CrunchME

The future is a policy choice

Addressing Infection-Associated Chronic Conditions

January 2025

Research into Infection-Associated Chronic Conditions is urgently needed

The pandemic presents an urgent challenge to medicine's blindspot on Infection-Associated Chronic Conditions



Medicine's blindspot

A great deal of medical progress has occurred over the last century, with the miracles of the 20th century taken for granted today. Scientists are now developing curative treatments for diseases long thought to be incurable, and many conditions previously considered a death sentence are no longer so.

Despite this, there remains a great deal of low-hanging fruit in the broader endeavour to improve human health. Infectious and chronic diseases continue to claim many lives and rob people of quality of life.

Medicine has long had a blind spot on the long-term chronic after-effects of infectious diseases. Post-Acute Infection Syndromes (PAIS) are well documented across many infectious diseases from Ebola to Zika [1], but little rigorous research has been conducted historically on why they occur, or how they can be prevented and treated.

The COVID-19 pandemic dramatically increased the number of people living with a PAIS, with as many as 400m people estimated to have had Long Covid [2]. This has led to improved general awareness and renewed research interest in the field.



Infection-Associated Chronic Conditions

There have been growing calls to unite research on these diseases under a new umbrella of Infection-Associated Chronic Conditions (IACC). This term places greater focus on the conditions, which have remarkably similar clinical presentations regardless of trigger, suggesting that they may share common root causes (e.g. chronic SARS-CoV-2 infection) or underlying pathology (e.g. neuroinflammation).

The IACC family contains conditions such as:

- Long Covid
- Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)
- Postural Orthostatic Tachycardia Syndrome (POTS)
- Mast Cell Activation Syndrome (MCAS)
- Fibromyalgia (FM)
- Chronic Lyme disease.

These conditions are far from rare and often cause a high degree of disability. Investing in research into these conditions is becoming ever more urgent as the number of sufferers continues to grow as a result of the COVID-19 and future pandemics.

IACCs include Long Covid, ME/CFS, POTS, and MCAS, among others

Studying conditions with similar presentations may provide critical insights, and IACC research may in turn yield benefits for understanding the role of infection in conditions like Alzheimer's disease



IACCs and related fields

The nascent IACC field primarily relates to the role of infections in driving conditions not yet well understood by medicine, including Long Covid, ME/CFS, POTS and MCAS.

As our understanding grows, it is becoming clear that infections play a critical role in many better-understood conditions, including Multiple Sclerosis and Alzheimer's disease [3, 4]. These may prove to be natural extensions of the field in time, and understanding developed from study of IACCs may lead to therapeutic insights in other diseases.

In addition, studying conditions with similar presentations (e.g. Gulf War Illness) or that are commonly comorbid (e.g. Ehlers-Danlos Syndrome) may provide insights into disease pathology.

For the purpose of encouraging investment in under-served diseases, the term IACC in this report will refer to these 'less-understood' diseases, as compared to the 'better-understood' diseases such as Alzheimer's.

Long Covid - Defined as new symptoms persisting for at least 12 weeks following a SARS-CoV-2 infection. Clinical presentation varies, and includes POTS, ME/CFS and MCAS; others have symptoms not aligned with one of these phenotypes, such as chronic migraine.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) - A disease characterised by severe energy limitations and a disproportionate response to physical or cognitive exertion, termed Post-Exertional Malaise (PEM), presenting as extreme weakness and exacerbation of symptoms.

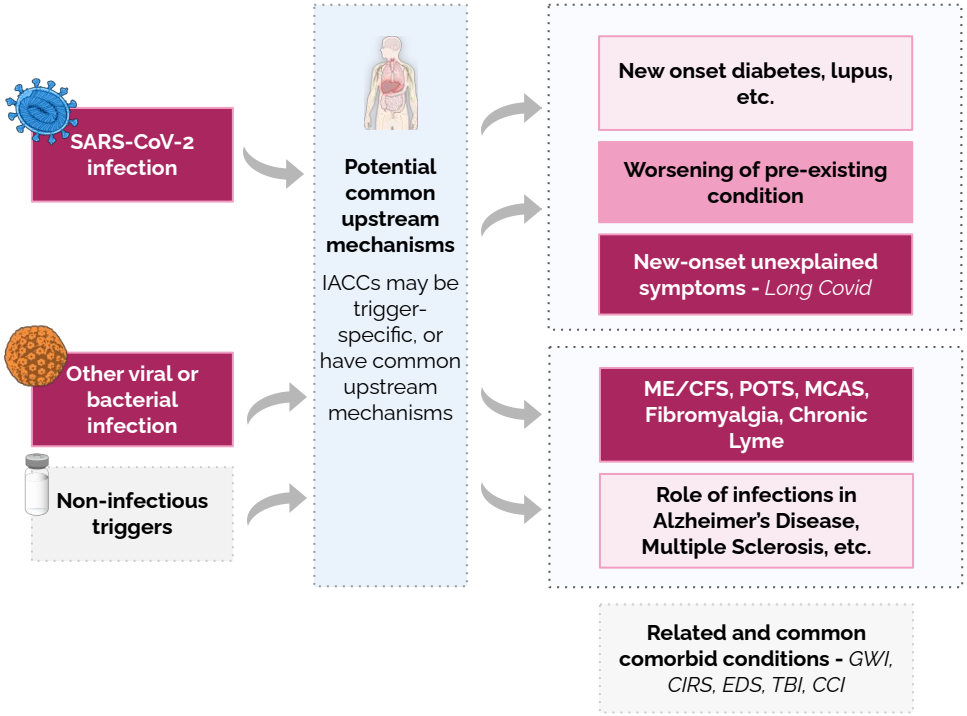
Postural Orthostatic Tachycardia Syndrome (POTS) - A disorder of the autonomic nervous system where the body has difficulty adjusting to gravity upon sitting or standing, with impairments in blood flow and cascading effects including rapid heart rate, dizziness, shortness of breath and chest pain.

Mast Cell Activation Syndrome (MCAS) - A disorder where mast cells, a type of white blood cell, become overactive, producing allergic symptoms including pain, rashes, headaches, as well as respiratory and gastrointestinal symptoms. MCAS patients often develop intolerances to a broad range of foods.

Ehlers-Danlos Syndrome (EDS) - A group of inherited disorders that mainly affect connective tissue - i.e. skin, joints and blood vessel walls. Symptoms include unstable joints and vulnerability to joint dislocation, fragile skin, chronic musculoskeletal pain and gastrointestinal symptoms.

A conceptual framework for Long Covid and IACCs

Treatment for IACCs may be trigger-specific, or address common upstream mechanisms



Some use the term Long Covid to mean all new health issues post SARS-CoV-2 infection, while others [e.g. 5] limit the term to symptoms not explained by an alternative diagnosis - i.e. post-COVID diabetes is excluded from Long Covid.

Until the biology is better understood, worsening of pre-existing POTS and other IACCs falls into an ambiguous category.

The core IACC agenda relates to less-understood conditions, primarily due to viral or bacterial infection

IACC research naturally also extends to understanding the role of infections in conditions such as Alzheimer's disease, Multiple Sclerosis and diabetes.

Studying related and often comorbid conditions, or IACCs without a clear infectious trigger may elucidate useful insights into disease pathology; e.g. the role of neuroinflammation is being studied across many IACCs as well as conditions like Gulf War Illness.

IACCs are far from rare, especially following the pandemic

Long Covid prevalence has been estimated at 3-5% of the US population, with Fibromyalgia at 2% and ME/CFS at 0.5-1.3%

Prevalence estimates

Until biomarkers and diagnostics are validated and commercialised for IACCs, the accuracy of prevalence estimates will remain limited. Nevertheless, the evidence from existing estimates (summarised in Table 1) suggests material prevalence of IACCs across the population of several developed countries.

Estimates of Long Covid vary, but are on the order of 3-5% of the adult population, and at 0.5% in children [6]. In other words, about 1 in 20 to 1 in 30 adults - some 10 million people - are estimated to be experiencing Long Covid in the US. The CDC estimates that up to a further 3 million people in the US had ME/CFS prior to the pandemic.

By comparison, a disease is considered rare in the US as defined in the Orphan Drug Act if it affects 200,000 or fewer people [7]. The autoimmune condition lupus is estimated to affect about 180,000 women and 20,000 men in the US [8], multiple sclerosis (MS) up to 800,000 people [9], rheumatoid arthritis 1.3 million people [10], and diabetes type 1 about 1.7 million adults [11].

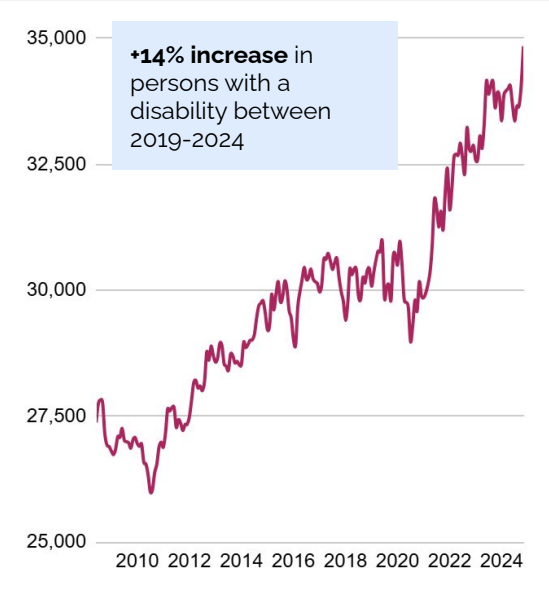
Table 1: Prevalence estimates of selected IACCs

Country	Condition	Estimated prevalence	Source, year
USA	Long Covid	**5.5%**	CDC, 2024 [12]
USA	Fibromyalgia	**2%**	CDC, 2022 [13]
USA	ME/CFS	**1.3%**	CDC, 2024 [14]
USA	POTS	**0.2%**	[15]
UK	Long Covid	**2.9%**	ONS, 2023 [16]
UK	ME/CFS	**0.6%**	[17]
Canada	Long Covid	**5.2%**	StatCan, 2023 [18]
Canada	ME/CFS	**0.4% - 1.1%**	[19]
Germany	ME/CFS	**0.7%**	[20]

Disability rates increased significantly during the pandemic

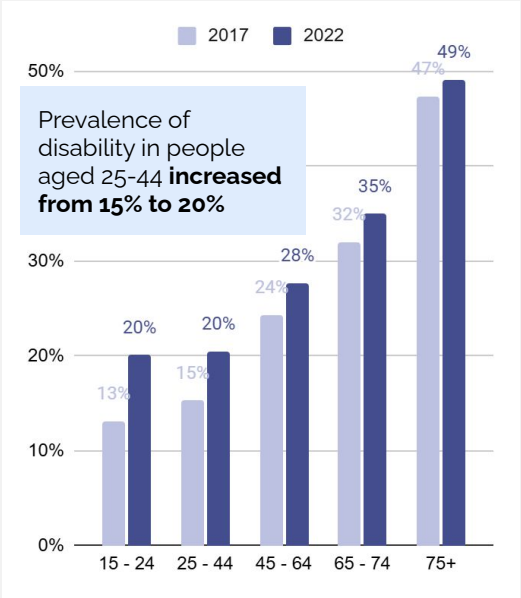
The number and prevalence of people with a disability increased during the pandemic across multiple countries, with particularly pronounced increases in young people

Figure 1: Persons with a disability, 16+, USA [21]



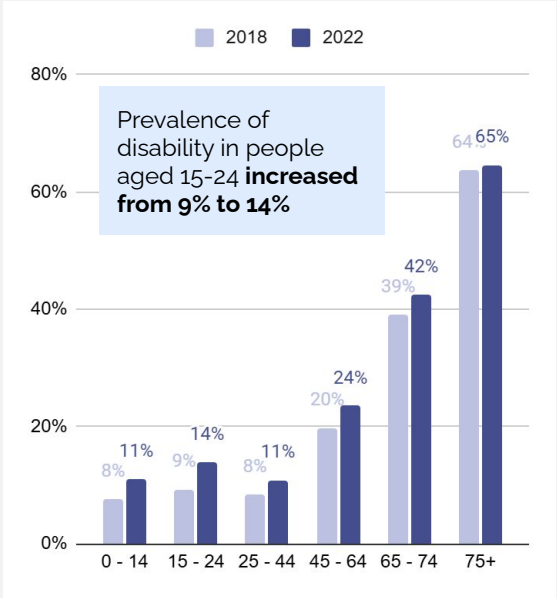
Source: US Bureau of Labor Statistics, Population - With a Disability, 16 Years and over, 2024

Figure 2: Persons with a disability, by age, Canada [22]



Source: Statistics Canada, Persons with and without disabilities aged 15 years and over, 2024

Figure 3: Persons with a disability, by age, Australia [23]



Source: Australian Bureau of Statistics, Disability, Ageing and Carers, Australia: Summary of Findings 2022

IACCs are debilitating and can be totally disabling

A substantial proportion of Long Covid and ME/CFS patients have difficulties performing household tasks and activities of daily living



Degree of disability

Despite their wide prevalence, the disease burden of Long Covid and other IACCs is likely larger than is reflected in these figures. IACCs frequently result in a profound degree of disability, with even so-called 'mild' forms restricting people from activities of daily living, engaging with social activities or participating in the labor force.

Some studies have estimated that 84% of Long Covid patients had difficulties performing household chores and work tasks, and that more than a third had difficulties performing activities of daily living (ADLs) [24]. Of adults currently experiencing Long Covid, the CDC's Household Pulse Survey finds that about one in five experience 'significant activity limitations' from Long Covid [25].

In its severe form, thought to affect about a quarter of patients [26], ME/CFS can be totally disabling; a case report of severe ME/CFS describes a patient who "spent the last four years of her life completely bed-bound… [with] severe exhaustion, body-wide muscle and joint pain." [27] The health-related quality of life measure of ME/CFS has been evaluated as being lower than rheumatoid arthritis and stroke [28].



Disease burden

Disease burden, as measured in Disability-Adjusted Life Years (DALYs) seeks to provide a comparable metric that incorporates both prevalence, degree of impairment, as well as mortality.

Taking a very rough estimate, using the prevalence of Long Covid and applying disability weights and mortality estimates at half the rate used to estimate ME/CFS DALYs, yields an annual US adult disease burden at 4.5 million DALYs[1]. This estimate uses a disability weight of 0.191 which is comparable to a disability weight of 0.203 for 'Moderate motor plus cognitive impairments due to encephalitis' or Crohn's Disease at 0.232 [29].

[1] We apply a US Long Covid prevalence of 5.5% as per the CDC's Household Pulse Survey, a composite estimate for disability weights of 0.191 and a YLL coefficient of half of the value used in Leonard, Pollack and Mirin's estimate [30] of 0.12, corresponding only to deaths due to cancer and heart disease. The composite estimate for disability weight uses three tiers of limitation severity; 'not limited' is assigned a disability weight of 0.018 based on a range of weights for minor conditions such as controlled asthma and mild lower back pain, 'limited' is assigned the disability weight of mild ME/CFS, 0.137, and 'a lot' is assigned the disability weight of moderate ME/CFS, 0.45. These are weighted according to severity proportions reflected in the Household Pulse Survey (20%, 55%, 25%) for ('not limited', 'limited', 'limited a lot').

IACCs carry a substantial disease burden, comparable to diabetes

Long Covid's estimated disease burden is comparable to diabetes, while ME/CFS has a greater disease burden than Multiple Sclerosis and Parkinson's disease combined

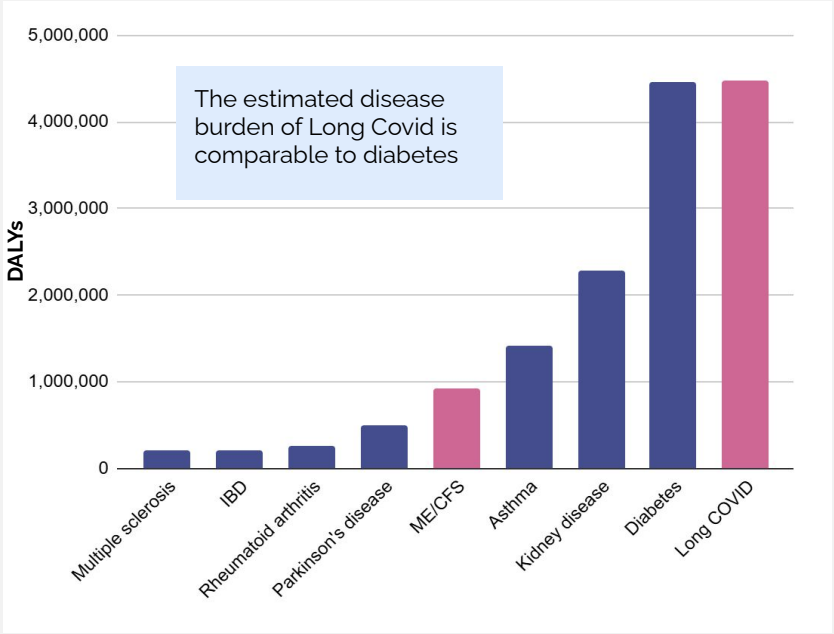
Disease burden

At 4.5 million DALYs, the disease burden of Long Covid would be greater than that of diabetes (types 1 and 2 combined), stroke, and chronic kidney disease. It would also be greater than the disease burden of Alzheimer's Disease, Parkinson's and Multiple Sclerosis combined, at 2.7 million DALYs [31].

DALY estimates of ME/CFS place its disease burden at double that of HIV, and half that of breast cancer [32, 33]. Prevalence and severity estimates of other IACCs are not yet available, but would only further add to the substantial disease burden of IACCs.

Despite this widespread prevalence and heavy disease burden, these conditions remain nearly invisible in the public sphere, in part due to their stigmatized nature [34]. This is despite the sizeable economic cost of Long Covid due to lost income and additional medical costs; in the US alone it has been estimated that between $101 and $430b of lost income has been accrued so far due to Long Covid, with a further $43bn to $172bn in medical costs [35].

Figure 4: US Disease burden of selected diseases [36]



Source: IHME, GBD Results, 2024; CrunchME analysis

A number of research programs are underway, but most are small in scale

A number of European and Anglosphere countries have funded discrete Long Covid and ME/CFS research programs, but long-term, large-scale research efforts remain scarce

Table 2: IACC research programs and funding by country GDP

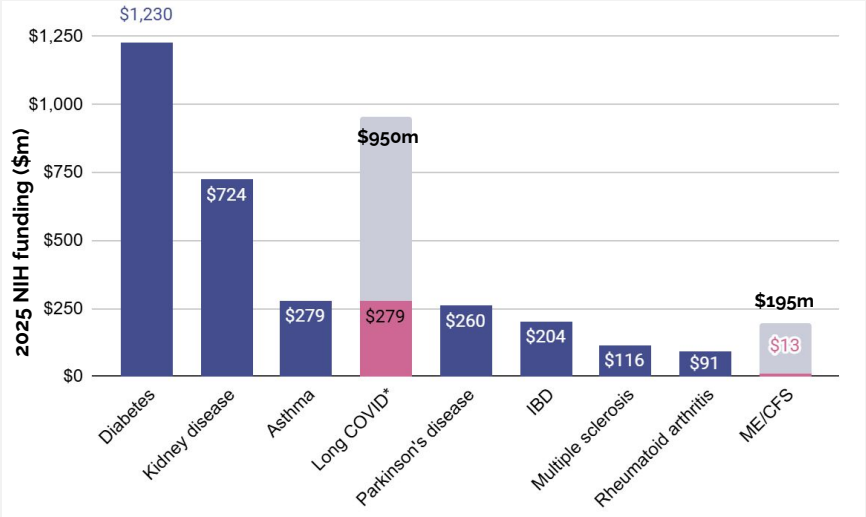
Country	GDP (2023) $t USD (Rank)	Funding	Initiatives
USA	**$27.4t (1)**	$662m USD (2025-29) $20m USD (2024-29)	**RECOVER** - National Institutes of Health run national research program for Long Covid comprising observational studies, biorepository and clinical trials. [37] **Lyme** - Prospective NIH study of 1,000 patients to understand Chronic Lyme disease announced late 2024 [38]
Germany	**$4.5t (3)**	€15m (2024-27) TBD	**ME/CFS research program** - Research program for ME/CFS including research networks on PEM, autoimmunity [39] **BMG Long Covid Initiative** - Federal Ministry of Health initiative for education, support and practice research [40]
UK	**$3.3t (6)**	TBD	**ME/CFS delivery plan** - Final delivery plan for ME/CFS expected in early 2025 following interim delivery plan in 2022 [41]
Canada	**$2.1t (10)**	$20m CAD (2023-) $2m CAD (2024-29)	**Long Covid Web** - $20m investment for a national network supporting and conducting research for Long Covid [42] **ICanCME** - $2m over 5 years for a national research network for ME/CFS [43]
Australia	**$1.7t (13)**	$50m AUD (2023-)	**Targeted research fund for Long Covid** - $50m for Long Covid research through the Medical Research Future Fund [44]
Netherlands	**$1.1t (17)**	€34m (2023-26) €28.5m (2021-31)	**Long Covid research program** - Funding for research infrastructure and program for Long Covid [45] **ME/CFS research program** - 10-year research program for biomedical research on ME/CFS [46]
Austria	**$0.5t (26)**	TBD	**Action Plan on Post-Acute Infectious Syndromes** - National Research Center for PAIS, establishment of hospital outpatient services, patient social support services, prevention strategies [47]

IACCs are deeply underfunded relative to their disease burden

If Long Covid and ME/CFS were funded at the same rate as asthma, they would be funded at $950m and $195m per year, respectively

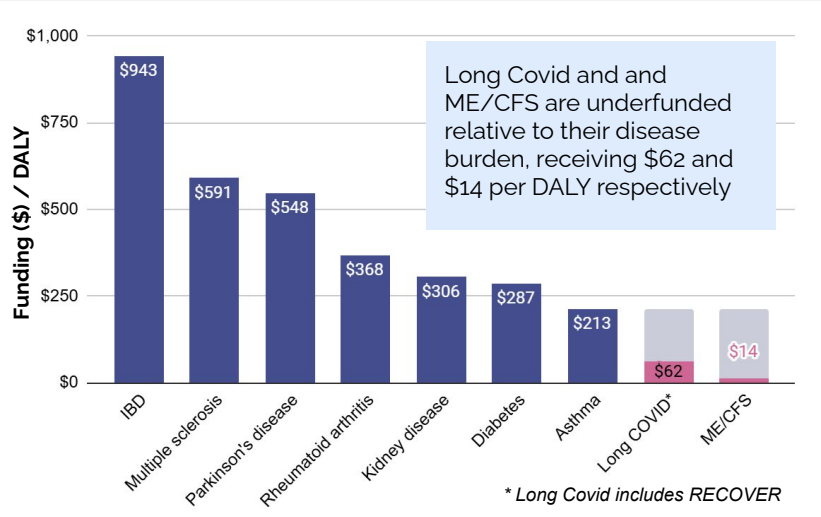
Estimated 2025 NIH funding per DALY for Long Covid and ME/CFS are $62/DALY and $14/DALY, respectively, compared to $213/DALY for asthma. **If Long Covid and ME/CFS were funded at the same rate as asthma, they would be funded at $950m and $195m per year, respectively**. Including POTS, MCAS, Chronic Lyme, Fibromyalgia and other IACCs, **funding commensurate with the overall disease burden of IACCs would be approximately $1.5b.**

Figure 5: Estimated 2025 NIH funding, selected diseases [48]



Source: NIH, Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC), 2024

Figure 6: Estimated 2025 NIH funding per DALY [49, 50]



Source: NIH, RCDC, 2024; IHME, GBD Results, 2024; CrunchME analysis

ME/CFS and Long Covid receive low, discrete levels of research funding

ME/CFS and Long Covid research receive no regular source of Government research funding in Australia and the UK, and at much lower levels than conditions like IBD, MS and Parkinson's disease

Tables 3 and 4 below show estimated levels of Government research funding across several years for ME/CFS, Long Covid and a number of comparison diseases, using manual and validated keyword filters of grant funding databases. ME/CFS and Long Covid received low levels of research funding across all years analysed compared to IBD, Lupus, MS and Parkinson's disease, with no funding in 2018-19 in the UK or 2021-2023 in Australia.

Table 3: Comparison of research funding, UK (£ millions) [51]

	2015	2016	2017	2018	2019	2020	Total
MS	£2.3	£1.4	£6.4	£0.9	£8.2	£3.1	£22.3
Parkinson's	£12.1	£4.8	£6.5	£19.6	£3.9	£6.1	£53.0
IBD	£5.0	£7.0	£5.0	£2.7	£7.7	£6.5	£33.9
ME/CFS	£1.0	£1.4	£0.2	-	-	£3.35	£6.0

Source: White, P., McGrath, S., Anatol. (2023). Unpublished analysis, via correspondence

Table 4: Comparison of research funding, Australia ($AUD millions) [52]

	2020	2021	2022	2023	2024	Total
Lupus	$5.0	$5.0	$1.9	$9.6	$0.8	$22.3
Parkinson's	$12.0	$6.8	$12.8	$10.6	$5.8	$48.1
MS	$12.3	$7.8	$6.0	$12.3	$6.5	$44.9
ME/CFS	$3.3	-	-	-	-	$3.3
Long Covid	-	-	-	-	$14.5	$14.5

Source: NHMRC, Research funding statistics and data, CrunchME analysis

Substantial progress has been made in understanding IACCs

Mechanisms of Long Covid, ME/CFS, POTS and other IACCs are starting to be uncovered, with a growing number of findings that need to be rapidly validated and built upon



Drivers of Long Covid

There is now a growing body of evidence for a number of mechanistic drivers and pathophysiological models for Long Covid, with potential therapeutic targets for each model.

Dozens of studies have found evidence for persistent SARS-CoV-2 in Long Covid patients, with viral protein and RNA found in blood and tissue recovered from biopsy and autopsy studies [53]. Scientists are now working to understand if and how persistence of the virus is causing symptoms in Long Covid patients, and whether it can be treated with monoclonal antibodies and antivirals [54].

There are also two highly compelling manuscripts in review finding a causal link between autoimmunity and Long Covid. Two research groups, one at Yale [55] and another in the Netherlands [56], reported preliminary results in 2024 that antibodies isolated from patients and injected into mice caused symptoms including increased pain sensitivity and dizziness.

Other biological drivers include latent virus reactivation, gut dysbiosis and mitochondrial dysfunction [57]. Further work is needed to understand these drivers and how they interact.



ME/CFS and POTS

While other IACCs have been historically under-researched, a broad and well-documented range of physiological anomalies in patients have been established in the literature. Researchers are now formulating better informed hypotheses of the underlying causes of patients' severe symptoms. These avenues need to be urgently pursued, and translated into clinical trials with both novel and repurposed drugs.

By way of example, extreme weakness and cognitive dysfunction in ME/CFS may be partially explained by muscle and cerebral hypoperfusion, and endothelial and mitochondrial dysfunction [58]. There is also some evidence for underlying drivers including persistent viral infections, reactivated viruses, gut dysbiosis and autoimmunity [59, 60, 61], which need urgent investigation to further elucidate.

The downstream mechanisms for POTS are better-conceptualised, though root causes remain unknown. POTS is understood to be driven by autonomic nervous system dysfunction, leading to orthostatic intolerance, that is, an inability for the body to adjust to the effects of gravity following changes in postural orientation [62]. Medications targeting blood volume and heart rate have some efficacy in treating POTS [63].

Scientific innovation has the potential to accelerate solutions for IACCs

Progress across biology, and new imaging and wearable technologies, hold promise for bringing treatment and cures for IACCs in the span of years, not decades



Biology's century

It has been said that the 21st century will be known as Biology's century. Advances made across immunology, neurology, infectious diseases and elsewhere mean that there is real potential to significantly accelerate progress and bring meaningful change for IACCs in years, not decades.

Technological advances such as AI has solved one of biology's 'grand challenges' [64] - the problem of protein folding - and is poised to revolutionize drug discovery and development.

Diseases previously thought to be incurable, including blood cancers and autoimmune diseases, are now the targets of new therapies such as CAR-T [65]. In a world first, a woman with type 1 diabetes has been successfully treated with stem cell therapy [66].

A new medication, efgartigimod (VYGART) has recently been approved for myasthenia gravis, and is expected to replace the use of the expensive (as much as $40,000 per month [67]), scarce biologic IVIg in clinical practice for a number of autoimmune conditions [68]



Imaging and wearable technologies

More directly relevant for IACCs, new technologies are now maturing that better allow scientists to directly study neuroinflammation [69], with studies recently identifying neuroinflammation in patients with fibromyalgia and others now underway for ME/CFS and Long Covid [70]. There is some evidence now also of a role for autoimmunity in Long Covid and POTS [71].

New wearables are continually being developed, allowing better tracking of a range of metrics. These include blood pressure, heart rate, continuous glucose and lactate monitoring, and a device currently in beta proposed to track postural changes in blood flow [72], previously only measurable using specialized techniques like transcranial doppler ultrasound. A new class of device therapy is also being developed that aims to directly modulate the nervous system, seeking to treat autonomic nervous system dysfunction and other conditions [73].

These devices, in addition to continual expansion of telehealth practices, has the potential to herald in a new era of decentralized clinical trials, a boon to a highly disabled patient population for whom healthcare access is often limited.

IACC research will advance understanding of chronic diseases

Meaningful investments in IACC research are necessary to address growing healthcare expenditure from chronic disease and ageing populations

Role of infections in chronic diseases

Some viruses have long been known to have serious health impacts, including human papillomavirus being causal in cervical cancer [74]. There is more evidence now for the role of infection in other chronic diseases; with EBV as a key trigger for MS [75], HSV-1 being implicated in Alzheimer's disease (AD) [76], and recent understanding of infection being causative for autoimmunity more generally [77].

Understanding the pathogenesis of IACCs has the potential to uncover the role of infections in many other chronic diseases, and possibly develop new curative treatment strategies.

"It would be unsurprising if many acute virus infections could cause long-term sequelae at different rates and contribute to complex diseases such as diabetes mellitus and systemic lupus Erythematosus"

- Holmes et al., Virology—The next fifty years [83]

Addressing chronic disease and women's health

Meaningfully investing in IACC research is necessary to address the increasing global burden of chronic disease. A recent US CDC study found that an increasing proportion of Americans are dealing with multiple chronic conditions, with 42% experiencing two or more, and over 10% dealing with at least five chronic conditions [78]. Further, over 90% of the annual $4.1 trillion in health care expenditure is attributed to the management of chronic conditions [79].

With fertility rates falling faster than expected [80] globally, issues related to ageing populations and in particular age-driven expenditure on health and disability care will become critical earlier than expected in not just high-income but also middle- and low-income countries. Treating IACCs will be an important part of reducing the rapidly rising demand on health services.

Developing understanding of IACC basic science and clinical research is also critical for progress in women's health, with women being overrepresented among IACC patients [81]. There is a growing understanding of sex differences in immunity, playing a role in the higher rates of autoimmune conditions and IACCs in women [82].

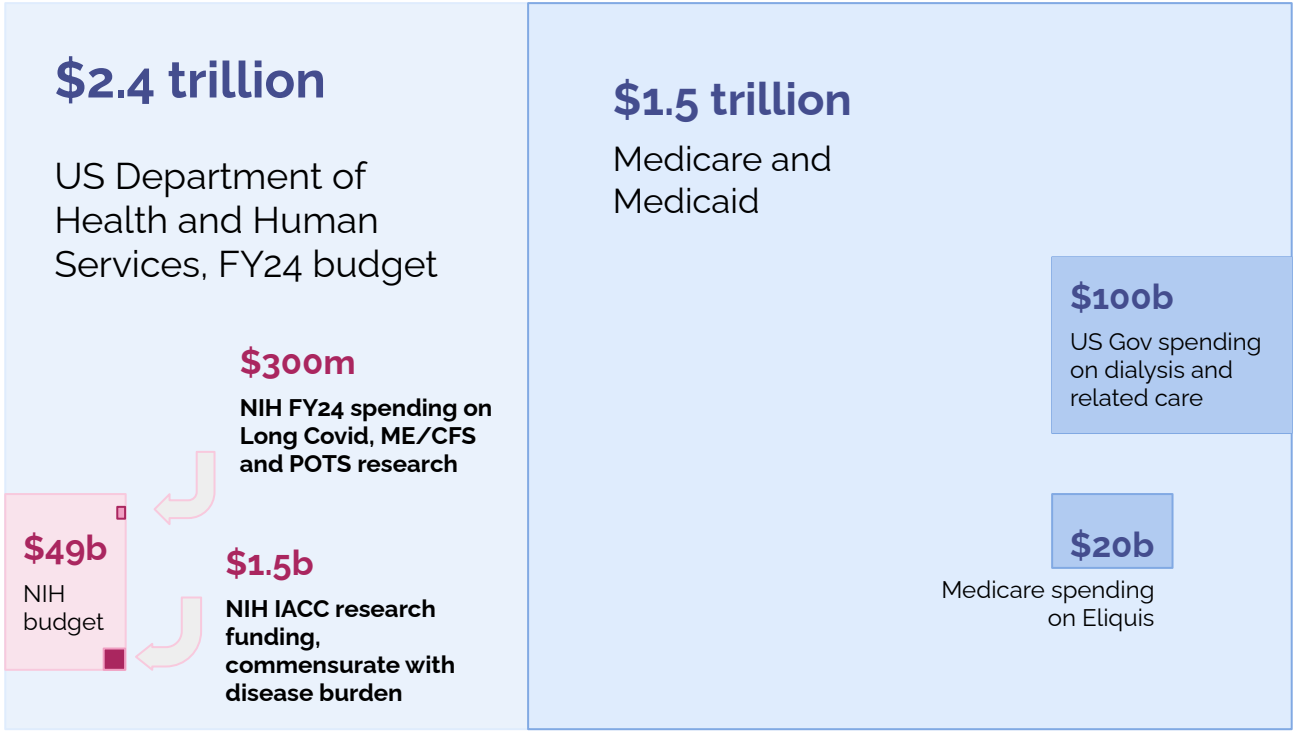
Research budgets are small compared to health expenditure

Funding IACC research at $1.5b per year would constitute approximately 3% of NIH's research budget, and just 0.06% of the budget of the US Department of Health and Human Services

The scale of investment required to meaningfully address IACCs is small.

Research funding commensurate with IACCs' estimated disease burden would be approximately $1.5b per year, about 0.06% of the $2.4 trillion annual budget of the US Department of Health and Human Services [84, 85].

By comparison, the US Government outlays over $100b every year on dialysis and related care [86] and the Medicare program spends about $2b per month on one drug, Eliquis, alone [87].



Medical breakthroughs are possible - and can be transformational

Recent breakthroughs in Cystic Fibrosis, ALS and MS show that targeted investments yield results. For IACCs, there is potential to alleviate suffering for tens or hundreds of millions of people



Breakthroughs are possible

Recent breakthroughs serve as reminders that diseases once thought to be incurable or fatal need not be so, sometimes even given modest investment. Cystic Fibrosis was long regarded as a fatal inherited disease of childhood, but with a 2019 breakthrough in the development of the highly effective CFTR modulator therapy, prognosis has improved so greatly that there are now more adults than children with the condition [88].

A similar transformation is underway for ALS. Over the last decade, NIH funding for ALS has increased from some $50m annually to over $200m in 2023 [89], and the number of FDA approved drug and drug formulations have increased from just 1 prior to 2014 to 7 today [90].

Just a generation ago, MS was a guarantee of profound disability, and a potential drug rejected by the NIH as 'biologically implausible.' [91] Breakthroughs in 2017 and 2020 of the development of ocrelizumab and ofatumumab now give many MS patients disability-free lives, with scientists now targeting a cure 'within our lifetime' [92]. It is not implausible that such a goal should be within reach for many IACCs, given meaningful investment.



Alleviating suffering

The pandemic and Long Covid's enormous disease burden have provided a great impetus for making the long needed paradigm shift into systematically considering the medium and long term effects of infectious diseases. The acceleration of research has yielded a great many insights and leads which now need replication and further exploration.

Symptom-improving treatments for IACCs have the potential to improve the quality of life and alleviate suffering for tens of millions, if not hundreds of millions of people worldwide. Treatments that support patients to improve their functionality would allow people to be more independent in their self-care and ADLs, participate more within their communities and re-engage with the labor force.

Curative treatments for IACCs hold enormous return-on-investment potential, especially as IACCs tend to have relatively early onset compared to many chronic diseases; one study found peaks of ME/CFS at onset at the 10-19 and 30-39 age groups [93]. A symptom-eliminating or curative treatment would provide decades of disability-free life to millions of young people today who may otherwise be locked out of having a family or career.

A number of barriers have slowed progress in IACC research

Until recently, IACC research has been obstructed by the slow progression of paradigm shifts in science, psychosocial diagnoses, and historical neglect on women's health

Despite their relative prevalence and waves of interest throughout the 20th century, research and policy interest on IACCs have remained scarce until recently. A number of barriers have presented as intractable challenges historically, though there have been signs of progress against each. Three are summarised below - the slow nature of paradigm shifts in science, psychosocial diagnoses, and historical neglect on women's health.



Paradigm shifts

Paradigm shifts in science can be slow. The archetypal example is the discovery of the role of H. Pylori in gastritis, which won Dr. Barry Marshall the Nobel Prize after he ingested a culture of the bacteria [94]. Others did not live to see their ideas take hold; advocating for the practice of handwashing in medicine cost Dr. Ignaz Semmelweis his career in the mid-1800s [95]. Scientists are not immune to misalignment in incentives, susceptible to everything from cognitive biases to outright misconduct. Dr. Eliezer Masliah, a senior Alzheimer's researcher, was recently found to have engaged in misconduct by a NIH investigation [96] casting into doubt his role in directing some $2.6b in annual research funding.



Mind over matter

A persistent paradigm presenting a barrier to IACC research is the psychosocial diagnoses. Conversion disorder, also known as Functional Neurological Disorder (FND), remains on the DSM, defined as neurological symptoms not better explained by another medical or mental disorder [97]. By definition, any patient with a condition that is difficult to diagnose or not yet well understood by medicine can be diagnosed with FND. This diagnosis presents a challenge to patients as they are typically offered only CBT and Graded exercise therapy (GET) as treatment, often resulting in a worsening in condition [98, 99], and to medical progress as it presents a barrier to research on less-understood neurological conditions. CBT and GET were recently removed from the UK's NICE Guidelines for ME/CFS [100].



Women's health

Women's health is historically underfunded - analysis of NIH research funding found that diseases predominantly affecting women were underfunded relative to their disease burden and that the impact of relatively well-funded diseases on women's health such as lung cancer and Alzheimer's Disease was understudied [101]. Recent efforts are seeking to rectify these issues, with a 2024 NASEM report calling for the NIH to enhance their efforts to study chronic conditions in women [102] and an Office for Autoimmune Disease Research was established in the NIH's Office of Research on Women's Health [103].

Implementation of policy recommendations has been inconsistent

Several countries have published delivery plans and inquiry reports but implementation remains pending

Table 5: IACC policy papers and recommendations, selected jurisdictions

Policy paper	Country, year	Selected recommendations	Implemented?
Aktionsplan zu postakuten Infektionssyndromen (Action Plan on Post-Acute Infectious Syndromes)	***Austria, 2024***	• Create a centralized research hub, establish a unified research framework for IACCs • Prioritize biomarker discovery, develop longitudinal cohort studies • Promote cross-disciplinary research and international collaboration	TBD
Dealing with the fallout: Post-COVID Condition and its continued impact on individuals and society	***Canada, 2024***	• Clinical practice guidance, improve training for healthcare providers, establish network of IACC clinics • Accelerate research on pathogenesis, expand clinical trials • Scale-up prevention interventions including improving ventilation in schools, workplaces and public spaces.	TBD
Sick and tired: Casting a long shadow; A report of the Parliamentary Inquiry into Long COVID and Repeated COVID Infections	***Australia, 2023***	• Establish a national research program to coordinate and fund Long Covid research • Support and education for GPs and other healthcare providers, outreach Long Covid clinics • Develop national indoor air quality standards • Fund ME/CFS research and patient support in consultation with peak bodies.	One recommendation partially implemented
National Research Action Plan on Long COVID	***US, 2022***	• Accelerating research and innovation in Long Covid, with seven research areas including diagnostics, pathophysiology, epidemiology, impact on wellbeing, therapeutics, human services, and health economics.	Partially implemented
My full reality: the interim delivery plan on ME/CFS	***UK, 2022***	• Establish a research working group, improve care for ME/CFS, support children and young people • Final delivery plan is due expected early 2025	Final delivery plan delayed by over two years

Recommendations: Accelerate research, Improve care, Prevent new cases

Governments should partner with industry, healthcare professionals and patients to accelerate the development of diagnostics and treatments, and improve care to reduce suffering in the meantime

Accelerate research

Governments should **partner with industry and patient groups to accelerate research** and **increase research funding** to a level commensurate with the disease burden of IACCs

- Partner with the pharmaceutical industry, patients and regulators to **streamline the development of IACC diagnostics and therapeutics and accelerate novel developments in Phase 2 and Phase 3**, including guidelines on definitions, diagnostic criteria, endpoints, expedited review pathways and Emergency Use Authorizations.
- **Commit to a sustained level of research funding for IACCs** commensurate with their disease burden and size of economy; as an indicative guideline, this would be on the order of $1.5b USD p.a. for the US, $250m for Germany, $200m for the UK, and $100m for Canada and Australia.
- **Establish specialist clinics working as translational research centers** that bridge the gap between cutting-edge research and patients
- **Establish targeted research programs and coordinating offices**, e.g. an Office for IACC research at the NIH, to prioritise and coordinate IACC research.
- **Develop international collaboration between governments** to encourage increased research spend by recognizing its cross-border benefits.
- **Provide research-supporting infrastructure, including biobanks**, patient and clinical trial registries.

Improve care

Medical professional training and IACC programs

- Improve access and quality of Long Covid and IACC care, and shorten time to diagnosis, through **updated guidelines, training of medical professionals and dedicated clinics**
- **Streamline access** to disability benefits and support services
- **Develop Severe ME/CFS Safe Hospital protocols** to prevent Severe ME/CFS deaths.

Prevent new cases

Public education and **cleaner indoor air**

- Prevent Covid reinfections, particularly in public settings such as schools and health facilities through **investments in ventilation and air filtration systems**
- **Public health communication** to improve the awareness of Long Covid and other IACCs to shorten time to diagnosis

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