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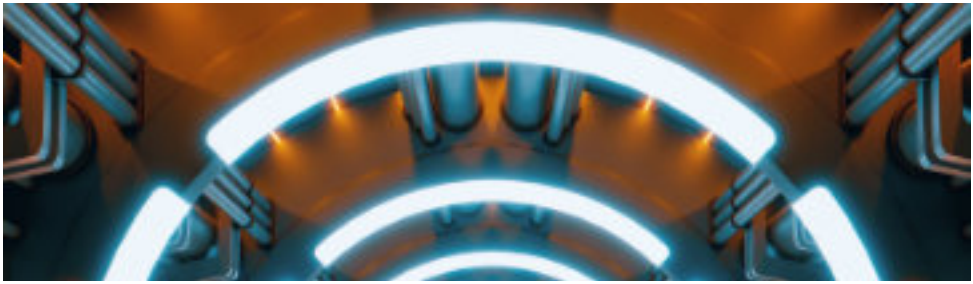


Breakthrough magazine is published by **ME RESEARCH UK**, a Scottish Charitable Incorporated Organisation with the principal aim of commissioning and funding high-quality scientific (biomedical) investigation into the causes, consequences and treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). We **INFLUENCE**, **INFORM** and **INVEST** in ME research globally by identifying potentially important areas for future biomedical research, and by producing high quality professional reviews and reports. *Breakthrough* is an open-access publication and, apart from images and illustrations, the content may be reproduced free of charge, subject to the terms and conditions found at meres.uk/bt-terms. **© ME Research UK, 2025 – SCIO Charity No. SC036942, The Gateway, North Methven Street, Perth, PH1 5PP, UK, Tel: 01738 451234, Email: contact@meresearch.org.uk, Web: www.meresearch.org.uk.**

EDITORIAL

Jonathan Davies
Chair, Board of Trustees

Welcome to our Spring 2025 issue of *Breakthrough*.

The last six months have seen us working hard (along with researchers, other charities and patient representatives) to inform and positively influence the outcome of the Government's Delivery Plan for ME/CFS. The process was started, to much fanfare, in June 2022 by the then Health Secretary Sajid Javid. Since then, we have seen Ministers and Governments come and go, with the perhaps inevitable loss of drive for substantive change so desperately needed. We do, however, give credit to the civil service team at the Department of Health for their perseverance in maintaining the process to a conclusion, with publication of the final plan promised for the end of March.

We feel almost certain that we will be disappointed with the outcome, with likely no additional government funding for desperately needed research, but we draw strength from the way the ME/CFS community has come together and spoken so strongly and consistently with one voice on the key issues. On research, in particular, our work with others will continue beyond the publication of the Delivery Plan, with the aim of achieving a positive change in the research landscape above and beyond the research we fund on your behalf.

In other areas, this work continues, with this issue providing a summary of Prof. Elisa Oltra's retrovirus work and Prof. Barnden's continuing brain imaging study, along with an interview with Jente Van Campenhout, one of the four PhD students we are currently able to support as a result of your fundraising and donations.

We also publish the winning entry in our inaugural Founders' Science Writing Award, won by Hollie Watmuff. Congratulations to both Hollie and Krista Clarke who was awarded second place.

As a charity we are entirely reliant on the generosity of all those who raise funds or donate money to allow us to invest in high-quality biomedical research. We were both delighted and humbled by your response to the Big Give Christmas Challenge in December; we raised a total of £56,732 (just over 100% of our target) and every penny will be invested in ME/CFS research. Thank you for your continued support – we can't do it without you!

Finally, I'm delighted to welcome Miki Fagerli-Schmidt to our small team. He will be working for us on a part-time basis as our Donor Relations Officer.

THE RIGHT TRACK

As trailed in the last issue of Breakthrough, *we recently awarded a research grant to Associate Professor Leighton Barnden and his team at Griffith University to continue their work tracking changes in the brain in ME/CFS.*

Many of the symptoms experienced by people with ME/CFS – including problems with concentration, memory, vision and heart-rate control – suggest abnormalities in the brain and nervous system.

In fact, research has confirmed that there are changes to the brain structure of ME/CFS patients, as well as impairments in the connectivity between different regions of the brain, and disruption to the autonomic nervous system (which regulates many body functions).

Associate Professor Barnden and his team at Griffith University and the University of Queensland have been particularly active in investigating this area, and have previously completed an ME Research UK-funded study using a powerful 7-Tesla magnetic resonance imaging (MRI) scanner to uncover a number of abnormalities in the brains of people with ME/CFS and long COVID. This work was all made possible thanks to the financial support of the Fred and Joan Davies Bequest.

Brain abnormalities in ME/CFS

In a series of publications, they have reported a number of findings in people with ME/CFS and those with long COVID:

- Brainstem volume changes (which correlated with pain, and breathing difficulties),
- Impaired functional connectivity between specific brain regions,
- Increased glutamate levels (which correlated with symptom severity),
- Enlargement of the hippocampus.

(The hippocampus is involved in memory and learning, and this last finding was recently reported nationally by ABC News in Australia.)

However, one important question remaining is whether all these abnormalities remain stable or get worse over time as the disease progresses.

Tracking progression

In this new study, the group therefore plans to use 7-Tesla MRI to track the progression of these brain abnormalities – as well as their association with clinical symptoms – in 40 people with ME/CFS over the course of three years. They will also assess 40 healthy individuals over the same time, as a control group.

All patients will fulfil the Canadian Consensus Criteria and International Consensus Criteria for a diagnosis of ME/CFS, and no participants will have any other condition that may affect the results.

Associate Professor Barnden's colleagues in this study include Dr Kiran Thapaliya and Professor Sonya Marshall-Gradisnik, who are also from Griffith University, and Dr Natalie Eaton-Fitch from the University of Queensland.

Brain structure and connectivity

Over the course of three years, the researchers will track changes in a wide range of parameters, including:

- Cortical volume, thickness and white matter (the cerebral cortex is responsible for cognition);
- Networks of brain activation and

functional connectivity (i.e. communication between different parts of the brain);
- Myelin and iron dysregulation (both of which affect nerve signal transmission);
- Myelin and axonal integrity (which also contribute to connections between regions of the brain); and
- Levels of various neurochemicals linked to neuroinflammation in the brain.

The participants will also undergo comprehensive assessments of their clinical symptoms and the impact of ME/CFS on their quality of life, and additional analyses will look at whether there are any relationships between the brain changes measured using MRI and the symptoms of ME/CFS.

Potential benefits

The researchers believe that this study has the potential to expand our knowledge of ME/CFS by providing valuable insights into brain changes in the disease over time, understanding how ME/CFS affects various brain regions, and identifying some of the underlying pathophysiological mechanisms.

In addition to providing a better understanding of how the brain is affected by ME/CFS, they hope that the findings will help in the identification of biomarkers that, in turn, will pave the way to the development of novel drugs targeting specific brain changes, and which may therefore have the potential to cure, slow or halt the progression of ME/CFS.

Name
Prof. Leighton Barnden

Position
Associate Professor

Institution
National Centre for Neuroimmunology and Emerging Diseases, Griffith University

Main research interests
Brain and neurological imaging and image processing in ME/CFS and long COVID

More information
experts.griffith.edu.au/8670-leighton-barnden

STANDING OUT

A short introduction to postural orthostatic tachycardia syndrome (PoTS), a condition experienced by many people with ME/CFS

Many people with ME/CFS are also affected by postural orthostatic tachycardia syndrome, or PoTS.

The main characteristic of PoTS is an abnormal rise in heart rate (tachycardia) when moving to an upright position, leading to the appearance or worsening of symptoms.

These symptoms can include dizziness or light-headedness (orthostatic intolerance), palpitations, fainting, chest pain, shortness of breath, cognitive difficulties, fatigue, gut problems and sleep disturbances.

So it is clear that ME/CFS and PoTS share some of the same symptoms, but there are also important differences between them which will influence the choice of treatment strategies (which are discussed later).

Characteristics of PoTS

PoTS is thought to affect at least 0.2% of the general population. The propor-

tion of people with ME/CFS who also have PoTS is less clear, but estimates range up to 70%.

PoTS can be so debilitating because many everyday activities can aggravate symptoms and have a major impact on quality of life. Identifying and diagnosing PoTS is important because management strategies can potentially alleviate some of the burden.

Many factors can trigger or worsen the symptoms, including dehydration, heat, alcohol, caffeine, large meals, menstruation, and prolonged standing, sitting or bed rest.

Types of PoTS

The underlying cause of PoTS is not fully understood. It often begins after a viral illness, pregnancy, surgery or trauma, with PoTS UK and Standing Up to POTS detailing three subtypes.

Hyperadrenergic PoTS is characterised by an overactive sympathetic nervous system, and symptoms include a more extreme rise in heart rate, increased blood pressure, migraines, nausea, anxiety and tremor.

In contrast, neuropathic PoTS is characterised by an impaired sympathetic nervous system, leading to blood pooling in the limbs and abdomen, cyanosis (turning blue) of the feet when standing or warm, and loss of sweating in the extremities.

Hypovolaemic PoTS is characterised by low blood volume, which leads to less blood returning to the heart and a compensatory increase in heart rate and force of heart contraction in order to improve blood circulation.

“While ME/CFS and PoTS share symptoms, there are also important differences between them

Diagnosis and treatment

The main diagnostic test for PoTS is the active stand test, which evaluates how a person’s cardiovascular system responds to a change in posture. Patients may undergo a tilt-table test, while other tests such as ECGs and blood tests are used to rule out other conditions.

A number of conditions can be associated with PoTS, including ME/CFS, Ehlers-Danlos syndrome and autoimmune disorders. It is therefore vital to diagnose PoTS separately, as management approaches for each of these conditions can be different.

Misdiagnosis of PoTS is a significant concern, primarily due to the overlap of symptoms with other conditions and limited awareness among many medical professionals.

The management of PoTS requires a multifaceted approach tailored to individual needs. Interventions can include general advice and lifestyle changes (such as avoiding triggers, increasing fluid intake and gentle exercise), the use of compression garments, and medications such as beta-blockers to control heart rate.

PoTS versus ME/CFS

The distinction between PoTS and ME/CFS is obviously of particular relevance to readers of *Breakthrough*. There are numerous commonalities, but there are also key differences.

For instance, both PoTS and ME/CFS are associated with fatigue. It is therefore important for people with ME/CFS who have comorbid PoTS to understand that treatment options are available for PoTS which may therefore potentially reduce their overall fatigue levels.

In addition, individuals with ME/CFS often report orthostatic intolerance despite not qualifying for a diagnosis of PoTS.

Perhaps the most important difference between PoTS and ME/CFS is the response to exercise. While exercise programmes can be beneficial for some PoTS patients when carefully managed, graded exercise therapy is not recommended in the NICE guideline for ME/CFS due to its potential for harm. For many people with ME/CFS, exercise can lead to post-exertional malaise and significant worsening of their symptoms.

In relation to prognosis, while individuals with ME/CFS may report improvements in symptoms over time, the prospects of recovery are much lower in ME/CFS than they are in PoTS.

Conclusion

Awareness of PoTS among healthcare professionals remains limited, and its significant symptom overlap with conditions such as ME/CFS likely contributes to underdiagnosis.

Living with PoTS is challenging and can significantly impact everyday activities, hence the importance of a timely diagnosis and appropriate management to improve quality of life.

By understanding more about the condition, and clarifying its differences from ME/CFS, we can foster a better understanding of both conditions.

MEET THE TEAM

MIKI FAGERLI-SCHMIDT

Donor Relations Officer

Hello everyone,

I am excited to start my new role as ME Research UK's Donor Relations Officer.

I am an educated journalist with a speciality in health journalism from the University of Stirling. I also have a background in charitable fundraising and communications. On a personal note, I moved to Scotland from Denmark seven years ago.

I am looking forward to getting started and to doing my best to help make a difference to ME research worldwide.

Miki

FOUNDERS' AWARD

THE FUTURE OF ME/CFS RESEARCH

ME Research UK's first Founders' Science Writing Award was won by Hollie Watmuff. Formerly a postdoctoral research associate at New York University, Hollie is now an Associate Medical Writer. Here is her winning entry on using non-coding RNA to diagnose ME/CFS.

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is an incurable, debilitating illness that is characterised by joint and muscle pain, brain fog, and extreme exhaustion followed by no improvement in symptoms after rest.

As symptoms are so broad, they often go unrecognised as ME/CFS by medical professionals who aren't familiar with the illness. Instead, patients can be misdiagnosed with a condition that presents in a similar way – such as depression or another chronic disease (an example being fibromyalgia). Ultimately, this can lead to unsuitable treatment and long wait times for a proper ME/CFS diagnosis.

DecodeME

The DecodeME study, the first of its kind, aims to address this issue by zooming in on the changes to the genetic code (DNA) of people with ME/CFS. By analysing the DNA present in saliva samples, researchers aim to identify significant differences between people with ME/CFS and healthy controls. In the future, these results could be used to diagnose ME/CFS through genetic testing.

Another exciting outcome from the DecodeME study is that it will aid in understanding the biological causes of ME/CFS. DNA contains all the instructions that our bodies need to function properly – providing the

blueprint for all the major systems of the body, including the immune, nervous and gastrointestinal systems. Any changes to a region of DNA that can be directly linked to a system that is abnormally regulated in ME/CFS could be highlighted for further study. With this in mind, an area of biology that is directly related to our DNA and has the potential to play a key role in the future of ME/CFS research is non-coding RNA.

What is non-coding RNA?

Prior to the 21st century, most processes in the body were thought to be carried out by molecules called proteins. The roadmap to produce proteins begins with DNA, whereby DNA is used as a template to make another molecule called RNA, which is then used as a template to make protein.

The body uses RNA as an intermediate step to allow for a quick response to changing bodily needs by rapidly destroying and removing the RNA – the body can't remove its DNA, otherwise it could never produce protein again! Therefore, the main role of this RNA "middleman" was thought to revolve around its ability to make protein. However, in the past 20 or so years, non-coding RNA molecules have gained huge traction as an exciting new area of research.

Non-coding RNAs come in all different shapes and sizes, but their common feature is that they don't make proteins. Instead, they have a wide variety of alternative tasks that are vital for proper functioning of the body. In relation to ME/CFS, current research shows that non-coding RNAs have functions within the immune response, the nervous system and metabolism – systems which are thought to be abnormally regulated in ME/CFS, potentially tying non-coding RNAs to the disease.

Using non-coding RNAs to diagnose ME/CFS

The link between non-coding RNA and ME/CFS is already beginning to be uncovered. In 2023, researchers collected blood samples from 40 ME/CFS patients and tested them for a difference in the types and amounts of a certain type of non-coding RNA: microRNA. Compared to healthy controls, they found a higher presence of three microRNAs and, interestingly, were able to link the amount of the microRNAs to the severity of ME/CFS.

A slightly older study, published in 2018, examined another class of non-coding RNA: long non-coding RNA. They chose to study 10 long non-coding RNAs tied to the function of the immune system, metabolism, nervous system and the body's response to stress – bodily functions that are thought to be abnormally regulated in ME/CFS patients.

From 44 blood samples, they found that three long non-coding RNAs were present in higher amounts and, similarly to the previous study, two of these three could be linked to ME/CFS severity. The two long non-coding RNAs linked to disease

severity were: NTT, a long non-coding RNA involved in the immune response, and EmX2OS, which is involved in the nervous system.

These two studies show that non-coding RNAs could be used to diagnose and gauge the severity of ME/CFS. However, a limitation is the small number of ME/CFS patients tested. To draw more concrete conclusions, a larger number of patients should be tested for non-coding RNA differences. This is one area where the DecodeME study will excel, as they are aiming to test the DNA of at least 20,000 people.

Does the future lie with non-coding RNAs?

The broad biological importance of non-coding RNA has only been uncovered in the past 20 or so years, making this a fast-growing and fascinating area of research. Additionally, due to the connection between DNA and non-coding RNA, the results of the pioneering DecodeME study may unlock further links between ME/CFS and non-coding RNAs.

As research into non-coding RNA and our understanding of ME/CFS evolve side-by-side, the scope for finding a non-coding RNA that could be used as a vitally needed diagnostic factor, or could be targeted for the treatment of ME/CFS, provides an exciting direction for the future of ME/CFS research.

This piece and the second-placed entry by Krista Clarke, from the University of Surrey, will be published on our website later in the year.

HOW MUCH WILL THE UK DELIVERY PLAN ACTUALLY DELIVER?

At the time of writing, we are still waiting for the publication of the UK Government's Delivery Plan for ME/CFS. However, on 17 February the ME community suffered two severe blows.

The Parliamentary Under-Secretary for Health and Social Care announced that the Government currently has no plans to allocate additional funding to the finalised Plan, and that a new centre of excellence for care and research specifically for post-viral or infection-associated conditions (such as ME/CFS) is not envisaged.

The Government's own consultation on the draft Delivery Plan showed that responders' top research priority was "ring-fencing funding, as well as securing more funding and parity of funding with other conditions". In addition, strong support was noted for the establishment of a centre for research excellence, as proposed in the APPG on ME Report.

Without additional funding how will the Government tackle the identified weaknesses in research? These were identified as:

1. Low capacity and capability among the research community to respond to research needs.
2. Low awareness of the need and scope for research into ME/CFS across the health and care research landscape.
3. Relatively low amount of biomedical research funded on ME/CFS, compared with disease burden.
4. A lack of trust between different stakeholders, including a perception of bias, expressed by patient and carer groups, about prioritisation and the peer-review process when applied to ME/CFS research.

THE HOLY GRAIL

Cort Johnson from healthrising.org looks at how close we are to finding a definitive biomarker for ME/CFS

Biomarkers! For as long as I can remember they've been like the holy grail for ME/CFS. If only we had a biomarker then we'd really make progress. And, indeed, in our molecular age, biomarkers play critical roles in understanding and treating diseases.

Still, many diseases without definitive biomarkers do have approved treatments. Depression, for instance, has no definitive biomarkers, but multiple drugs have been approved for it. Similarly, despite similar public funding levels, three drugs have been FDA-approved for fibromyalgia, and several other large-scale drug trials have been done. And yet, fibromyalgia has no biomarkers either.

So, why does fibromyalgia have three FDA-approved drugs and attention from big pharma, while ME/CFS hasn't gotten a sniff from a single

large pharmaceutical company in its entire history? The answer to this question demonstrates why ME/CFS, of all diseases, so needs a biomarker.

Why no biomarker for ME/CFS?

ME/CFS has three strikes against it that fibromyalgia does not. Firstly, being able to track a treatment's effectiveness – a critical need in drug trials – can be easily done in fibromyalgia but not in ME/CFS. Pain can be tracked simply by applying an objective amount of heat or pressure and determining how the patient reacts. That's not true for the fatigue in ME/CFS, and tracking post-exertional malaise is even more difficult.

Secondly, fibromyalgia has FDA-validated symptom assessment questionnaires that drug companies can use to get their drugs approved. ME/CFS does not.

Thirdly, we know much more about how pain is produced in the body than we do about fatigue. We know, for instance, that the pain-producing pathways involving nerve centres in the body, in the spinal cord, and in at least six regions in the brain are dysregulated in fibromyalgia. Nothing close to that has been achieved with regard to fatigue in ME/CFS.

The ME/CFS field, then, needs a biomarker much more than fibromyalgia does.

Long COVID, a closer cousin to ME/CFS, is in the same basket. UCSF researcher, Michael Peluso, asserted that even with the simpler long COVID, with its one trigger, symptoms vary too much to be used to assess treatments. That heterogeneity has left big pharma sitting on the fence with long COVID, just as it has with ME/CFS. Without a biomarker, it's hard to see drug companies getting interested in these diseases.

> **"It might seem surprising, but ME/CFS is swimming in a virtual ocean of possible biomarkers**

Kinds of biomarker

We know the ME/CFS field needs a biomarker, but what kind of biomarker? There are four different kinds, and all four could be useful for ME/CFS.

Mechanistic biomarkers that tell us how severe a disease is can be really good at helping to find subgroups of patients. A diagnostic biomarker could tell us whether or not someone has ME/CFS (an important step forward for a stigmatised and often misdiagnosed disease), and help us understand the disease better. Predictive biomarkers suggest if someone is at risk of a disease, or at risk of developing a severe case. However, the best biomarker for ME/CFS would be a sur-

rogate biomarker – a marker that goes up or down depending on how a patient responds to a treatment.

Once a surrogate biomarker is found, things can really take off. It took fifteen years to find a surrogate biomarker for HIV, but once it was found the drug possibilities exploded and treatments were soon found.

Potential candidates

So what about ME/CFS? While the disease doesn't have any definitive biomarkers, one could be present and we just don't know it. It might seem surprising, but ME/CFS is swimming in a virtual ocean of possible biomarkers. A recent UK Biobank study uncovered more than five hundred possible blood-based biomarkers, and was able to independently replicate 166 of them.

The mitochondria, the immune system, the metabolism and various biochemical pathways all provide numerous options for a biomarker. Two of the more exotic – and exciting – possibilities involve the nanoneedle and Raman spectroscopy.

Developed at Stanford and now being researched in the UK [in a study at the University of Surrey, funded by ME Research UK and the ME Association], the nanoneedle is in a world of its own. Remarkably, while we don't know what it's telling us about ME/CFS, it appears to track patients with the disease really well, and presents the possibility of a cheap and easy test that could be done in a doctor's office.

Cort Johnson

Artificial intelligence-driven Raman spectroscopy (also being explored in the UK) provides the enticing possibility of a quick, easy and cheap diagnostic test. Furthermore, mitochondrial, metabolomic, ion channels and the immune system present other possibilities.

What's the hold-up?

If so many possibilities exist, why don't we have a definitive biomarker? Three main factors appear to be holding us up: the disease's heterogeneous presentation (subgroups), insufficient funding, and a disorganised field. If distinct biological subgroups are present, then trying to find a biomarker that represents all of ME/CFS is fruitless, and we should be looking for biomarkers in subgroups instead. The field has also lacked the funding

and organisation to methodically track and test biomarkers at sufficient scale.

Hope for the future

Artificial intelligence and long COVID may help though. Artifical intelligence's ability to pour through vast amounts of complex biological data and identify patterns that constitute or point to biomarkers seems ready made for complex diseases such as ME/CFS and long COVID.

Plus, while ME/CFS funding remains low, its sister disease, long COVID, is getting substantial funding. Given the enormous growth in technology that's occurred over the past 15 years, Dr Peluso believes that long COVID biomarkers will start becoming clear over the next year. With the similarities between the two diseases, it's possible that the ME/CFS field could piggyback on them.

It is also possible, though, with the creative work being done with the nanoneedle and Raman spectroscopy, that the little ME/CFS field could lead the way.

RESEARCH BITES

BIOMARKER REVIEW

Clarke, J Transl Med, 2025

Dr Krista Clarke (whose project we co-funded with the ME Association) and colleagues have reviewed some of the properties of blood which are altered in people with ME/CFS, and which could be used to develop an accessible and non-invasive diagnostic marker. Potential techniques include profiling immune cells, measuring the electrical properties of blood, assessing the levels of different metabolites, and measuring mitochondrial dysfunction. The authors emphasise the need for larger studies, and to consider their practicality in a clinical setting.

CEREBROSPINAL FLUID

Baranuik, Int J Mol Sci, 2025

Cerebrospinal fluid is found in the tissue that surrounds the brain and spinal cord, and helps protect them from injury as well as providing nutrients. A recent study measured levels of a variety of markers (including metabolites and lipids) in the cerebrospinal fluid of people with ME/CFS. The findings were complex, but there were marked changes in the ME/CFS patients compared with healthy controls, which were also affected by exercise. The researchers suggest that these changes may be related to the development of post-exertional malaise.

NETWORK MEDICINE

Hung, Front Hum Neurosci, 2025

Network analysis is a tool to understand more about the links within a complex system, and is increasingly being used to study diseases. One study has used this approach to analyse whole-genome-sequencing data, and the researchers reported potential associations between ME/CFS and COVID-19, Epstein-Barr virus infection, neurodegenerative diseases, cortisol pathways, and oestrogen signalling. Although at an early stage, they claim that the results provide insights into the pathogenesis of ME/CFS and could help identify therapeutic targets.

DIETARY SUPPLEMENTS

Dorczok, Nutrients, 2025

Many people with ME/CFS take dietary supplements in the hope they provide some symptom relief, but it is unclear whether any of these actually have benefits. Researchers have completed a systematic review of 14 studies investigating dietary supplements in people with ME/CFS. Some of these (including L-carnitine and guanidinoacetic acid) did appear to lead to improvements in fatigue and cognitive function, but the studies were limited by small sample sizes, selection bias and inconsistent results, meaning that firm conclusions could not be drawn.

A GROWING PROBLEM

We are often called on to quote the number of people living with ME/CFS, but how certain are we of the available figures, and what can we do to improve our understanding as well as the accuracy of current prevalence estimates? This is a summary of a series of articles originally published on our website, which you can find in full here: bit.ly/3CSQye6.

Why is prevalence important?
The prevalence of a disease is the number of people in a population who have that disease at a given time or over a specified period.

Prevalence is important because it is a measure of the impact of a disease on society, and can be used to allocate healthcare resources and research funding.

Charities and campaigners would argue that resources and funding for ME/CFS are not allocated in a way that reflects the prevalence and impact of the disease. However, determining prevalence figures for ME/CFS is not a straightforward matter, and is further complicated by the different definitions of the disease in use.

How many people have ME/CFS?
Although the exact prevalence of ME/CFS is unknown, and studies vary in the methods used to arrive at their figures, several estimates exist both for the UK and elsewhere in the world. The most recent Government reports in the UK suggest that:

- "250,000 people have ME/CFS in the UK" (NICE guideline for ME/CFS, 2021)
- "Around 20,000 people in Scotland are living with the condition (ME/CFS)" (report from the Scottish Government, 2022)
- "There are more than 7,000 cases (of ME/CFS) in Northern Ireland" (Position Statement, 2016)

While the UK estimate of 250,000 may actually only be for England and Wales, it corresponds to a prevalence rate of 0.448% (from 2018 research using data from the UK Biobank). However, this finding was based on cases of "CFS" which were self-reported and not assessed against any ME/CFS diagnostic criteria.

In addition, the UK Biobank data lack ethnic diversity and only include adults aged between 40 and 69 years. These limitations mean that it may not be appropriate to generalise a prevalence of 0.448% to the wider UK population, as was done in the NICE guideline.

Has prevalence increased?

There have been no peer-reviewed studies providing estimates of ME/CFS prevalence in the UK since the 2018 UK Biobank study, and no research accurately captures the situation in 2025.

Last year, Gemma Samms and Prof. Chris Ponting from the University of Edinburgh made available the results of their study suggesting a UK ME/CFS prevalence rate of 0.585% based on data for England. This would equate to 390,195 people with ME/CFS in the UK based on the population size for 2022 (or 399,351 for 2023), and is a significant increase from previous estimates.

However, the researchers suggest that this is likely to be an underestimate of the true figure because the data used only reflect diagnoses recorded in hospital records. It is also important to note that these findings have not yet been published in a peer-reviewed scientific journal.

Elsewhere in the world, prevalence rates of between 0.1% and 1.7% have been reported, often with limitations noted about the nature of the diagnoses being recorded.

The situation is further complicated by the fact that the prevalence of ME/CFS is likely to have increased in recent years due to the rise in numbers of people meeting ME/CFS diagnostic criteria following the development of long COVID.

Estimates from the USA suggest a prevalence of between 5 and 9 million individuals following the pandemic, while figures of 750,000 or even 1.3 million people in the UK living with ME/CFS have appeared in various sources, although it is unclear exactly where these estimates have come from.

Conclusions?

So can we draw any firm conclusions about the current prevalence of ME/CFS in the UK and worldwide? Not at the moment, unfortunately.

Applying the previously reported prevalence rate of 0.448% to the 2023 UK population of around 68 million gives a prevalence of 305,828 people with ME/CFS. But this only captures the impact of population growth over time, and not any changes in prevalence rate due to factors such as the COVID-19 pandemic.

Reported estimates for the prevalence rate in the UK actually range from 0.1% to 2.6%, which would translate to

between 68,265 and 1,774,895 people. Notably, this includes the most recent estimate from Samms and Ponting of 0.585% (which equates to 399,351 people when applied to the 2023 UK population).

So the evidence does suggest that there are now more than 250,000 people with ME/CFS in the UK, but research has yet to provide a universally acceptable figure on what the prevalence is now in 2025.

What are the next steps?

Obtaining an accurate estimate for the prevalence of ME/CFS in the UK – or elsewhere in the world – is a highly complex task, and one that a single research team alone would probably be unable to solve.

Instead, a multidisciplinary collaboration may be required, and the best next step could be to conduct a roundtable discussion with experts in the field, including ME/CFS researchers and clinicians, methodological and statistical experts, representatives from ME/CFS charities, Royal Colleges and the NHS, and people with lived experience of ME/CFS.

Within this discussion, it would be important to:

- Establish whether it is possible to obtain a more accurate estimate for the prevalence of ME/CFS than those which already exist.
- Specify the methodology that could be used to obtain such an estimate – especially how people with ME/CFS would be identified accurately.
- Estimate what the cost of such a project would be – and consider whether this cost would be worth the additional knowledge.
- Gain consensus on whether an accurate prevalence estimate falls into existing research priorities for ME/CFS.

INTERVIEW

JENTE VAN CAMPENHOUT

Jente's PhD project with Prof. Jo Nijs at Vrije Universiteit Brussel in Belgium is looking at links between mitochondrial function and the autonomic nervous system in ME/CFS. The project is funded by ME Research UK with the financial assistance of the Fred and Joan Davies Bequest. Here, Jente shares more about her background and research.

Could you tell us a bit about yourself?
I completed my degree at Vrije Universiteit Brussel, and during my masters programme I focused on cancer-related topics. This experience let me refine my practical laboratory skills, and I also collaborated closely with other students who had a very strong passion for research. Working in such a positive environment sparked my own interest in starting a research career.

What is your PhD project about?
My PhD project focuses on two key factors. Mitochondria are the powerhouses that are present in our cells and provide us with the energy that we need to do our daily tasks. The autonomic nervous system (ANS) regulates many functions in our bodies that happen automatically (without our conscious control) such as breathing and heart function.

Given the symptoms experienced by people with ME/CFS, it seems logical to study both the mitochondria and the ANS, and especially the connection between the two. Additionally, our research aims to identify subgroups of people with ME/CFS based on their autonomic profile, and to examine differences in mitochondrial function between these groups.

What inspired your interest in ME/CFS?
I first encountered ME/CFS when I came across the PhD position in the Pain in Motion research group. The topic immediately intrigued me, and I began reading more about it. I had some prior experience researching mitochondrial mechanisms from my masters project, so as I learned more about the disease mechanisms in ME/CFS – including mitochondrial dysfunction – I realised that the project was a natural progression of my interests.

Have you been surprised by anything you've learned since starting your PhD?
I have been surprised by how little is known about ME/CFS – particularly, that there are so many aspects of the disease that remain unexplained, and that, despite the large number of people living with the disease, there is still no known cause or cure available. It also really surprised me how little budget there is available for the research that we do.

What does a typical working day look like for you?
Typically, my working day starts by welcoming participants who want to take part in our study (including people with ME/CFS and healthy controls) who come and visit us at the hospital. Here, they do two types of experiment and provide us with a blood sample. When the experiments are finished, I take the blood samples to the laboratory where I process and store them. After this, I have a couple of hours left in the afternoon to do some computer work like replying to emails from people who are interested in taking part in the study, or other administrative work. That's how my day looks right now – approximately one year into the project – but when we have included all our participants, we will go further into the laboratory and data analysis.

Can you tell us a bit about where you are doing your PhD?
The university where I am doing my PhD – Vrije Universiteit Brussel in Belgium – is next to the hospital. This is beneficial as participants can visit us at the hospital and then within ten minutes I am able to go directly to the lab to process the blood samples, meaning the study can run very efficiently.

What support do you have to help you complete your work?
The Pain in Motion research group which I am part of have already conducted studies including people with ME/CFS, meaning that I work closely with people who are very experienced in this area of research. Additionally, in the hospital we have nurses who are highly skilled in collecting blood samples for us, so within a short time I can process the blood samples in our lab. I think efficiency is a key factor ensuring the smooth operation of our research activities.

Why did you choose mitochondria and the ANS as the focus of your work? What do we already know about them, and what are you trying to find out?
Mitochondrial function is logical for researchers to study because it is important for the energy production in our body, and people with ME/CFS do not have enough energy. Currently, there are conflicting results – some papers say that there is nothing wrong with the mitochondria, while others really highlight that there is mitochondrial dysfunction in ME/CFS. So it is clear that more research – like my PhD project – is needed. Furthermore, research considering the function of the ANS has identified that participants with ME/CFS can be split into four different subgroups depending on how well their ANS works. In my PhD research, I want to investigate mitochondrial dysfunction within these subgroups. For example, in one group there might not be anything wrong with the mitochondria, but then in another group of patients there could be mitochondrial dysfunction that relates to the ANS dysfunction – really, we want to find the link between these two factors.

What is the most challenging aspect of the science and mitochondrial research you have read so far relating to ME/CFS?
To me, the most challenging aspect is that there are many conflicting results about mitochondria in people with ME/CFS. This makes it very difficult for us to form a clear picture of whether, and how, mitochondrial function is truly affected in people with the disease. We really hope that we can find some answers looking at how we can link mitochondrial function to the ANS.

What have you have enjoyed most so far, and what has been the most challenging part of your PhD?
I really value the research environment among all the PhD students in our

group. There is so much that we can learn from one another, and we are able to support each other, which I really think is incredible. In terms of challenges, I am only in the early stages of my PhD, so I haven't encountered many challenges yet. However, I sometimes like to be challenged as it helps me to grow as a researcher.

Where do you see yourself five years after completing your PhD?
I think that the PhD I am doing now will provide me with a solid basis to stay in research – I think there is a lot more to discover about ME/CFS.

What advice would you offer bioscience students who are considering a PhD in ME/CFS?
Start with a PhD – it is a nice journey, and although there are difficult parts to it, it gives you the opportunity to grow as a researcher. In the field of ME/CFS it is also extremely important to collaborate with other research groups that have experience of the disease, especially as ME/CFS is a complex disease which affects so many mechanisms in our body. If we do this, I believe that our contributions really will have a significant impact on the future.

Thank you for the opportunity to share more about my PhD research. I would also like to extend my gratitude to ME Research UK and the Fred and Joan Davies Bequest for funding our project and making this research possible.

BigGive

Thank you so much to our Pledgers, to The Big Give Trust, and to every donor and supporter who has contributed to making last year's Big Give Christmas Challenge such a huge success.

Believe us when we say that we know it has been a financially tough year for so many people and we are immensely grateful and heartened by each and every donation received.

Thanks to your support, we raised a total of £56,732 (101% of our campaign target) and every penny will be invested in ME/CFS research globally.

BLAST FROM THE PAST

The role of viral infections in the pathogenesis of ME/CFS continues to be a hot topic, and Prof. Elisa Oltra and colleagues have published more results from their study looking at human endogenous retroviruses.

Human endogenous retroviruses (HERVs) are remnants of ancient retroviruses contained within the human genome. That is, their DNA has become part of our DNA and is passed on from generation to generation.

Most HERVs are thought to be inactive, like genomic fossils, but evidence suggests that some have a role in the development of diseases such as multiple sclerosis, diabetes and schizophrenia. And they have also been proposed as potential triggers of ME/CFS.

HERV activation

Prof. Elisa Oltra and her team at the Catholic University of Valencia have been investigating the role of HERVs in ME/CFS, and in previous (still to be published) work they identified a subgroup of patients with activated HERVs. These may lead to an innate immune response, and the resulting flu-like symptoms and autoimmune problems that are characteristic of ME/CFS.

The group then turned to look at factors that might be linked to HERV activation, and which may therefore provide insight into the mechanisms underlying ME/CFS, as well as diagnostic markers for the disease.

Possible triggers

In this study, Prof. Oltra and her colleagues explored the possibility that HERV activation in people with ME/CFS may be triggered by immunological disturbances caused by active viral infections.

They analysed viral RNA sequences in immune cells (peripheral

blood mononuclear cells) extracted from blood samples from eight ME/CFS patients previously found to have activated HERVs. They also sampled people with fibromyalgia, those with both fibromyalgia and ME/CFS, and healthy control subjects.

RNA is a molecule which uses the genetic information in DNA to build proteins, and some viruses have RNA as their main genetic material. These RNA viruses are responsible for many human diseases, including the common cold, influenza, COVID-19 and hepatitis C.

The researchers extracted RNA from the immune cells, and then used a high-density microarray and computer analyses to assess the expression levels of 289 viruses.

The viruses analysed represented several different families but, on the whole, expression levels of these virus families did not differ between the various subject groups.

Torque Teno Mini Virus 9

However, when the researchers analysed individual viruses, they found increased RNA levels of the Torque Teno Mini Virus 9 (TTMV9) in the subgroup of ME/CFS patients with activated HERVs, compared with the other subject groups.

TTMV9 belongs to a family of viruses called anelloviruses, which are found very commonly in many tissues of the human body, but do not appear to have been linked previously with any diseases (although one study found a species of TTMV in patients with gum disease).

Interestingly, TTMV9 was the only member of the anellovirus family with

increased RNA levels in this ME/CFS subgroup.

TTMV9 levels correlated with several other measures, including HERV levels and the expression of a number of immune-related genes.

The researchers also performed an analysis showing that TTMV9 RNA levels could discriminate well between the ME/CFS subgroup with activated HERVs and the other patient subgroups, indicating its potential value as a biomarker for this subgroup.

Limitations

It is worth noting that these analyses were performed in a relatively small number of subjects (particularly when divided into subgroups), and these findings would need to be confirmed in much larger numbers.

The researchers also highlight that there are a number of viruses that the microarrays they used are not able to detect, including some previously implicated in ME/CFS. And they will not have been able to take account of coinfections with bacteria or other microorganisms.

Conclusions

These increased levels of TTMV9 virus in people with ME/CFS and activated HERVs do suggest that it has potential as a biomarker for the disease.

While TTMV9 is normally found in humans, high levels could indicate altered immunity, and the researchers found associations between TTMV9 and abnormal HERV and immunological profiles in these patients.

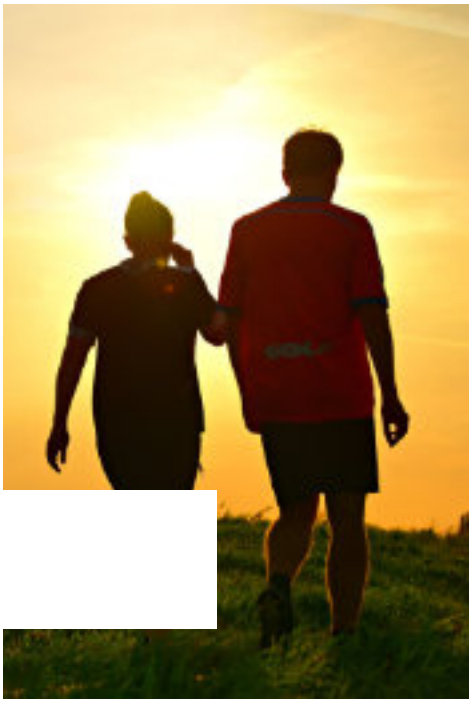
Name
Prof. Elisa Oltra

Position
Professor of Cell and Molecular Biology

Institution
Catholic University of Valencia

Main research interests
Cell biology and the genetics of fibromyalgia, ME/CFS and long COVID, including identification of molecular biomarkers

More information
researchgate.net/profile/Elisa-Oltra



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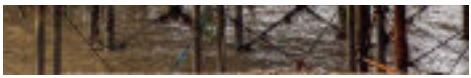

BRIGHTON MARATHON

Joseph Murray and Thomas Ridgebriger are both fundraising for ME Research UK when they run the Brighton Marathon on 6th April. Joseph chose our charity to support because he has a personal connection to ME/CFS, while Thomas has lived with the disease and been fortunate enough to recover over the course of several years. "It is utterly incredible to me that I can even contemplate running a marathon when I look back to how I was not so long ago." Many thanks to Joseph and Thomas, and the very best of luck for your runs.

WALK FOR ME

ME Research UK is grateful once again to be chosen as one of the featured charities for 2025's Walk for ME scheme. Now in its thirteenth consecutive year, the scheme encorages supporters to walk, run, swim and ride for two ME biomedical research-focused charities. Supporting ME Research UK for the fourth year in a row as part of Walk for ME 2025, Grace and Tracey Mitchell will be walking 20 miles in total through the forest in a departure from their past coastal walks. We are immensely grateful to Grace, Tracey and Walk for ME for their staunch support for research funding over the years.

CARDIFF HALF MARATHON

The Cardiff Half Marathon is one of the UK's most iconic and scenic races, and in this year's event we have a team of five running in aid of ME Research UK. Since the first run in 2003, it has grown to become one of Europe's largest half marathons. The event offers runners a flat, fast course passing all of the city's most breathtaking scenery and iconic landmarks, including Cardiff Castle, the Principality Stadium, the Civic Centre and the iconic Cardiff Bay. Thank you to everyone running on our behalf, and if you are inspired to take part in an event yourself, please visit our website for advice.

GO FUND ME

To mark the end of her fourth year living with long COVID, and recognising that many long COVID patients meet diagnostic criteria for ME/CFS, Clare Daly decided to raise money for ME Research UK using the crowdfunding platform, GoFundMe. Incredibly, she raised more than £1,000 for the charity, and we are extremely grateful to Clare and her supporters. As Clare says, "Every donation will help move the science forward for this life-altering illness."

For more inspiration about ways you can help raise funds, please visit ***meresearch.org.uk/support-us***.


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