

WHAT YOU NEED TO KNOW ABOUT ME/CFS

EVIDENCE-BASED KNOWLEDGE AND
EXPERT MEDICAL OPINION



ME/CFS Background

Context

The NICE Guideline on ME/CFS

Research evidence: disease pathology

Advancing ME/CFS Research

How you can help





What you need to know about ME/CFS was written by **Dr Katrina Pears**, Research Coordinator for The ME Association.

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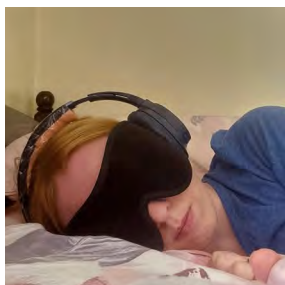
ME Connect is not intended to be a substitute for personalised medical advice or treatment. You should consult your doctor whenever a new symptom arises, or an existing symptom worsens. It is important to obtain medical advice that considers other causes and possible treatments. Do not assume that new or worsened symptoms are solely because of ME/CFS or Long Covid.



WHAT YOU NEED TO KNOW ABOUT ME/CFS

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ME/CFS affects everyone differently and its impact varies widely – for some people symptoms still allow them to carry out some activities, whereas for others they cause substantial incapacity.



INTRODUCTION

This booklet provides a summary of what you need to know about ME/CFS and is based on the evidence-based NICE Guideline, expert medical opinion, and the result of medical research. It considers key symptoms, diagnosis, multidisciplinary care, what might cause the disease, predisposing, precipitating and perpetuating factors, and explains what the research has been telling us about the underlying disease process.

BACKGROUND

- ME/CFS is a complex, chronic medical condition affecting multiple body systems and its pathophysiology is still being investigated.
- It can cause many different symptoms, which can be triggered or worsened by any kind of effort or activity.
- It affects everyone differently and its impact varies widely – for some people symptoms still allow them to carry out some activities, whereas for others they cause substantial incapacity.
- It is a fluctuating condition in which a person's symptoms can change unpredictably in nature and severity over a day, week or longer.
- It can affect different aspects of the lives of both people with ME/CFS and their families and carers, including activities of daily living, family life, social life, emotional wellbeing, work and education.
- People with ME/CFS may have experienced prejudice and disbelief and could feel stigmatised by others (including family, friends, health and social care professionals, and teachers) who do not understand their illness.
- Because it can look like many other illnesses, people often face uncertainty and delays in diagnosis.
- Symptoms include sleep difficulties, brain fog, debilitating fatigue that is unlike normal tiredness, orthostatic intolerance, as well as post-exertional malaise (PEM) - the worsening of symptoms that can follow minimal cognitive, physical, emotional or social activity, or activity that could previously be tolerated.
- People may also experience chronic pain, headaches, nausea, digestive problems, and sensitivity to light, sound and other stimuli.

The quality of life of people with ME/CFS is lower than that of many people with other severe chronic conditions, including multiple sclerosis and some forms of cancer.



BACKGROUND

- Symptoms often fluctuate in both nature and severity, causing distress and disrupting people's lives.
- There are options that can help people manage their ME/CFS, but the most important is to pace mental and physical activity. See more information in our MEA information leaflets which cover all aspects of symptom management:

<https://meassociation.org.uk/free-literature-downloads/>

CONTEXT

- Over 404,000 people in the UK have ME/CFS, however, the exact prevalence in the UK is unknown, especially given the rise in incidence after the Covid-19 pandemic.
- About 2.4 times as many women are affected as men.
- ME/CFS can affect people of all ages. It is a complex, multi-system, chronic medical condition that has considerable personal, social and economic consequences and a significant impact on a person's quality of life, including their psychological, emotional and social wellbeing.
- Everyday life for people with ME/CFS, their family and carers is disrupted and unpredictable. Many people with the condition are unemployed, and less than a fifth work full-time.
- Approximately 25% have severe or very severe disease and remain housebound or bedbound.
- The quality of life of people with ME/CFS is lower than that of many people with other severe chronic conditions, including multiple sclerosis and some forms of cancer.
- It is not clear what causes ME/CFS. In many cases, symptoms are thought to have been triggered by an infection, but it is not simple post-illness fatigue. It lasts longer and even minimal mental or physical activity can make symptoms worse.
- There is no diagnostic test or universally-accepted definition for ME/CFS. People with the condition report delays in diagnosis, and many healthcare professionals lack the confidence and knowledge to recognise, diagnose and manage it.



CONTEXT

■ The terms myalgic encephalomyelitis (ME; or encephalopathy), chronic fatigue syndrome (CFS), CFS/ME and ME/CFS have all been used for this condition and there are different clinical and research definitions for each name.

■ There is no sound pathological evidence of widespread inflammation involving the brain and spinal cord, which makes the term 'encephalomyelitis' problematic.



■ Myalgic encephalomyelitis is classified by World Health Organisation (WHO) under diseases of the nervous system in the SNOMED CT and ICD10 (G93.3), ICD11 (8E49).

■ Many people with ME/CFS consider the name 'chronic fatigue syndrome' too broad, simplistic and judgemental.

■ For consistency, the abbreviation ME/CFS is used by the ME Association and by the National Institute for Health and Care Excellence (NICE) in its guideline.

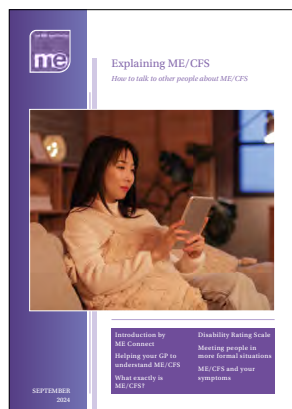
People with ME/CFS report a lack of belief and acknowledgement from health and social care professionals about their condition and related problems, which may lead them to be dissatisfied with care and to disengage from service.

■ Fatigue associated with another chronic disease may be confused with ME/CFS and some practitioners are reluctant to positively diagnose ME/CFS when no other causes are found.

■ People with ME/CFS report a lack of belief and acknowledgement from health and social care professionals about their condition and related problems, which may lead them to be dissatisfied with care and to disengage from services.

■ There are added issues for children and young people if illness makes school attendance difficult, bringing families to the attention of educational and social care services.





Explaining ME/CFS to other people

In this booklet we consider just how much of an added burden it can be when others in your life do not understand ME/CFS, and we examine ways in which communication can be improved.

You can download a free PDF file of this item here:

<https://meassociation.org.uk/5t5e>

THE NICE GUIDELINE ON ME/CFS

The National Institute for Health and Care Excellence (NICE) provides evidence-based clinical recommendations to healthcare professionals in England which are also recognised in Northern Ireland, Scotland and Wales.

In October 2021, NICE produced a new guideline on ME/CFS following extensive stakeholder consultation, and we recommend that any patient, carer or family member takes the time to read the recommendations it contains and learn what can be expected from the NHS and social care services.

We fully endorse the recommendations and will continue to work with national and local healthcare providers to ensure the guideline is implemented effectively as it offers the best chance of improving health outcomes for people with ME/CFS.

The MEA has produced a booklet, NICE Guideline on ME/CFS: An ME Association Summary. You can download it free here:

<https://meassociation.org.uk/9d0l>

Key Symptoms

■ Suspect ME/CFS if:

- the person has had all of the persistent symptoms in **Box A: Symptoms for suspecting ME/CFS** on page 7 for a minimum of six weeks in adults and four weeks in children and young people and,
- the person's ability to engage in occupational, educational, social or personal activities is significantly reduced from pre-illness levels and,
- symptoms are not explained by another condition.



THE NICE GUIDELINE ON ME/CFS

BOX A: SYMPTOMS FOR SUSPECTING ME/CFS

All of these symptoms should be present:

1. Debilitating fatigue that is worsened by activity, is not caused by excessive cognitive, physical, emotional or social exertion, and is not significantly relieved by rest.

2. Post-exertional malaise after activity in which the worsening of symptoms:

- is often delayed in onset by hours or days.
- is disproportionate to the activity.
- has a prolonged recovery time that may last hours, days, weeks or longer.

3. Unrefreshing sleep or sleep disturbance (or both), which may include:

- feeling exhausted, feeling flu-like and stiff on waking
- broken or shallow sleep, altered sleep pattern or hypersomnia.

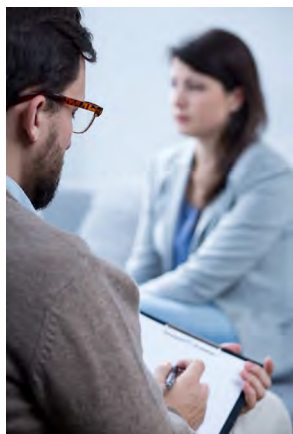
4. Cognitive difficulties (sometimes described as 'brain fog'), which may include problems finding words or numbers, difficulty in speaking, slowed responsiveness, short-term memory problems, and difficulty concentrating or multitasking.

Other common symptoms

■ Be aware that the following symptoms may also be associated with, but are not exclusive to, ME/CFS:

- Pain which can affect muscles (myalgia), joints (arthralgia) and nerves (neuropathic) but is minimal or not present at all in a minority of people. Pain is often difficult to alleviate with simple analgesics and may be accompanied by sensory disturbances/ paraesthesia.
- Poor temperature control/thermoregulation including increased sensitivity to hot and cold environments, sweating episodes, feeling feverish.
- On-going flu-like symptoms including sore throats and tender glands without pathological enlargement.
- Intolerance or increased sensitivity to alcohol, chemicals and medications – especially psychotropic (antidepressant) drugs.
- Headaches of a new type or severity that may have a migrainous quality





Refer adults directly to an ME/CFS specialist team to confirm their diagnosis and develop a care and support plan.



THE NICE GUIDELINE ON ME/CFS

- Sensory disturbances including paraesthesiae ('pins and needles') and increased sensitivity to touch, noise (hyperacusis) and bright light (photophobia)
- Digestive disturbances consistent with irritable bowel syndrome (i.e. abdominal pain, bloating, change in bowel habit) which may develop following the onset of ME/CFS and can be exacerbated by certain foods

Diagnosis

- Explain to people presenting with possible symptoms of ME/CFS that there currently is no diagnostic test for ME/CFS, and it is recognised on clinical grounds alone.
- Diagnose ME/CFS in a child, young person or adult who has key symptoms that have persisted for 3 months and are not explained by another condition.
 - Primary healthcare professionals should consider seeking advice from an appropriate specialist if there is uncertainty about interpreting signs and symptoms at 3 months and whether further investigations are needed.
- Refer adults directly to an ME/CFS specialist team (see **Box B** on page 9) to confirm their diagnosis and develop a care and support plan.
- Refer children and young people who have been diagnosed with ME/CFS after assessment by a paediatrician directly to a paediatric ME/CFS specialist team (see **Box B: ME/CFS Specialist Team** on page 9) to confirm their diagnosis and develop a care and support plan.

THE NICE GUIDELINE ON ME/CFS

Box B: ME/CFS Specialist Team

- Specialist teams consist of a range of healthcare professionals with training and experience in assessing, diagnosing, treating and managing ME/CFS.
- They commonly have medically-trained clinicians from a variety of specialisms (including rheumatology, rehabilitation medicine, endocrinology, infectious diseases, neurology, immunology, general practice and paediatrics) as

well as access to other healthcare professionals specialising in ME/CFS.

- These may include physiotherapists, exercise physiologists, occupational therapists, dietitians, and clinical or counselling psychologists.
- Children and young people are likely to be cared for under local or regional paediatric teams who have experience of working with children and young people with ME/CFS in collaboration with ME/CFS specialist centres.



People with mild ME/CFS care for themselves and do some light domestic tasks (sometimes needing support) but may have difficulties with mobility.



Severity of ME/CFS

Definitions of severity are not clear cut because individual symptoms vary widely in severity and people may have some symptoms more severely than others. The definitions below provide a guide to the level of impact of symptoms on everyday functioning.

■ Mild ME/CFS

People with mild ME/CFS care for themselves and do some light domestic tasks (sometimes needing support) but may have difficulties with mobility. Most are still working or in education, but to do this they have probably stopped all leisure and social pursuits. They often have reduced hours, take days off and use the weekend to cope with the rest of the week.

■ Moderate ME/CFS

People with moderate ME/CFS have reduced mobility and are restricted in all activities of daily living, although they may have peaks and troughs in their level of symptoms and ability to do activities. They have usually stopped work or education, and need rest periods, often resting in the afternoon for 1 or 2 hours. Their sleep at night is generally poor quality and disturbed.

■ Severe ME/CFS

People with severe ME/CFS are unable to do any activity for themselves or can carry out minimal daily tasks only (such as face washing or



People with very severe ME/CFS are in bed all day and dependent on care. They need help with personal hygiene and eating and are very sensitive to sensory stimuli.



THE NICE GUIDELINE ON ME/CFS

cleaning teeth). They have severe cognitive difficulties and may depend on a wheelchair for mobility. They are often unable to leave the house or have a severe and prolonged after-effect if they do so. They may also spend most of their time in bed and are often extremely sensitive to light and sound.

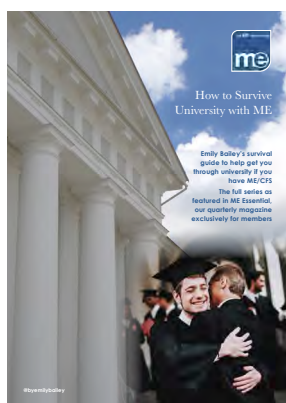
■ Very severe ME/CFS

People with very severe ME/CFS are in bed all day and dependent on care. They need help with personal hygiene and eating and are very sensitive to sensory stimuli. Some people may not be able to swallow and may need to be tube-fed.

Multidisciplinary care

■ Provide care for people with ME/CFS using a coordinated multidisciplinary approach. Based on the person's needs, include access to health and social care professionals with expertise in the following as a minimum, with additional expertise depending on symptoms:

- medical assessment and diagnosis.
- developing personalised care and support plans.
- self-management strategies, including energy management.
- symptom management, including prescribing and medicines management.
- managing flare-ups and relapses.
- activities of daily living, including dental health.
- psychological, emotional and social wellbeing, including family and sexual relationships.
- diet and nutrition.
- mobility, avoiding falls and problems from loss of dexterity, including access to aids and rehabilitation services.
- social care and support.
- support to engage in work, education, social activities and hobbies.



THE NICE GUIDELINE ON ME/CFS

- Care for people whose ME/CFS is managed in primary care should be supported by advice and direct clinical consultation from an ME/CFS specialist team.
- Give adults, children and young people with ME/CFS and their family or carers (as appropriate) a named contact in their primary care and/or ME/CFS specialist team to coordinate their care and support plan, help them access services and support them during periods of relapse.
- Provide children and young people with ME/CFS and their family or carers (as appropriate) with details of a named professional in the ME/CFS specialist team who they can contact with any concerns about the child or young person's health, education or social life.

Source:

The 2021 NICE Guideline on ME/CFS: diagnosis and management.

<https://www.nice.org.uk/guidance/ng206>.

MORE INFORMATION

- The ME Association has produced a wide range of FREE literature about ME/CFS and Long Covid written by topic experts for you to download:

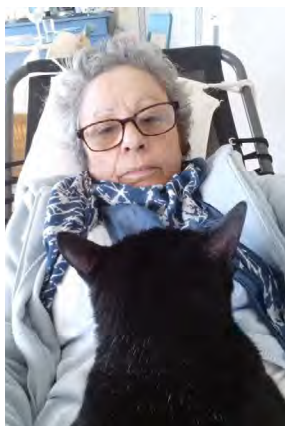
- Diagnosis of ME/CFS: <https://meassociation.org.uk/dmec>
- Management: <https://meassociation.org.uk/a7x9>
- Long Covid & ME/CFS: Are they the same condition?: <https://meassociation.org.uk/vqei>
- Benefits: <https://meassociation.org.uk/btci>
- Employment : <https://meassociation.org.uk/vo36>
- Education: <https://meassociation.org.uk/9mme>

- You can also find the NICE Guideline on ME/CFS (and the NICE Rapid Guideline on Long Covid) on the website.

- The final delivery plan on ME/CFS was developed in consultation with a wide range of government, NHS and external stakeholders. It can be found on the government website, here:

<https://tinyurl.com/2uewhxk6>

ME/CFS is most often triggered by an infection leading to a chronic disease state in susceptible individuals, resulting in key symptoms that cause functional impairments and a reduced quality of life.



THE NICE GUIDELINE ON ME/CFS

Causation

The underlying cause of ME/CFS is still subject to medical debate. This is one of the reasons why a few doctors can hold differing views on how people with the condition should be managed.

However, with the NICE Guideline on ME/CFS, the DHSC Delivery Plan and renewed interest in this field as a result of Long Covid, there is now a widely-held consensus view that ME/CFS is perpetuated by a physical disease process.

Traditionally there were three main views held by the medical profession:

1. That ME/CFS is most often triggered by an infection leading to a chronic disease state in susceptible individuals, resulting in key symptoms that cause functional impairments and a reduced quality of life.

■ This is the view that has been held by the ME Association since we were established in 1980 and is one that is gaining much wider acceptance.

■ An increasing number of research studies have shown that the disease process involves for example, the brain and nervous systems, the immune system, the endocrine (hormone-producing) system, muscle, and mitochondria (energy-producing cells).

■ However, while these studies have produced interesting results, they are often small and in need of replication. But the recent interest in Long Covid is having a positive effect as studies are revealing similar results on a larger scale.

■ In regard to emotional and behavioural issues, we believe they are a perfectly understandable result of living with – and not a cause of – ME/CFS and should be treated, where appropriate, by mental health professionals who form part of multidisciplinary ME/CFS specialist services.



While ME/CFS is not a genetic disorder in the sense that it can be passed from parent to child, there is growing evidence that some people have a genetic make-up that increases the risk of ME/CFS developing when a trigger factor, such as an infection, occurs at a particular time in their life.



THE NICE GUIDELINE ON ME/CFS

2. That ME/CFS involves a combination of physical, psychological, and social factors: the biopsychosocial (BPS) model.

■ This model assumes that, although ME/CFS is often triggered by a physical stressor such as infection, ongoing ill health is primarily sustained by maladaptive behaviours, unhelpful illness beliefs, and inactivity leading to physical deconditioning. It has also been linked to outdated views that frame ME/CFS as a somatic symptom disorder or a mental health condition, rather than a complex biomedical illness. These assumptions have contributed to stigma, misdiagnosis, and the promotion of inappropriate treatments that fail to address the biological basis of the disease.

3. That ME/CFS is a psychiatric disorder with no physical disease process.

■ A few doctors still take the view that ME/CFS does not exist or is just a form of atypical depression or hysteria, despite evidence to the contrary.

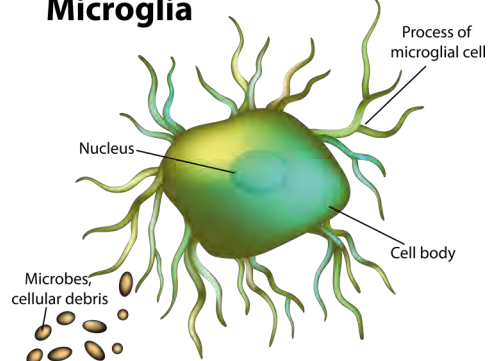
The model and the belief that ME/CFS is a psychiatric disorder are linked to claims that graded exercise therapy (GET), and cognitive behaviour therapy (CBT), are effective treatments. However, following a detailed review of the evidence, the NICE guideline committee concluded that GET should not be recommended to people with ME/CFS and that CBT was not curative but might be used to help people who were struggling to cope with the condition.

The ME Association (MEA) does not endorse the biopsychosocial (BPS) model for ME/CFS and firmly states that ME/CFS is not a psychiatric disorder. It opposes graded exercise therapy (GET) and supports cautious use of cognitive behavioural therapy (CBT) only as a supportive tool to help patients cope with the impact of chronic illness — not as a cure.

With the NICE Guideline on ME/CFS and other more recent developments, the NHS and social care providers should have an improved awareness and an increased understanding of ME/CFS. We hope that people with this very real disease will now feel believed, have their experiences validated and receive a much better standard of care and support from healthcare providers.

THE NICE GUIDELINE ON ME/CFS

Microglia



Microglial cells, found in the central nervous system (CNS). Structure of microglia

New research on brain structure and function suggests that infections, or events prior to the onset of ME/CFS, may help to prime or activate immune-system cells in the brain called microglia.

Is ME/CFS a three-stage illness?

There is a considerable degree of agreement emerging that we are dealing with a three-stage process in ME/CFS. This involves specific factors that predispose, precipitate and perpetuate the various symptoms.

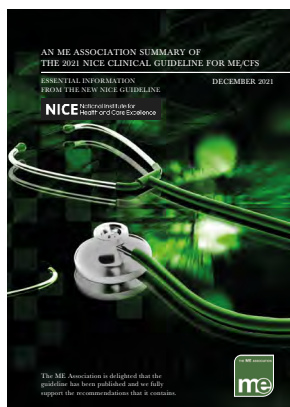
■ Predisposing factors:

- As with many chronic diseases – arthritis, cancer, heart disease, etc. – it appears that genetic factors may play a role.
- While ME/CFS is not a genetic disorder in the sense that it can be passed from parent to child, there is growing evidence that some people have a genetic make-up that increases the risk of ME/CFS developing when a trigger factor, such as an infection, occurs at a particular time in their life.
- This genetic predisposition may also help to explain why there are families with more than one member who has ME/CFS.
- New research on brain structure and function suggests that infections, or events prior to the onset of ME/CFS, may help to prime or activate immune-system cells in the brain called microglia. When faced with another infection, this priming of the microglia may then make some people more vulnerable to developing ME/CFS.

■ Precipitating factors:

- One area where there is a considerable degree of medical agreement relates to what triggers or precipitates ME/CFS.
- Most people with this illness pre-date the onset of their symptoms to an infection – normally viral but sometimes bacterial – from which they ‘fail to recover’ and continue to have ‘flu-like symptoms’, along with the very characteristic muscle and brain symptoms that are associated with ME/CFS.
- Evidence suggests that the Epstein Barr virus (EBV) which can cause glandular fever, and the influenza viruses which can cause the Flu, are two of the most common viral triggers, but anecdotal and research evidence indicates that a wide range of





NICE Guideline on ME/CFS: An ME Association Summary

This booklet is recommended reading. It lets you know what to expect from the NHS and social care services with regard to symptom recognition, diagnosis, management, referral, and ongoing care and support.

You can download a free PDF file of this item here:

[https://
meassociation.org.
uk/9d0l](https://meassociation.org.uk/9d0l)



THE NICE GUIDELINE ON ME/CFS

viral or bacterial infection has the potential to trigger ME/CFS in susceptible individuals.

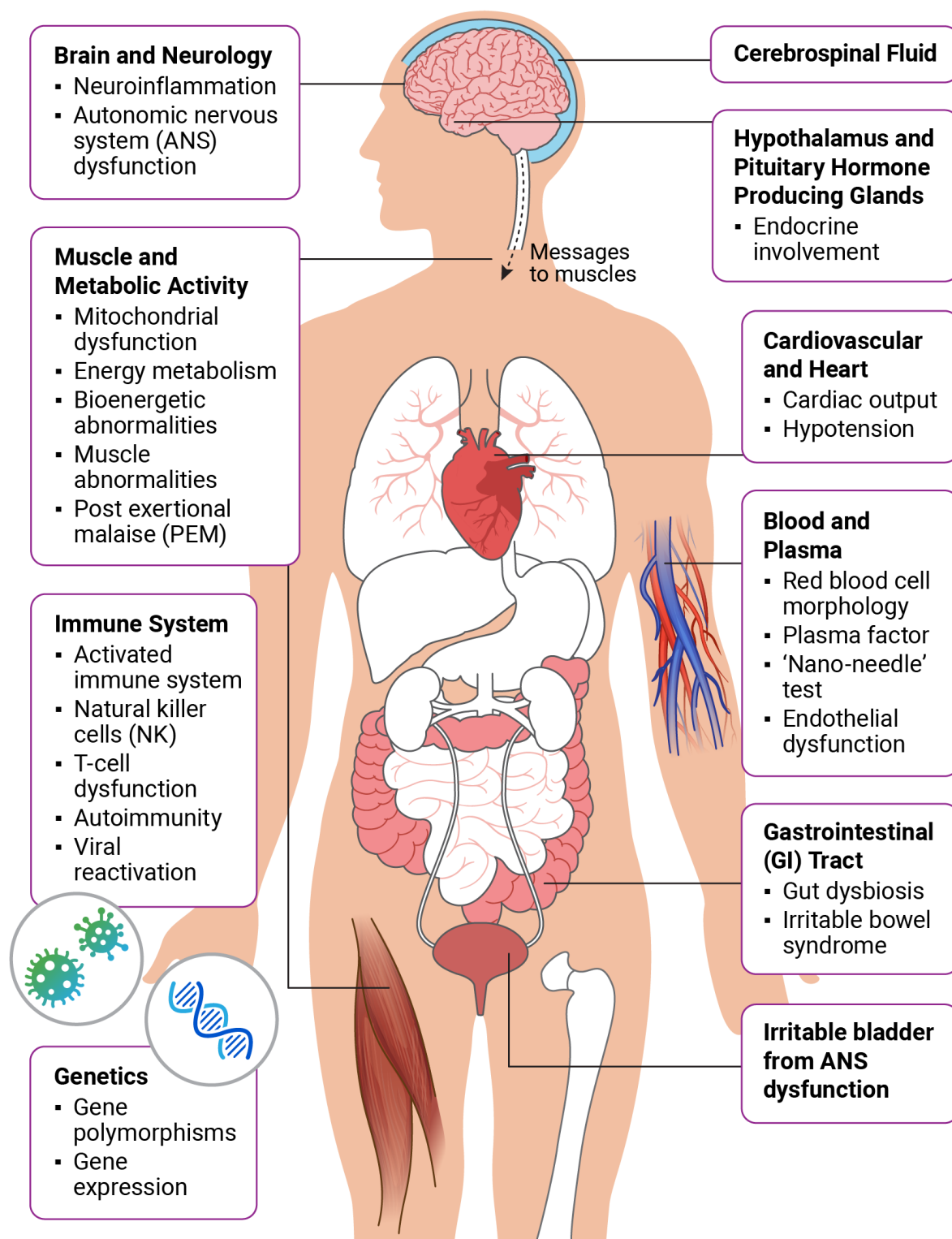
- Other types of immune-system stressors – vaccinations, trauma, pregnancy, surgery – can also occasionally trigger ME/CFS.
- Stress – physical, mental, emotional, or a combination of all three – around the time of a triggering event, or during the period of convalescence, can be an important co-factor in determining whether someone develops ME/CFS and whether the individual is able to return to pre-illness levels of functional ability.

■ Perpetuating factors:

- This is where the situation becomes far more uncertain, and where disagreements emerge in relation to what then perpetuates or keeps the illness going.
- Those who – like the ME Association – adhere to the physical model of causation believe that ME/CFS is perpetuated by a complex interaction involving changes to the way in which the brain, nervous system, muscle, immune and endocrine systems respond to the triggering viral infection, or other immune-system stressor. When the infection or other event has passed, the body fails to return to its normal state, symptoms persist and new symptoms develop, and functional incapacity continues or worsens.
- Studies have consistently shown immune dysregulation, neuroinflammation, energy metabolism impairments, and autonomic dysfunction in ME/CFS. These are not secondary effects of inactivity or anxiety – they are primary disease mechanisms, supporting the physical model of causation.
- Those who incorrectly believe that ME/CFS is a mental health or somatic symptom disorders disorder argue that symptoms are largely prolonged by what are called abnormal illness beliefs and behaviours, along with physical deconditioning. And that any physical abnormalities are caused by factors such as sleep disturbance and inactivity, despite there being no evidence to support these theories.

There is an array of research evidence for the disease pathology throughout the body. The exact cause of ME/CFS is unknown, with many different systems showing some form

of dysfunction. Consequently, this adds to the medical debate on the underlying causes of ME/CFS, with a combination of factors being most likely.



Studies have shown cytokine-mediated, low-level immune-system activation, in the blood and cerebrospinal fluid (cytokines are produced in response to any type of infection).

RESEARCH EVIDENCE: DISEASE PATHOLOGY

GENETICS

Gene polymorphisms

■ (variations in DNA sequences) have been identified, which are involved in various processes such as immune modulation, oxidative stress and energy metabolism.

Gene expression

■ Under and over-expression of certain genes and miRNAs (small molecules that regulate gene expression) may explain some symptoms and also account for an increased susceptibility to developing ME/CFS.

■ They also represent potential biomarkers for diagnosis and drug treatment targets. miRNAs might be used to place patients into subgroups.

Genome-Wide Association Study (GWAS)

DecodeME, the world's largest ME/CFS study (£3.2m), analysed DNA from over 15,000 people. The initial findings have shown:

■ ME/CFS has a genetic basis. While it is not a genetic disease in the sense of being inherited, certain genetic factors may influence how the illness develops.

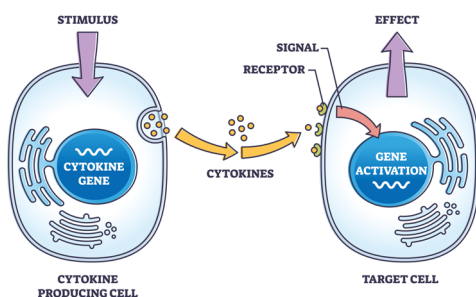
■ Eight DNA signals were identified, pointing to immune-system regulation, neurological function, and infection response =highlighting biological pathways that could help explain what causes ME/CFS.

■ No genetic link was found to depression or anxiety.

■ Sex differences remain unexplained.

■ These findings give researchers clearer targets in the search for the underlying mechanisms of the illness.

CYTOKINES



RESEARCH EVIDENCE: DISEASE PATHOLOGY

3D Genomic profiling

One small study used 3D epigenomic mapping, a technique that examines how DNA is folded and organised in three-dimensional space inside cells. This folding influences which genes are active and how the immune system functions.



Using this method, researchers scanned the entire genome and identified 200 epigenetic markers that were consistently different in people with ME/CFS compared to healthy controls. These markers are linked to immune activity, inflammation, and energy metabolism — all areas believed to play a role in ME/CFS.

The authors suggest that their findings could help in developing a diagnostic blood test for ME/CFS, but further rigorous testing is required.

<https://meassociation.org.uk/7bnj>

IMMUNE SYSTEM

Activated immune system:

■ Studies have shown cytokine-mediated, low-level immune system activation, in the blood and cerebrospinal fluid (cytokines are produced in response to any type of infection).

■ This results in low-grade inflammation and a general 'sickness response', involving decreased appetite, wanting to sleep a lot and flu-like malaise and pain.

■ Several studies have demonstrated altered levels of inflammatory markers, called cytokines, and activated immune cells, such as lymphocytes. Prolonged higher levels of cytokines affect the body's ability to respond to stress, which may result in the development of disease, like ME/CFS.

■ UK ME/CFS Biobank researchers have found highly increased levels of a type of immune cell called MAIT (Mucosal Associated Invariant T-cell) cells in severely affected patients. The study was the feature of a research review.

Cliff *et al.* (2019) Cellular Immune Function in ME/CFS:

<https://tinyurl.com/3ztrmpnh>

*The UK ME/
CFS Biobank
researchers have
reported no
differences in
NK-cell number
and function in
patients compared
to controls.*



RESEARCH EVIDENCE: DISEASE PATHOLOGY

Natural killer cells (NK):

- Reduced NK-cell activity is a common research finding.
- NK-cells are a type of white-blood cell that comprise part of the immune system and act like security guards, circulating round the body looking for potential threats.
- However, UK ME/CFS Biobank researchers have reported no differences in NK-cell number and function in patients compared to controls. This study was the feature of a research review:

<https://meassociation.org.uk/4e59>

T-cell dysfunction:

- Studies have shown that there are problems in the way the immune T-cells produce energy, with ME/CFS having decreased levels of glycolysis (the process by which cells break down glucose to extract energy) at rest..
- Some patients have also shown difference in markers of T-cell activation, which suppress or activate an immune response.

Autoimmunity:

- Some studies have found activated T- and B-cells, as well as an increased incidence of autoantibodies (immune cells, that attack tissues of your own body, instead of targeting foreign cells, such as bacteria).
- Whether ME/CFS really is an autoimmune disease – like multiple sclerosis (MS) for example – is still being debated.

Viral reactivation

- There is conflicting evidence over the role of human herpesviruses (HHV) in ME/CFS.
- A common HHV is the Epstein Barr virus (EBV) which often results in glandular fever and is among the top recognised triggers that lead to the development on ME/CFS in susceptible individuals.



Studies have found disturbances involving the HPA axis, mainly demonstrating defects in the output of the hormone cortisol from the adrenal glands, which sit above the kidneys (lower level of cortisol = hypo-cortisolaemia).

RESEARCH EVIDENCE: DISEASE PATHOLOGY

■ HHVs can remain dormant in the body after the initial infection has passed and can be reactivated because of an immune-system stressor - which might be a cause of continuing or worsening symptoms and disability.

■ Evidence for this has been found in ME/CFS and Long Covid, and the topic was subject to a research review:

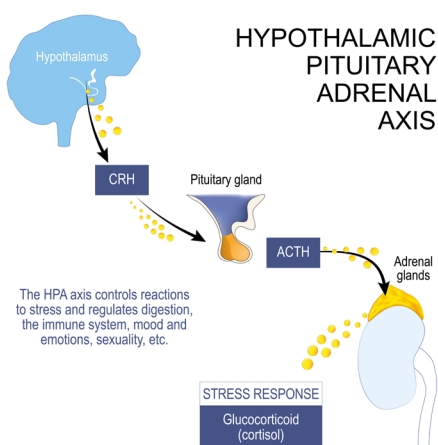
<https://meassociation.org.uk/hhml>

BRAIN AND NEUROLOGY

There is growing evidence of significant abnormalities involving the brain and central nervous system in ME/CFS and similar findings have been made in Long Covid.

Endocrine involvement: hormone-producing glands

■ This is one of the most consistent findings in research, involving the down-regulation of the hypothalamic-pituitary-adrenal (HPA) axis.



■ The hypothalamus and pituitary are small glands inside the brain that play a key role in the control and production of hormones.

■ Studies have found disturbances involving the HPA axis, mainly demonstrating defects in the output of the hormone cortisol from the adrenal glands, which sit above the kidneys (lower level of cortisol = hypocortisolaemia).

■ This could explain key symptoms such as fatigue, sleep dysfunction and temperature regulation.

Neuroinflammation

■ Several studies support the presence of neurobiological and spinal fluid abnormalities, some of which are consistent with low-level neuroinflammation. Studies from America found increased temperature inside the brains of ME/ CFS patients, as well as increased levels of metabolites, including lactate and choline.

■ bladder symptoms are very common.



RESEARCH EVIDENCE: DISEASE PATHOLOGY

Central Nervous System

■ Defects have been found in the basal ganglia pathways (areas of the brain which are extremely sensitive to cytokines). Post-mortem research has also found dorsal root ganglionitis (inflammation in a part of the peripheral nervous system). Abnormal microglia activation (immune cells in the brain) has been found in ME/CFS, a marker of inflammation.

Cerebrospinal fluid

■ Studies have shown abnormalities in proteins and white blood cells.

Autonomic nervous system (ANS) dysfunction

■ Abnormalities have been consistently reported in the ANS, this part of the brain is not under conscious control and sends messages to “speed up” or “slow down” to vital organs, such as the heart, bowel and bladder.

■ Studies have shown disturbances in the autonomic regulation of cardiovascular reflexes in a subgroup of patients.

■ POTS (Postural orthostatic tachycardia syndrome – represented by an abnormal increase in heart rate upon sitting or standing) is often also diagnosed as Neurally-mediated hypotension.

■ The ANS also controls circulation, which may help to explain why people with ME/CFS experience problems with cold extremities, and temperature regulation. ANS dysfunction may also explain why irritable bowel and bladder symptoms are very common.

Symptoms of Autonomic Dysfunction



Vertigo,
dizziness and
fainting



Fast, slow
or irregular
heartbeat



Chest pain



Low blood
pressure



Nausea



Weakness



Anxiety



Tremors



Concentration
and memory
problems



Migraines



Mood swings



Breathing
difficulties



Poor appetite



Stomach
upsets



Disrupted
sleep

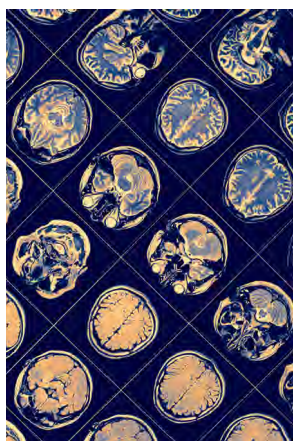


Fatigue and
intolerance to
exercise

Neuroimaging

■ Studies have demonstrated a number of structural and functional abnormalities compared to controls, including differences in the volume of white and grey matter in the brain, reduced cerebral blood flow,





Studies have demonstrated a number of structural and functional abnormalities compared to controls. This could help to explain symptoms of cognitive dysfunction, as well as pain.



RESEARCH EVIDENCE: DISEASE PATHOLOGY

neuroinflammation, larger brainstem volumes, altered cortical volume and thickness, volumetric difference in the hippocampal subfields and neuronal microstructural changes. This could help to explain symptoms of cognitive dysfunction, as well as pain.

MUSCLE AND METABOLIC ACTIVITY

Energy, or lack thereof, is a significant concern in ME/CFS and in Long Covid. There is growing evidence of dysfunction in mitochondria, which are often called the powerhouses of the cell, and are specialised structures that produce most of our cellular energy.

Energy metabolism pathways

■ Research suggests problems in the energy metabolism pathways, such as functional impairments involving an enzyme (a type of protein that acts as a catalyst for chemical reactions in the body) called pyruvate dehydrogenase and impairments in the activation of another enzyme called AMPK, leading to impaired glucose uptake.

Bioenergetic abnormalities

■ Researchers from Newcastle University reported cellular bioenergetic abnormalities. Several measures of mitochondrial function were found to be affected, but maximal respiration was found to be lower.

■ This suggests that, when the cells experience physiological stress, they are less able to elevate their respiration rate to fulfil cellular energy demands. However, the same research group in 2019 demonstrated that the activity of the enzyme complexes within the mitochondria are functioning normally.

■ This then suggests the abnormalities in energy production previously observed might be caused by something situated upstream of the mitochondria and do not represent problems with the mitochondria themselves. This topic was the subject of a research review on the role of mitochondria in ME/CFS:

<https://meassociation.org.uk/34hb>

Muscle biopsies have shown evidence of mitochondrial degeneration, deletions of mitochondrial DNA (DNA, located inside the mitochondria, which is inherited from your mother) and reduction of mitochondrial activity.



RESEARCH EVIDENCE: DISEASE PATHOLOGY

Mitochondrial dysfunction

■ Muscle biopsies have shown evidence of mitochondrial degeneration, deletions of mitochondrial DNA (DNA, located inside the mitochondria, which is inherited from your mother) and reduction of mitochondrial activity.

Muscle abnormalities

■ Several muscle abnormalities have been reported, including defects in muscle-energy metabolism, changes in muscle-fibre types, prolonged production of lactic acid (following exercise) and demonstrating PEM using repetitive isometric quadriceps exercise testing. These findings demonstrate that muscle symptoms cannot be due to inactivity/deconditioning.

Exercise-pathology: Post-Exertional Malaise (PEM)

■ Exercise-pathology research has demonstrated that a 2-day cardiopulmonary exercise test (CPET) can objectively confirm the presence of PEM and could be used as a diagnostic test.

■ This testing method has determined that PEM cannot be due to inactivity or deconditioning.

■ Recent research using metabolomics has shown that ME/CFS patients have a different response to exercise which affects their ability to recover previous functional ability. This has been subject to one of our research reviews:

<https://meassociation.org.uk/3h01>

BLOOD AND PLASMA

Red blood cell morphology

■ Research has shown that red blood cells from ME/CFS patients are 'stiffer' and less able to change shape (called deformability) to squeeze through small capillaries. This suggests blood flow and oxygen supply to cells may be reduced in ME/CFS. This study was the subject of a research review:

<https://meassociation.org.uk/dpvn>



Exercise-physiology research has demonstrated that a 2-day cardiopulmonary exercise test (CPET) can objectively confirm the presence of PEM and could be used as a diagnostic test.

Image courtesy of
Wiki Commons



RESEARCH EVIDENCE: DISEASE PATHOLOGY

Plasma factor

- Preliminary, unpublished studies from several independent groups have now found that a factor in the blood plasma (a component of the blood that doesn't include red blood cells) can affect cell metabolism in ME/CFS and that the effect can be transferred to healthy cells.
- They found that adding plasma from ME/CFS patients to healthy control cells made them increase their oxygen consumption, indicating the mitochondria were working harder. The factor in the blood responsible for these changes is yet to be identified.

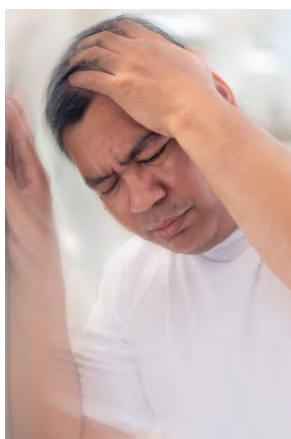
'Nano-needle' test

- Results from a pilot-study testing electrical impedance (ability of a current to pass through cells) in ME/CFS and healthy cells in plasma show that putting the cells under 'stress' and making them work harder resulted in a dramatic change in signal. It's as though the cells were unable to keep up with the added demand put on them.
- Interestingly, when plasma from ME/CFS patients was applied to healthy-control cells, the same signal occurred. This suggests a factor in the plasma was affecting the functioning of the cells.

Endothelial dysfunction

- The endothelium is a thin layer of cells lining the heart and blood vessels. Endothelial cells release substances that control vascular relaxation and contraction (by nitric oxide gas) as well as enzymes that control blood clotting, immune function and platelet (a colourless substance in the blood) adhesion.
- Impaired endothelial function could cause symptoms of chronic fatigue, and post-exertional malaise. This has been subject to a research review:

<https://meassociation.org.uk/04he>



There is some evidence of hypotension (low blood pressure), especially on standing, which could explain symptoms such as fatigue, dizziness, cognitive issues, tremors and nausea.



RESEARCH EVIDENCE: DISEASE PATHOLOGY

CARDIOVASCULAR / HEART

- **Cardiac output** - Some studies have found results suggesting low cardiac output as an explanation for poor physical stamina and chronic fatigue (as a symptom).
- **Hypotension** - There is also some evidence of hypotension (low blood pressure), especially on standing, which could explain symptoms such as fatigue, dizziness, cognitive issues, tremors and nausea.

GASTROINTESTINAL (GI) TRACT

Gut dysbiosis

- Gut dysbiosis means an imbalance of gut flora diversity – not enough beneficial bacteria and an overgrowth of bad bacteria.
- Researchers are currently investigating the role of the microbiome (the collection of different types of microbes, such as bacteria in the gut), with findings that indicate gut dysbiosis with altered composition and greater heterogeneity of microbes.
- This might contribute to general inflammation and to symptoms like fatigue and gastrointestinal symptoms.
- Other **gastrointestinal** findings show altered gut-brain activity, increased gut permeability, gut dysmotility and altered gut microbiome, which also vary depending on the duration of illness.
- However, studies in this area haven't established whether microbiome changes cause or contribute to the development of ME/CFS and resulting symptoms or whether these changes are in fact caused by patients being ill and unable to maintain a healthy balanced diet, for example.
- Similar findings have also been established in Long Covid.

METABOLISM



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RESEARCH EVIDENCE: DISEASE PATHOLOGY

Metabolic pathways

- Recent studies have found abnormalities in several metabolic (chemical) pathways, particularly those involved in glucose metabolism suggesting that there may be problems in converting glucose to energy.
- Other findings point towards a redox imbalance (where there are too many oxidising molecules compared to antioxidant molecules) and oxidative stress (where cells are overburdened with toxic by-products from metabolic reactions and don't have enough antioxidants to clear them), which may lead to a lack of oxygen in cells.
- Metabolic studies looking at chemical reactions at a cellular level are high-output studies, meaning a lot of data is produced, which provide a high chance of finding significant results. More about metabolomics can be read in **Medical Matters** on the website:

<https://meassociation.org.uk/i89w>

CONCLUSION

The most widely accepted model for ME/CFS is that it is a complex, multisystem disease that is triggered by an immune-system stressor, commonly an infection, in a genetically predisposed individual. The disease is then perpetuated by interaction of various changes in the brain, muscles, immune and endocrine (hormone-producing) systems.

We need a better understanding of the underlying disease pathways, and the various clinical and pathological sub-groups, and are pushing for new research investment. However, important clues have emerged, and new types of drug treatment are being assessed on the basis of these abnormalities.

The Covid-19 pandemic has served to highlight ME/CFS and the ME Association were the first to draw attention to the similarities with Long Covid back in May 2020. The seriousness of the pandemic and the much larger number of people affected initially led to a fairly quick response from governments around the world.

We are now in a situation where increasing numbers of scientists and clinicians are viewing ME/CFS and Long Covid as similar 'post-infectious

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CONCLUSION

syndromes' and we are now seeing more people whose trigger was Covid-19 being diagnosed with ME/CFS rather than Long Covid.

Research provides the best chance we have of really improving the lives of people affected by these debilitating diseases and of preventing them from developing in the future. The need for better research is being taken seriously in the UK and we hope that effective forms of treatment will eventually emerge.

MORE INFORMATION

We produce detailed explanations and references for research published on ME/CFS and Long Covid in several formats:

- The ME/CFS/PVFS Clinical and Research Guide:

<https://meassociation.org.uk/pbme>

Also available on Kindle:

<https://meassociation.org.uk/4nop>

- The Research Index:

<https://meassociation.org.uk/rime>

- Research Reviews:

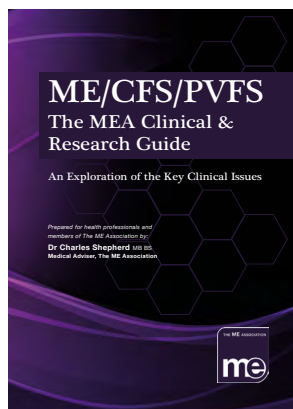
<https://meassociation.org.uk/4hrv>

- Research Roundups:

<https://meassociation.org.uk/08m5>

We need:

- much larger studies in order to see more definitive research and the removal of any false positives.
- well-defined patient cohorts and greater use of sedentary and other relevant controls.
- to have a great representation of all ME severities.
- to identify subgroups. There is a general consensus amongst researchers that there are several subgroups of patients which present with slightly different symptoms and pathologies. These need to be defined in order to study them separately.



ME Association ME/ CFS/PVFS Clinical & Research Guide 2022 Edition (The 'Purple Book')

The most comprehensive, evidence-based summary of ME/CFS/PVFS currently available. It contains everything that health professionals, patients, and the people who care for them, need to know about this devastating neurological disease.



ADVANCING ME/CFS RESEARCH

- to use new investigative techniques – including genomics, metabolomics and proteomics to find out what is happening at a cellular level.
- improved collaboration between different areas of research in order to see the 'whole picture'.
- more funding!
 - The Medical Research Council (MRC) regards ME/CFS as a research priority and issued a highlight notice in 2011 to encourage research applications, but very little has happened despite this encouragement.

In July 2025, the Department of Health and Social Care (DHSC) published a Delivery Plan on ME/CFS, aiming to strengthen research, improve professional attitudes and education, and enhance support for people living with the condition.

However, the plan has been met with disappointment from many in the community. Notably, it lacks a bold, long-term research strategy- raising concerns that most future research will continue to rely on funding from the charity sector rather than sustained government investment.

<https://meassociation.org.uk/zwka>

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ADVANCING ME/CFS RESEARCH

The MEA Ramsay Research Fund

The ME Association supports biomedical research by issuing grants to suitable applicants via The MEA Ramsay Research Fund. In the last 40 years, thanks to the generosity of our supporters and our commitment to biomedical research, we have invested over £4,000,000 in research studies and infrastructure projects. This equates to an average of £108,000 every year.

In 2025, we will be announcing investment in the largest single study we have ever funded, making a recognition that in order to advance this field, we need to support bigger and better research.

We cannot rely on the government and the UK Research and Innovation government Department (UKRI) to fund the research we need. To a great extent we have to increase our own efforts to raise funds. But we hope that with the DHSC Delivery Plan and its research focus, we will be able to work on more projects in collaboration with the Medical Research Council (MRC) and the National Institute for Health and Care Research (NIHR), to benefit from their expertise and help spread the risk of large and necessary investments.

We continue to seek good quality research investments that will advance our knowledge of ME/CFS and Long Covid and bring us closer to effective treatments.

<https://meassociation.org.uk/ramsay-research>



Our currently funded projects include:

- The UK ME/CFS Biobank (UKMEB) was launched in August 2011 with funding and input from the ME Association. The Biobank has an international reputation for quality and efficiency providing samples to researchers across the globe allowing research to focus on improving recognition, diagnosis and treatment of ME/CFS.



ADVANCING ME/CFS RESEARCH



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*The UK ME/CFS Biobank:
Photography by Yas Crawford
yascrawford.com*



The UKMEB contains samples from mild to severely affected people aged 18-60, as well as healthy controls and people with multiple sclerosis (MS). Blood samples have been aliquoted into serum, plasma, peripheral blood mononuclear cells (PBMC), red blood cells/granulocyte pellet, whole blood, and RNA.

The MEA Ramsay Research Fund has continued to provide annual grants since 2011 as we believe it to be a vital infrastructure project. The Ramsay Research Fund now covers all the basic running costs of this vital and unique project.

We have confirmed this funding arrangement for a further two years, and this will bring the total investment since 2011 in this worthwhile project to £962,000.

The UK ME/CFS Biobank: <https://meassociation.org.uk/CMEB>

■ Since 2016, The MEA Ramsay Research Fund has provided grants of over £300,000 to the Morten Group, Oxford who have investigated the role of mitochondria, the “powerhouse of the cell” in health and disease. The research group, led by Dr Karl Morten has become a hub for ME/CFS research starting out with the Acumen mitochondrial test to access cellular energy dysfunction to new approaches to finding biomarkers using single-cell Raman micro-spectroscopy.

The Morten Group Oxford: <https://www.mortengroup.org.uk>

■ In 2023, we established an arrangement with the Manchester Brain Bank to continue the study of tissue from post-mortem examinations of people with ME/CFS that will hopefully shed further light on the role of the brain and nervous systems.

The MEA Ramsay Research Fund will be funding detailed examinations of the brain, spinal cord and dorsal root ganglion in at least five people with a firm diagnosis ME/CFS who were aged between 18 and 50 at the time of death. We will then review the results and decide whether to proceed with funding further examinations.

The upper age limit of 50 is in place to try and ensure that any abnormalities that are found in the brain and spinal cord are not age-related and are more likely to be relevant to ME/CFS.

ADVANCING ME/CFS RESEARCH

If you wish to donate your brain and spinal cord to post-mortem medical research into ME/CFS, you must have had a firm diagnosis of ME/CFS from a doctor and understand that we can only proceed if you are aged 18 to 50 at the time of death.

If you wish to register your interest:



1. Complete the MEA Statement of Intent and make sure that your next of kin and solicitor (if you have one) are aware of it.

<https://meassociation.org.uk/fcik>

2. Include this information if you are making a Power of Attorney for Health and Welfare.

3. Send a copy of the completed MEA Statement of Intent by email to the Manchester Brain Bank – contact details are on the Statement of Intent:

phillip.tinkler@manchester.ac.uk

Manchester Brain Bank:

<https://meassociation.org.uk/s96p>

■ The UK ME/CFS Biobank (UKMEB) was launched in August 2011 with funding and input from the ME Association. The Ramsay Research Fund has continued to provide annual grants since 2011 and now covers all the basic running costs of this vital and unique project.

The UK ME/CFS Biobank:

<https://tinyurl.com/mr384x3u>

■ Please visit the ME Association website to read about:

The MEA Ramsay Research Fund - research announcements:

<https://meassociation.org.uk/0e4m>

Published research studies:

<https://meassociation.org.uk/rime>

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HOW YOU CAN HELP

Please help us to build on the success of The MEA Ramsay Research Fund and join us in expanding its vital work. We will learn why only certain people develop these diseases, the cause of symptoms and ongoing disability, and develop effective forms of treatment and prevention. With your support, these goals will be achieved much sooner.



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to build on the
success of The MEA
Ramsay Research
Fund and join us
in expanding its
vital work.*

If you would like to help The MEA Ramsay Research Fund:

- You can make a website donation:
<https://meassociation.org.uk/rcth>
- You can telephone head office: 01280 818963 (9.30am – 3.00pm Monday – Friday).
- You can send a cheque (made payable to: The MEA Association Ramsay Research Fund) to:

The ME Association, 7 Apollo Office Court, Radcliffe Road, Gawcott, Bucks MK18 4DF.

- Or, if you would like to create a fundraising event, please visit our JustGiving page:

<https://tinyurl.com/bdjdh2mh>





“Thank you for producing such a helpful magazine. The standard is consistently high and each edition is interesting and varied. I need all the help I can get and this magazine is consistently encouraging, realistic, and helpful.”



THE ME ASSOCIATION

Changing attitudes and improving lives...

■ **COMMUNITY:** We provide a safe and welcoming community for people affected by ME/CFS and Long Covid who come together and benefit from sharing their experiences. We provide membership, an essential support service, excellent website resources and we host engaging discussions on the most popular social media channels. Knowing that you are not alone can be a great comfort and we are happy to answer your questions and share helpful tips.

■ **MEMBERSHIP:** We put the interests of members at the heart of everything we do. Your subscription means that we can support more people, campaign more effectively and fund more medical research. Members receive the exclusive ME Essential magazine which carries the latest news, medical information, personal stories, and feature articles. **Join us today.**

■ **SUPPORT:** ME Connect is the charity's support and information service. We listen and we understand. All our staff and volunteers have knowledge and understanding of these medical conditions. We provide a personalised service and we're here when you need us most. You can contact us via our telephone support line (this is a freephone number) or by email. Please see back page for more details. To view the ME Connect telephone support line opening hours, please visit: <https://www.meassociation.org.uk/me-connect>

■ **INFORMATION:** We produce reliable and timely information written by topic experts and have the **largest range of free literature covering all aspects of life with ME/CFS and Long Covid**. We can show you how to recognise and manage symptoms, get an accurate diagnosis, a referral to specialists, and to obtain the healthcare that you deserve. We also provide an **e-newsletter** and free access on the website to **Medical Matters** and other relevant information.

■ **RESEARCH:** We fund medical research via the **Ramsay Research Fund** and are especially interested in research that can find diagnostic markers, causes, and treatments. We support the UK ME/CFS Biobank and the Manchester Brain Bank, and have invested over £1m in medical research in the last 10 years.

■ **MEDICAL EDUCATION:** We arrange training for healthcare professionals, offer a medical magazine, ME Medical, and are working with the Government, NHS, Royal Colleges of Medicine, and Local Authorities to implement the recommendations of the 2021 NICE Clinical Guideline on ME/CFS – the successful result of 14 years lobbying and hard work.

“The MEA is doing exactly what it said it would by providing support, actively lobbying for recognition, improvements to health and social care, and funding biomedical research.”



The ME Association
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Gawcott
Buckinghamshire
MK18 4DF

Tel: 01280 818963

Email: admin@meassociation.org.uk

Registered Charity
Number 801279



THE ME ASSOCIATION

Changing attitudes and improving lives...

■ **LOBBYING:** We campaign to raise awareness and bring about positive change. We believe in collaboration and work with the NHS and social care services, the Department of Health and Social Care, the British Association of Clinicians in ME/CFS (BACME), Forward-ME, the ME Research Collaborative (MERC), DecodeME, the All-Party Parliamentary Group (APPG) on ME, Physios4ME, the Chronic Illness Inclusion project (CII), Hidden Disabilities Sunflower, and Long Covid initiatives.

■ **HEALTH & SOCIAL CARE:** The charity works with healthcare providers to successfully implement the NICE Guideline recommendations on ME/CFS and Long Covid to ensure that everyone receives the very best healthcare, wherever they live in the UK. We want well-trained healthcare professionals providing excellent services because timely intervention can lead to better health outcomes and improved quality of life.

■ **DONATIONS:** In order to help more people and invest in medical research we depend on your generosity. If you feel able to make a donation or want to raise funds in other ways, please get in touch with the fundraising team: fundraising@meassociation.org.uk or you can **make a direct donation via the website.**

WHAT ARE ME/CFS AND LONG COVID?

We answer key questions about these medical conditions and compare similarities and differences. You'll also find the NICE Guideline reproduced in full in an easy-to-use **database**.

MEDICAL MATTERS

Medical Matters is an easy to use online supplement to the more detailed literature. The same topic experts provide answers to commonly asked questions.

NHS REFERRAL SERVICES

If you need to locate an ME/CFS specialist service or Long Covid Clinic then we can help. We have listed all secondary care referral services in an easy-to-use **database**.



THE ME ASSOCIATION

me



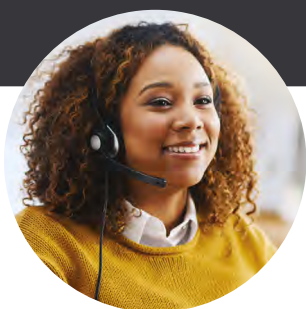
Freephone
0808 801 0484

For opening hours visit:
meassociation.org.uk/mec

ME CONNECT

The Support and Information Service
for people affected by ME/CFS/PVFS
and Long Covid

Contact ME Connect
HOW TO GET IN TOUCH:
by phone or email



HERE TO LISTEN

We are here to listen,
validate and empathise
with any issues you might
be facing.



VITAL SUPPORT

We are here to help
you reach an informed
decision.



SAFE ENVIRONMENT

We provide a safe,
confidential and
understanding
environment where
you can be heard
and understood.

We're here for you!



meconnect@meassociation.org.uk

For all information relating to ME Connect visit: <https://meassociation.org.uk/mec>

meassociation.org.uk