while many patients reported significant overlap in symptoms, including 89.1% who experienced post-exertional malaise, the hallmark symptom of ME/CFS, only 14.7% of patients had been diagnosed with ME/CFS.[90] It is concerning that few clinicians are thinking of ME/CFS as a diagnosis, despite the significant overlap in the diseases.

If like ME/CFS, 90% of Long COVID patients are misdiagnosed or undiagnosed, the actual numbers of people with Long COVID are already much higher than this research suggests.[91, 92, 93] Long COVID studies such as these imply that there will be a considerable increase in the number of people with ME/CFS in the foreseeable future.[94]

[80] S. Marshall-Gradisnik & N. Eaton-Fitch. 'Understanding myalgic encephalomyelitis' *Science*, 377:6611, (2022).
[81] A. Komaroff and L. Bateman. 'Will COVID-19 Lead to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome?' *Frontiers in Medicine*, 7 (2021).
[82] Komaroff and Lipkin. 'Insights from ME/CFS'.
[83] D. Ayoubkhani, et al. 'Technical article: Updated estimates of the prevalence of post-acute symptoms among people with coronavirus (COVID-19) in the UK: 26 April 2020 to 1 August 2021' *Office for National Statistics* (2021). Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/technicalarticleupdatedestimatesoftheprevalenceofpostacutesymptomsamongpeoplewithcoronaviruscovid19intheuk/26april2020to1august2021#approach-1-.
[84] J. Soriano, et al. 'A clinical case definition of postCOVID-19 condition by a Delphi consensus' *The Lancet Infectious Diseases*. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1.
[85] Komaroff and Lipkin, 'Insights from ME/CFS'.
[86] B. Paul, et al. 'Redox imbalance links COVID-19 and myalgic encephalomyelitis/ chronic fatigue syndrome' *PNAS*, 118:34 (2021).
[87] M. Haffke, et al. 'Endothelial dysfunction and altered endothelial biomarkers in patients with post-COVID-19 syndrome and chronic fatigue syndrome (ME/CFS)'. *J Transl Med* **20**, 138 (2022).
[88] T. Wong and D. Weitzer. 'Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)—A Systemic Review and Comparison of Clinical Presentation and Symptomatology.' *Medicina,* 57:418 (2021).
[89] C. Kedor, et al. 'A prospective observational study of post-COVID-19 chronic fatigue syndrome following the first pandemic wave in Germany and biomarkers associated with symptom severity'. *Nature communications*, 13:1 (2022).
[90] H. Davis, et al. 'Characterizing long COVID in an international cohort: 7 months of symptoms and their impact' *EClinicalMedicine,* 38:101019 (2021).
[91] Committee on the Diagnostic Criteria for ME/CFS. 'Beyond Myalgic Encephalomyelitis'.
[92] Reyes, et al. 'Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas'.
[93] Jason. 'A community-based study of chronic fatigue syndrome'.
[94] Nabavi. 'Long covid: How to define it'.

2. State of the Nation: Burden of ME/CFS

This section describes the burden of disease for ME/CFS. Subsection 2.1 discusses the individual burden on people living with the disease, while 2.2 considers the broader impacts on the economy. The forthcoming wave of people living with Long COVID will significantly add to the individual and system wide implications described here.

It continues to be common for patients to have their symptoms disbelieved and dismissed. In subsection 2.3, the contribution that disbelief makes to inadequate clinical care for individuals is explained.

2.1. Disability and wellbeing

ME/CFS is a debilitating disease, experienced as a permanent disease by most patients.[95, 96] Despite its prevalence, severity and permanent nature for most patients, there is inadequate data explaining disease burden in Australia.[97]

National longitudinal and one-off health and wellbeing research studies rarely consider the impacts of ME/CFS on the Australian population. Australia's national disease survey, the Australian Burden of Disease Study (ABDS), conducted by the Australian Institute of Health and Welfare (AIHW), has not listed ME/CFS as a separate disease since 2003. In the 2011 ABDS study, ME/CFS was excluded as a separate disease due to outdated prevalence estimates used in 2003.[98]

Up-to-date statistics are essential to enable Australia's health and social care systems to support ME/CFS patients, including those who have Long COVID. Emerge Australia advocates for ME/CFS to be included as a separate disease in the next ABDS, and in all subsequent national health surveys. This inclusion was similarly recommended to the NHMRC in 2019.[99]

People with ME/CFS experience a number of symptoms that may contribute to impairment or disability. These symptoms include, but are not limited to, post-exertional malaise, fatigue, cognitive dysfunction, pain, sleep disturbance, and secondary depression or anxiety.[100] Such symptoms impact all facets of life, occupational, educational, social and personal activities. The degree of impairment exceeds that of other well-known diseases such as rheumatoid arthritis, multiple sclerosis, depression, heart disease, cancer and lung disease.[101, 102, 103]

Figure 2 shows ME/CFS patients scored lower than Multiple Sclerosis (MS) patients across all functions measured, with the data particularly stark for social function.

[95] Baraniuk. 'Chronic Fatigue Syndrome: BMJ Best Practice guideline'.
[96] R. Nisenbaum, et al. 'A population-based study of the clinical course of chronic fatigue syndrome' *Health and Quality of Life Outcomes*, 1:1 (2003).
[97] ME/CFS Advisory Committee. 'Report to the NHMRC'.
[98] ME/CFS Advisory Committee. 'Report to the NHMRC', p 9.
[99] ME/CFS Advisory Committee. 'Report to the NHMRC'.
[100] Committee on the Diagnostic Criteria for ME/CFS. 'Beyond Myalgic Encephalomyelitis', pp. 31–33.
[101] C. Kingdon, et al. 'Functional Status and Well-Being in People with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Compared with People with Multiple Sclerosis and Healthy Controls' *PharmacoEconomics- Open,* 2:4 (2018).
[102] L. Nacul, et al. 'The functional status and well being of people with myalgic encephalomyelitis/chronic fatigue syndrome and their carers' *BMC Public Health,* 11 (2011).
[103] M. Núñez, et al. 'Health-related quality of life in chronic fatigue syndrome versus rheumatoid arthritis as control group' *Journal of Chronic Fatigue Syndrome,* 14 (2008).

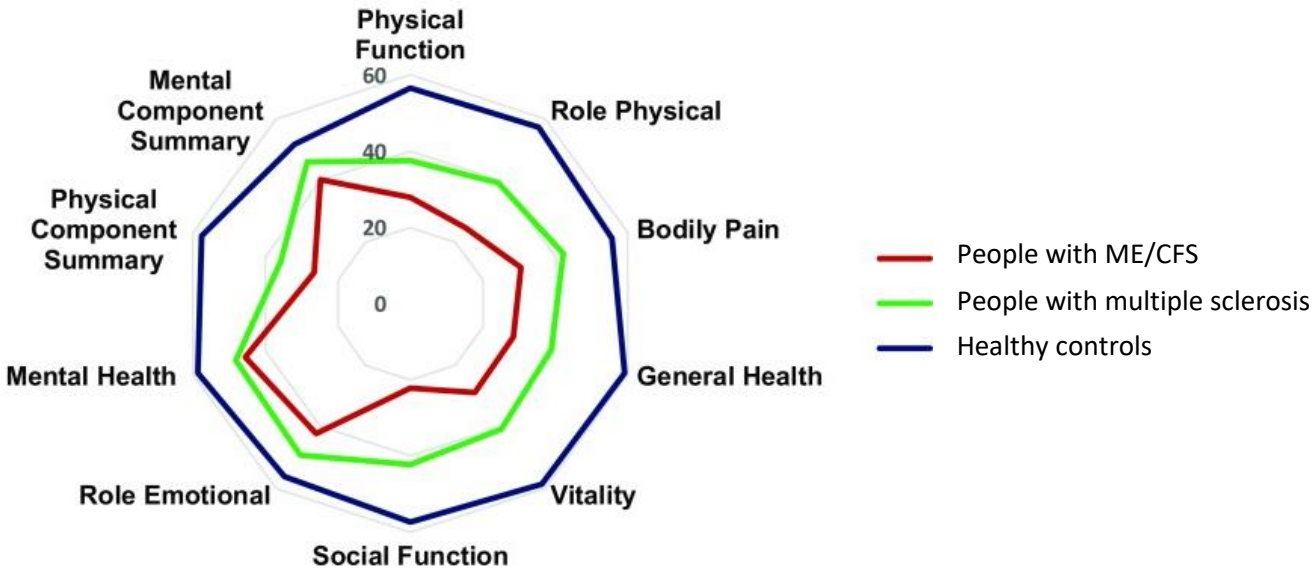

Figure 1: People with ME/CFS have worse functional measures than people with Multiple Sclerosis[104]

Emerge Australia's robust health and wellbeing survey, conducted every three years, supports this data. Of the 1055 people surveyed in 2019 who live with ME/CFS, 85% said that ME/CFS had significantly affected their ability to engage in social activities. This rose to 98% for people with severe or very severe symptoms. This indicates significant wellbeing implications for people living with ME/CFS and highlights need for social support.

Figure 1 also shows people with ME/CFS score significantly lower than those with MS in the areas of physical capacity, pain and general health. Despite the overall greater impact of ME/CFS on wellbeing, ME/CFS patients' mental health is generally no worse than people with MS, although it is unsurprisingly poorer than for healthy controls.

2.2. Economic impacts

Data on the impact of ME/CFS on the Australian economy is scarce. However, given that most patients experience ME/CFS as a permanent disease, the lifelong cost to the individual and Australia's economy is significant. The most recent estimate of economic impact estimated cost to the Australian economy in 2020 was $14.5 billion.[105] 70% of this was due to loss of income, 24% to direct personal out of pocket costs and 6% incurred as a cost to government and the health care system.[106]

[104] Kingdon, et al. 'Functional Status and Well-Being in People with Myalgic Encephalomyelitis'.
[105] Close, et al. 'The Economic Impacts of Myalgic Encephalomyelitis'.
[106] Close, et al. 'The Economic Impacts of Myalgic Encephalomyelitis'.

More data exists about the financial burden of ME/CFS on the individual. ME/CFS affects the individual's economic position in a number of ways. Capacity to work is typically severely affected with high unemployment rates.[107] As shown in Figure 2, people with ME/CFS are able to work less hours per week than people with MS.[108]

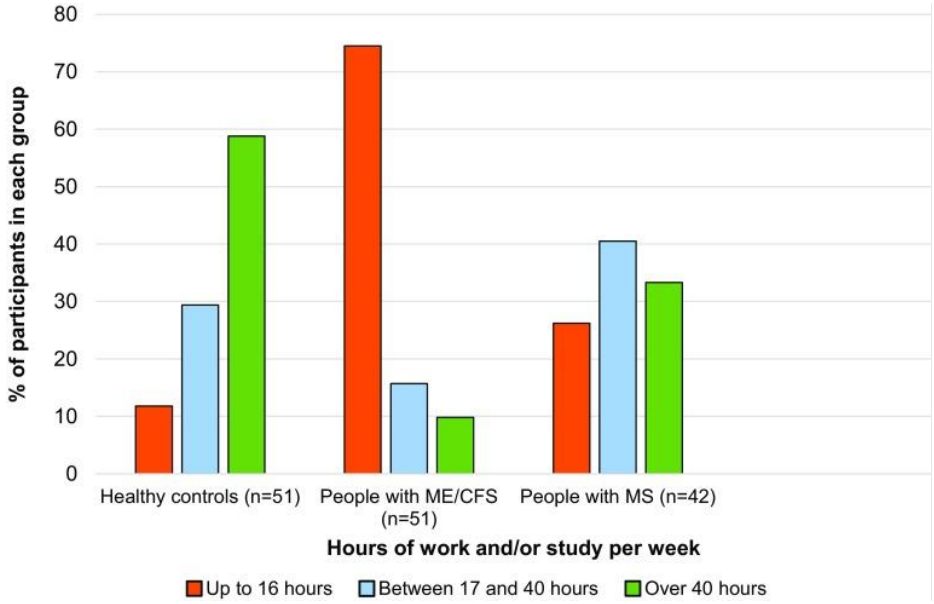

Figure 2: Work/study capacity by hours per week, comparing healthy people with ME/CFS and multiple sclerosis[109]

Emerge Australia's health and wellbeing survey found 89% of respondents ceased or significantly reduced paid work after illness onset, and more than two-thirds of patients live below the poverty line.[110] Another study found unemployment rates ranged from 35% to 69%.[111]

The total average, annual cost per person with ME/CFS in Australia is $75,697. Most of this cost was borne by the patient at $71,215, compared to healthcare costs borne by the government at $4,482.[112]

People with ME/CFS spend considerably more on health care than the general population and visit healthcare providers more often.[113, 114] This is despite most experiencing difficulties accessing healthcare due to their illness and financial considerations, further described at sections 2.3 and 3.[115, 116, 117]

[107] Committee on the Diagnostic Criteria for ME/CFS. 'Beyond Myalgic Encephalomyelitis'.
[108] Kingdon, et al. 'Functional Status and Well-Being in People with Myalgic Encephalomyelitis'.
[109] Kingdon, et al. 'Functional Status and Well-Being in People with Myalgic Encephalomyelitis'.
[110] Emerge Australia. 'Health and Wellbeing Survey 2019', available at https://www.emerge.org.au/health-and-wellbeing-survey-2019.
[111] R. Taylor and G. Kielhofner. 'Work-related impairment and employment-focused rehabilitation options for individuals with chronic fatigue syndrome: A review' *Journal of Mental Health,* 14:3 (2005).
[112] Close, et al. 'The Economic Impacts of Myalgic Encephalomyelitis'.
[113] S. Twemlow, et al. 'Patterns of utilization of medical care and perceptions of the relationship between doctor and patient with chronic illness including chronic fatigue syndrome' *Psychological Reports,* 80:2 (1997).
[114] S. Thanawala and R. Taylor. 'Service utilization, barriers to service access, and coping in adults with chronic fatigue syndrome' *Journal of Chronic Fatigue Syndrome,* 14:1 (2007).
[115] J. Lin, et al. 'The economic impact of chronic fatigue syndrome in Georgia: Direct and indirect costs' *Cost Effectiveness and Resource Allocation*, 9:1 (2011).
[116] Committee on the Diagnostic Criteria for ME/CFS. 'Beyond Myalgic Encephalomyelitis', pp. 31-33.
[117] Thanawala and Taylor. 'Service utilization'.

ME/CFS also has a profound impact on carers, particularly those who provide support to the 25% of patients who are house or bed-bound. Emerge Australia's 2019 health and wellbeing survey reported 90% of carers were financially unsupported in their role as carer.[118] This causes inter-generational financial burden in the case of parents, and compounds financial stress for domestic partners.[119]

2.3. Impacts of disbelief and inadequate clinical care

Despite being proven not to be a psychiatric illness, many medical practitioners continue to deny the biological and pathological roots of ME/CFS,[120] making it difficult for patients to access appropriate care. Only 31% of respondents to Emerge Australia's 2019 survey regarded health professionals as a key source of information about their disease.[121] Dismissive attitudes by many doctors have contributed to persistent misconceptions about ME/CFS. Ongoing, inadequate teaching of ME/CFS to undergraduate and post-graduate students perpetuates this cycle.[122]

Numerous research studies have identified patients feeling dismissed, negatively stereotyped and stigmatised after attending health care services.[123, 124, 125] ME/CFS patients whose disease is questioned and stigmatised by clinicians, family and friends are more likely to experience suicidal ideation than those who do not experience such stigma.[126] Unnecessarily, the same mistakes are being made with Long COVID.[127]

Delays in diagnosis

GPs' lack of knowledge and understanding of ME/CFS often leads to long delays in diagnosis.[128] From onset of symptoms, it takes on average takes two to five years to receive a diagnosis of ME/CFS. During this delay in diagnosis, patients can experience exacerbation of symptoms and disability,[129] which can be permanent.

Decades of poor experiences with medical services have left many patients disempowered, and it is crucial that efforts are made to build trusting relationships between practitioners and those in their care. See subsection 3.4 for further detail about the ongoing legacy of harmful treatments.

Accessing experienced GPs is difficult

Accessing the small number of GPs who do have expertise in ME/CFS is difficult due to overwhelming demand and prohibitive costs. The multi-system, heterogenous nature of ME/CFS means GPs often require lengthy consultation time with patients, which is not supported by the

[118] Emerge Australia. 'Health and Wellbeing Survey 2019'.
[119] Emerge Australia. 'Health and Wellbeing Survey 2019'.
[120] ME/CFS Advisory Committee. 'Report to the NHMRC'.
[121] Emerge Australia. 'Health and Wellbeing Survey 2019'.
[122] D. Pheby, et al. 'A literature review of GP knowledge and understanding of ME/CFS: A report from the socioeconomic working group of the European network on ME/CFS' *Medicina* (Lithuania), 57 (2021).
[123] V. Anderson, et al. 'A review and meta-synthesis of qualitative studies on myalgic encephalomyelitis/chronic fatigue syndrome' *Patient education and counselling,* 86:2 (2012).
[124] C. Blease, H. Carel and K. Geraghty K. 'Epistemic injustice in healthcare encounters: evidence from chronic fatigue syndrome' *Journal of Medical Ethics,* 43 (2017).
[125] M. Drachler, et al. 'The expressed needs of people with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: A systematic review', *BMC Public Health* 9:458 (2009).
[126] S. McManimen, D. McClellan, J. Stoothoff and L. Jason. 'Effects of unsupportive social interactions, stigma, and symptoms on patients with myalgic encephalomyelitis and chronic fatigue syndrome' *J Community Psychol,* 46:8 (2018).
[127] Goldberg. 'A new clinical challenge: supporting patients coping with the long-term effects of COVID-19.'
[128] Pheby, et al. 'A Literature Review of GP Knowledge'.
[129] F. Friedberg, M. Sunnquist and L. Nacul. 'Rethinking the Standard of Care for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome' *Journal of General Internal Medicine,* 35 (2020).

Australian healthcare system. Medicare rebates reduce for longer consultations for complex conditions, leaving patients with large out of pocket expenses. This limits access to those who can afford it.

For patients in regional areas, access to specialised care is usually even further out of reach and limited to those who have the means and the ability to travel considerable distances. Telehealth offers rural and remote patients, as well as those who find attending appointments exacerbates their symptoms, a solution to greater access to care. However, the current Medicare rebates for telehealth are undermining this resource for these patients. Section 3.5 expands on this topic and advocates for special telehealth provisions for people with ME/CFS.

3. Priority actions to improve outcomes for people living with ME/CFS, Long COVID and post-infection diseases

This section describes feasible priority actions to improve quality of life for people living with ME/CFS, Long COVID and post-infection diseases. These actions carry a common theme: don't reinvent the wheel, or make the same mistakes again. Although research into ME/CFS has been underfunded, the ME/CFS community, Emerge Australia and a small but growing number of health and social care experts are informed by soundly researched knowledge about the disease, its effect on people who live with it, and the issues they face. This knowledge should be used to guide the implementation of actions described here, including the development of research and clinical guidelines, healthcare practitioner education, prioritisation of post-infection disease through systemic health system response, and improved access to healthcare and financial support.

3.1. GP education

Educate doctors to diagnose ME/CFS and Long COVID and provide evidence-based support to people with these diseases

Underdiagnosis, misdiagnosis, disbelief and inappropriate management from GPs prevent patients from receiving correct care for their condition. There is a significant need for greater GP education for those already practicing and for medical trainees in undergraduate programs. This will ensure the next generation of people with diseases like ME/CFS and Long COVID don't suffer the same stigma or poorly informed healthcare.

Research estimates 90% of people with ME/CFS have not been diagnosed and GPs often lack knowledge and confidence in diagnosing the disease.[130] This data is consistent with Emerge Australia's survey of people living with ME/CFS, which found:

- 48% said their GP was either poorly or very poorly informed about ME/CFS
- 60% were diagnosed within 2 years, while the remainder waited anywhere from 3 to 10 years
- 73% said lack of knowledge from their healthcare provider was an obstacle to accessing healthcare.[131]

In addition to underdiagnosis, misdiagnosis is also common, and has significant implications for patient care. One study found that more than a third of patients diagnosed by their GP with ME/CFS either didn't meet the criteria for ME/CFS or had other exclusionary conditions, which meant they couldn't be diagnosed with ME/CFS.[132]

GPs also need to be educated about safe symptom management approaches that can provide relief from symptoms and improve a patient's quality of life. There are two recommended approaches: pacing and stepwise symptom management, described below. Some patients with Long COVID may also benefit from approaches such as pacing.[133]

[130] Pheby, et al. 'A Literature Review of GP Knowledge'.
[131] Emerge Australia. 'Health and Wellbeing Survey 2019'.
[132] Johnston, Staines & Marshall-Gradisnik, 'Epidemiological characteristics of chronic fatigue syndrome/myalgic encephalomyelitis in Australian patients' *Clin Epidemiol*, 8 (2016).
[133] Decary, et al. 'Humility and Acceptance'.

The patient: pacing and rest

Pacing is proven to be safe, effective and practical for the majority of people living with ME/CFS.[134] To implement pacing, patients must: STOP pushing their limits; REST before they feel symptoms and PACE their daily mental and physical activities[135]

Pacing involves undertaking less activity than what the patient has energy for on a given day, and breaking activities down into short bursts, with added rest breaks. The aim is to help manage limited energy and reduce how often the person experiences post-exertional malaise.

Pacing activity in ME/CFS is "symptom contingent", which means the person with ME/CFS will have to adjust how much or little they do based on how they respond to activity. The amount a person can do may change from day to day. This is in contrast to some forms of pacing that are 'quota contingent', meaning that the patient does a set amount of activity each day regardless of their symptoms.

The healthcare practitioner: stepwise symptom management

While pacing and rest are self-management approaches, doctors and healthcare practitioners can help with stepwise symptom management. This involves ranking symptoms from most to least problematic and exploring options to help reduce symptoms, starting with the most problematic. This approach to management isn't treating the underlying cause of ME/CFS or Long COVID, but it can help to improve overall quality of life.

As evident from these brief explanations, pacing and rest and stepwise symptom management are basic but practical steps that can be taken to attempt to gain some control over symptoms. They do, however, have limited application and limited results for many, particularly those who are very unwell.

3.2. Coordination of care and allied health support services

Create an Optimal Care Referral Pathway placing people with ME/CFS at the centre of care decisions

People with ME/CFS and post-infection diseases do not routinely receive appropriate, coordinated care shared care. Further, they face barriers accessing evidence-based information and integrated non-clinical support, all of which can inhibit symptom management and recovery. It is critical that ME/CFS and Long COVID patients are empowered to understand their unique needs and become partners in their own care.

Clinical guidelines provide support to GPs. However, GPs cannot meet all care support needs for Australian patients with these diseases. Optimal Care Referral Pathways (OCRPs) support integrated shared care across the entire health system. Such innovative approaches to the coordination of non-clinical service delivery have achieved improved outcomes for patients in other settings.

For example, shared care, in which care is shared between specialist and primary care or other health professionals, has been implemented successfully for people with diabetes, cancer, paediatric

[134] Decary, et al. 'Humility and Acceptance'.

[135] Decary, et al. 'Humility and Acceptance'.

oncology and those requiring obstetric care.[136] Shared care enables multi-disciplinary collaboration between specialist/ hospital care and primary care clinicians.

An OCP for ME/CFS and Long COVID would ensure each patient receives equitable and safe care from a breadth of healthcare professionals. Allied health professionals like physiotherapists, exercise physiologists, occupational therapists and psychologists can provide critical support with symptom management. Similarly, specialists including cardiologists, gastroenterologists and rheumatologists can help with symptoms of ME/CFS and Long COVID and common comorbid conditions, like postural orthostatic tachycardia syndrome, irritable bowel syndrome and fibromyalgia.

The OCRP should be developed though a multi-disciplinary clinician consensus process that includes people with ME/CFS, carers and allied health professionals to establish the elements of quality care that should be offered. A thorough monitoring and evaluation process would similarly ensure the OCP is delivering efficient, appropriate and equitable care.

3.3. Funding for collaborative translational research

Ensure knowledge from ME/CFS research and the emerging field of Long COVID is shared and integrated

As demonstrated in *1.5 Relationship with Long COVID,* researchers have already established strong links between ME/CFS, Long COVID and other post-infection diseases. This high degree of similarity offers opportunities for researchers to work across both diseases at the same time.

There are many highly qualified researchers and centres that need support to conduct these correlation studies. For example, Emerge Australia, in partnership with La Trobe University, manages Australia's only ME/CFS Biobank. This partnership aims to expand Australia's ME/CFS Biobank to include Long COVID samples, allowing researchers to compare patient cohorts. This will be a unique resource in Australia.

Any new research would be more efficient and effective if researchers:

a) Don't reinvent the wheel: use findings from ME/CFS research to inform research topics, design, recruitment and analysis

There is no need to start from scratch with Long COVID research. Existing findings from ME/CFS research can provide clear guidance for research into cause and treatment options. If treatments are found that help people with Long COVID, these are potentially applicable for people with ME/CFS.[137] People with ME/CFS should be used as comparison cohorts to people with Long COVID, in addition to healthy controls.

b) Researchers should partner with ME/CFS and Long COVID patients to design, conduct and analyse research

[136] W. Brodribb. 'Maternity care in general practice' *The Medical Journal of Australia* 201:11 (2014).
[137] Wong and Weitzer. 'Long COVID and Myalgic Encephalomyelitis'.

Underfunded biomedical research lacking patient codesign has contributed to the poor health and wellbeing outcomes post-infection patients experience today. It has also contributed to a mistrustful relationship between patients, researchers and clinicians. ME/CFS and Long COVD research must involve patients in codesign and recruitment to ensure research efforts are not wasted and to deliver relevant and better outcomes.

3.4. Update Australia's clinical guidelines

Update Australia's clinical guidelines to increase safety and quality of care and establish shared care

It is a matter of urgency for Australia to update its clinical guidelines for ME/CFS, to ensure Australian ME/CFS patients have access to the best possible care, based on current understanding of the disease and latest evidence. As ME/CFS research continues to evolve, clinical guidelines quickly become outdated. Current Australian clinical management of ME/CFS is out of step with international best practice and ME/CFS patients are at risk of harm. In reviewing these issues, the 2019 report of NHMRC's ME/CFS Advisory Committee recommended that Australia's clinical guidelines for ME/CFS be updated.[138]

Emerge Australia believes that new ME/CFS guidelines should be living documents which are regularly updated by a standing committee of clinicians, researchers, patients and carers, as new evidence comes to light. Australia's current clinical guidelines were published in 2002, by a working group under the auspices of the Royal Australia College of Physicians and reflect standard clinical management of ME/CFS at the time.[139] Australia's 2002 clinical guidelines use the Fukuda (1994) criteria,[140] developed by the US Centers' for Disease Control and Prevention. These criteria are no longer recommended, as they do not include post-exertional malaise as a mandatory criterion for diagnosis, despite it being a core feature of the disease.[141] The CDC itself no longer recommends these diagnostic criteria.[142]

Further, Australia's current clinical guidelines focus on physical rehabilitation and encourage ME/CFS patients to undertake exercise, while discouraging excessive rest and activity avoidance. They suggest patient concerns that physical activity may be harmful are "unwarranted", despite current consensus that physical activity beyond a person's tolerance for movement can trigger or exacerbate post-exertional malaise in ME/CFS patients.[143] The guidelines also falsely that claim graded exercise programs have been shown to be effective treatments for ME/CFS.[144] Proponents of graded exercise therapy for ME/CFS claim that avoiding activity so symptom exacerbation does not occur can become a vicious cycle of increased disability and more avoidance, and that patients' beliefs about

[138] ME/CFS Advisory Committee. 'Report to the NHMRC'.
[139] Working group of The Royal Australasian College of Physicians (RACP). 'Clinical practice guideline: Chronic Fatigue Syndrome' *The Medical Journal of Australia*, 176:9 (2002).
[140] K. Fukuda, S. Straus, I. Hickie, M. Sharpe, J. Dobbins, A. Komaroff & International Chronic Fatigue Syndrome Study Group. 'The chronic fatigue syndrome: a comprehensive approach to its definition and study.' *Annals of internal medicine*, 121:12 (1994).
[141] ME/CFS Advisory Committee. 'Report to the NHMRC'.
[142] Centers for Disease Control and Prevention. 'CDC: IOM 2015 Diagnostic Criteria'.
[143] L. Bateman, et al. 'Myalgic encephalomyelitis/chronic fatigue syndrome: Essentials of diagnosis and management'. *Mayo Clinic Proceedings*, 96:11 (2021).
[144] Graded exercise therapy (GET) is based on the false assumption that ME/CFS symptoms are due to physical deconditioning. The treatment aims to reduce symptoms by improving physical fitness through gradually increasing exercise, regardless of symptom exacerbation.

their disease contribute to their prognosis. This approach to managing ME/CFS is no longer recommended.[145, 146, 147]

The harmful nature of Graded Exercise Therapy and Cognitive Behaviour Therapy

In the past, graded exercise therapy (GET) and cognitive behaviour therapy (CBT) have been commonly recommended treatments for ME/CFS. GET assumes the symptoms of ME/CFS are largely the result of physical deconditioning, due to lack of activity. GET has often been combined with cognitive behaviour therapy (CBT) on the assumption that activity avoidance in people with ME/CFS was fear-based, and the treatment focussed on challenging these presumed fears and encouraging increased activity.

It was assumed GET and CBT treatment would reverse both activity avoidance and deconditioning. This would lead to a reduction in symptoms and even full recovery. However, biomedical research into ME/CFS does not support the deconditioning hypothesis of ME/CFS, while GET and CBT studies do not show the high rates of recovery and improvement which would be predicted by the deconditioning hypothesis.

Mistakes of the past managing people with ME/CFS are reoccurring in the management of people with Long COVID. For example, the RACGP guide[148] fails to acknowledge the second most commonly reported symptom in people with Long COVID, post-exertional malaise (PEM).[149] In addition, the RACGP guide highly promotes the use of exercise as treatment, with almost no caution. The guide suggests to reduce exercise if symptoms increase but offers no explanation why these patients would experience increased symptoms after exercise. However, just as evidence suggests that graded exercise therapy may accentuate post-exertional malaise in ME/CFS[150, 151, 152], the same effect has been observed in Long COVID patient narratives.[153, 154, 155] For this reason, graded exercise therapy should not be prescribed for management of Long COVID.[156]

[145] Bateman. 'Myalgic encephalomyelitis/chronic fatigue syndrome: Essentials'.
[146] Centers for Disease Control and Prevention. 'Clinical care for patients with ME/CFS' (2021). Available at: https://www.cdc.gov/me-cfs/healthcare-providers/clinical-care-patients-mecfs/index.html.
[147] National Institute for Health and Care Excellence. 'Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management' (2021). Available at: https://www.nice.org.uk/guidance/ng206.
[148] RACGP. 'Patient resource: Managing post-COVID-19 symptoms', available at: https://www.racgp.org.au/clinical-resources/covid-19-resources/patient-resources/patient-resource-managing-post-covid-19-symptoms/introduction (2022).
[149] Davis et al. 'Characterizing long COVID'.
[150] T. Kindlon. 'Reporting of Harms Associated with Graded Exercise Therapy and Cognitive Behavioural Therapy in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome' *Bull IACFS ME,* 19 (2011).
[151] D. Kim, et al. 'Systematic review of randomized controlled trials for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME)' *Journal of Translational Medicine,* 18 (2020).
[152] L. Larun, et al. 'Exercise therapy for chronic fatigue syndrome' *Cochrane Database of Systematic Reviews,* (2019).
[153] H. Salisbury. 'Helen Salisbury: When will we be well again?' *The BMJ,* 369 (2020).
[154] M. Peel. 'What can we tell patients with prolonged covid-19' *The BMJ,* 370 (2020).
[155] R. Perrin, et al. 'Into the looking glass: Post-viral syndrome post COVID-19' *Medical Hypotheses,* 144 (2020).
[156] Decary, et al, 'Humility and Acceptance: Working Within Our Limits with Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome' *Journal of Orthopaedic & Sports Physical Therapy,* 51:5 (2021).

3.5. Recommendations for policy changes

a) Advocacy for a Health System Response

The burden of disease for ME/CFS, as described above, should be read as a warning about the potential impact of Long COVID. We may anticipate that as COVID-19 becomes endemic in the future, so too will be an ongoing stream of patients whose infections develop into Long COVID, even if they have been vaccinated. This new cohort of post-infection patients is in addition to the 250,000 people in Australia who already experience the frustrations of Australia's current, siloed approach to health care. Our health systems must move quickly to support this growing cohort of post-infection patients, and to manage the impending public health crisis and consequent economic impacts posed by Long COVID.

Since 1999, the Federal Department of Health has sought to focus public attention and health policy on areas considered to contribute significantly to the burden of disease in Australia, and for which there is potential for health gain. Accordingly, as a collaborative effort involving Commonwealth, State and Territory governments, nine National Health Priority Areas (NHPA's) have been created.

Current predictions suggest up to 325,000 people may be affected by Long COVID, in addition to the 250,000 living with ME/CFS. With more than half a million people affected by post-infection disease in the coming years, **Emerge Australia advocates Post-infection Disease becomes the 10th NHPA.**

In addition, Emerge Australia advocates for the collaborative development of a **National Post-infection Disease Strategy** to address the impact of Long COVID, ME/CFS and other post-infection diseases. A National Post-infection Disease Strategy would allow for the allocation of funds that address the interface between post-infection disease, addressing them systemically and programmatically. Such a strategy would contribute to alleviate the current siloed approach, providing a platform to address the needs of Australia's 250,000 people with ME/CFS, plus the hundreds of thousands of other people with other post-infection illnesses.

b) Expand access to Telehealth to increase access to care for those who are bed and house bound

In March 2020 the Federal Government provided access to a range of Medicare-subsidised services via phone or video call in response to COVID-19. This decision enabled some people with ME/CFS to access essential health services for the first time in years. Previously, these patients could not attend in-person clinics because of the severe effect on their health. Attending appointments in-person can cause people living with ME/CFS to experience post-exertional malaise for hours, days or weeks afterwards.

Telehealth works for people with ME/CFS

In June 2020, Emerge Australia conducted an online survey of 419 people to understand how ME/CFS patients and their carers experienced telehealth services. Results found the introduction of Medicare rebates had improved access to health services for 82% of respondents.[157] Results also found telehealth worked to:

- reduce the risk of experiencing the disabling effects of PEM
- reduce the number of appointments cancelled at the last minute
- alleviate burden on carers who accompany patients to-and-from appointments
- increase patient independence.

While some telehealth services are now permanently accessible through Medicare, rebates for complex specialist consultations and longer telehealth consults ceased in June 2022. Emerge Australia urges the Federal Government to make Medicare rebates permanently available for long and short consultations for people with chronic illnesses, who are otherwise unable to attend clinics.

Further, Emerge Australia advocates for the requirement for an annual, face-to-face GP appointment be removed for chronically unwell people. This requirement excludes patients who are entirely bed-bound – those who are most unwell – from accessing services they need. Alternatively, where an annual face-to-face appointment is required, funding should be made available for home visits to ensure patients receive the care they need. An appropriate MBS item needs to be developed for remuneration of necessary home visits as part of the Telehealth Program for bed-bound and housebound patients.

c) Enable equitable access to government support for people with ME/CFS, Long COVID and post-infection diseases

Develop appropriate assessment guidelines

Just as many medical practitioners face challenges providing appropriate care to their patients due to out-of-date clinical guidelines (see subsection 3.4), Centrelink and National Disability Insurance Scheme (NDIS) assessment staff similarly lack access to information to accurately assess clients with ME/CFS.

Anecdotal evidence suggests many people with ME/CFS are rejected from the NDIS or Disability Support Pension (DSP) because their disease was considered temporary and treatable. However, many gain access on appeal. This apparent pattern of rejection followed by a successful appeal suggests that ME/CFS is poorly understood by assessors.

Improving assessment accuracy is critical to reduce the number of incorrect first round assessment decisions and subsequent assessment rounds. This would improve timely access to the support people disabled by ME/CFS need, while reducing operating costs sustained through the appeals process.

Tailored guidelines are needed to provide assessors with accurate information about the fluctuating nature and permanency of ME/CFS for most patients. Such guidance would also help build understanding of the disabling nature of symptoms and the delayed response of post-exertional

[157] Emerge Australia. 'Telehealth campaign'. Available at: https://www.emerge.org.au/telehealth-campaign (accessed 20 January 2022).

malaise. Emerge Australia would welcome the opportunity to collaborate on the development of such guidelines with the National Disability Insurance Agency (NDIA), Centrelink, the ME/CFS community and clinical experts.

Utilise 'Link' workers to support patients

The United Kingdom's National Health Service employs 'link' workers to support patients to navigate health and social care systems.[158, 159] Emerge Australia advocates for link workers to similarly be funded in Australia to support people who face barriers to access the care they need. Such support from link workers is particularly important for people whose disease/s is poorly understood in medical and social care spheres.[160]

Link workers can be funded and embedded within primary care services, to connect individuals to a range of relevant social and community resources and supports.[161] Link worker roles could also be funded within community organisations through PHN commissioning arrangements. Alternatively, a national link worker service for post-infection diseases could be established, enabling national consistency and quality with localised and community tailored delivery.

For people living with ME/CFS, the process of applying for the NDIS or DSP and appealing inaccurate decisions comes with a significant cost to health and wellbeing. Navigating the application and appeal processes can trigger post-exertional malaise, leading to a worsening of symptoms for days, weeks or even months.

Emerge Australia has a strong understanding of the health and social care landscape in Australia and is the leading source of trusted information for many ME/CFS patients. Emerge Australia is well-positioned to design and deliver a national linking function to triage patients accessing Telehealth Nurse Case Management and Patient Support Information services into the NDIS and other relevant services.

[158] National Health Service. 'Social Prescribing' *NHS England.* Available at: www.england.nhs.uk/personalisedcare/social-prescribing/ (accessed 5 February 2022).
[159] E. Hazeldine, et al. 'Link worker perspectives of early implementation of social prescribing: A 'Researcher-in-Residence' study' *Health Soc Care Community,* 29 (2021).
[160] S. Moffatt S, et al. 'Link Worker social prescribing to improve health and well-being for people with long-term conditions: qualitative study of service user perceptions' *BMJ Open,* 7 (2017).
[161] K. Husk, et al. 'What approaches to social prescribing work, for whom, and in what circumstances? A realist review' *Health Soc Care Community,* 28 (2020).

Conclusion

ME/CFS has been overlooked for too long. This highly disabling disease affects up to 250,000 Australians, up to 10 times more than multiple sclerosis. The degree of impairment exceeds that of other well-known diseases like multiple sclerosis, depression and cancer.

Despite these numbers and severity, ME/CFS has had only recent and limited research funding. Consequently, causes of the disease remain unknown and there is no biomarker to aid diagnosis. Further, people with ME/CFS have no evidence-based treatment options. At best, patients have the management techniques of pacing and rest, at worst, they are prescribed harmful graded exercise therapy. Many people with Long COVID have now joined this patient cohort. As with ME/CFS, there is considerable risk that harmful management techniques are being prescribed

The burden of ME/CFS on the individual and the economy is large. It is currently estimated ME/CFS costs the national economy $14.5 billion annually. Post-infection syndromes, whether ME/CFS, Long COVID or some other post-infection disease, will affect many people in our community for a long time.

This outlook is unlikely to change unless a number of steps are taken. This report has outlined the multitude of issues that people with ME/CFS face within the healthcare system. It has also presented solutions, and outlined five priority actions for governments, healthcare and research sectors in section 3. These steps have a central theme: no need to reinvent the wheel, and don’t repeat the mistakes made in ME/CFS.

The highly disabling, life-altering nature of ME/CFS, and the lack of support people living with it have been provided, MUST be acknowledged. All individuals living with ME/CFS and post-infection diseases like Long COVID, and their carers should receive appropriate care and support to help them recover and improve their health to the extent they are able across the lifetime of their disease. This will enable them to better manage their personal lives and participate socially and economically to the extent they are able.

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