THE ME ASSOCIATION

POST-EXERTIONAL MALAISE

Research Review

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Post-Exertional Malaise was written by **Dr Katrina Pears**, Research Correspondentfor the ME Association.

Katrina became the charity's Research Correspondent in 2021 and produces the weekly research update, research reviews, conference reports, and other related content.

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"The worsening of symptoms that can follow minimal cognitive, physical, emotional or social activity, or activity that could previously be tolerated. Symptoms can typically worsen 12 to 48 hours after activity and last for days or even weeks, sometimes leading to a relapse. Post-exertional malaise may also be referred to as post-exertional symptom exacerbation."

The National Institute for Health and Care Excellence (NICE)

INTRODUCTION

There are key biological changes that occur during PEM in many different systems of the body. Research evidence shows that the presence of PEM cannot be disputed and is not due to inactivity or deconditioning.

A brief summary of some of the key findings reveal:

- different areas of brain activation during and after exertion have been demonstrated with neuroimaging.
- impaired cardiac function, with orthostatic stress being a significant stressor to induced PEM.
- gut studies that found an insufficient acute-phase innate immune response following maximal exercise.
- numerous changes in blood, plasma and urine following exercise, for example: higher blood lactate levels following exercise with more elevated levels resulting in more severe PEM.
- disturbed metabolic pathways (a series of chemical reactions which start with a substrate and finish with a product) after exercise, that demonstrate a lack of adaption to physical exercise and suggest insufficient energy is being produced to meet demands (2 of these studies are reviewed in detail below).
- gene expression changes, showing distinct profiles in ME/CFS as well as sex-related differences. These studies also demonstrated that participants were unable to facilitate the transcriptomic changes (gene expression for molecules which help make proteins) that are needed for bodies to recover effectively from exercise (a detailed review of this evidence is presented below).

The evidence from the studies reviewed shows that people with ME/CFS have a different response to exercise than healthy controls, and the findings could be the reasoning behind experiencing PEM and exercise intolerance.

WHAT IS POST-EXERTIONAL MALAISE?

"Post Exertional Malaise is much more than fatigue and stiffness. I would describe it as a worsening of all ME-related symptoms and it is caused by physical, cognitive, or emotional exertions. It is unpredictable..."

Description of PEM by an anonymous MEA supporter

The National Institute for Health and Care Excellence (NICE) define PEM as:

"The worsening of symptoms that can follow minimal cognitive, physical, emotional or social activity, or activity that could previously be tolerated. Symptoms can typically worsen 12 to 48 hours after activity and last for days or even weeks, sometimes leading to a relapse. Post-exertional malaise may also be referred to as post-exertional symptom exacerbation."

The NICE Guideline on ME/CFS: Definitions:
https://tinyurl.com/mrb5m3u6

It is one of the four key symptoms that are required to be present before a diagnosis of ME/CFS can be made (and it has also emerged as a key symptom in people with Long Covid):

"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."

The NICE Guideline on ME/CFS: Symptoms:
https://tinyurl.com/3bhtvu5n

"Post Exertional Malaise is much more than fatigue and stiffness. I would describe it as a worsening of all ME-related symptoms and it is caused by physical, cognitive, or emotional exertions. It is unpredictable..."

Description of PEM by an anonymous MEA supporter. The full account can be read on the ME Association website, here:

https://tinyurl.com/5bys4bmw

We have discussed PEM and how to manage it in a recent Medical Matters answer from Dr Shepherd (Hon. Medical Adviser to the ME Association).

Medical Matters: https://meassociation.org.uk/medm

WHAT IS POST-EXERTIONAL MALAISE (PEM)?

90% of people with ME/CFS, fatigue was the most exacerbated symptom. Cognitive difficulties, sleep disturbances, headaches, muscle pain, and Flu-like symptoms were experienced by over 30%

Chu *et al.*, 2018

Detailed descriptions and the characterisation of PEM have also been completed in several research studies.

Some of the key findings include:

- **Chu *et al.***, 2018 found that PEM was present in 90% of people with ME/CFS and that fatigue was the most exacerbated other symptom. Cognitive difficulties, sleep disturbances, headaches, muscle pain, and Flu-like symptoms were experienced by over 30%.

Chu *et al.*, 2018: **https://tinyurl.com/5n8vn5ry**

- **Brown and Jason**, 2020, conducted a meta-analysis finding that PEM is 10.4 times more likely in people with ME/CFS than controls, and that PEM is a hallmark symptom of ME/CFS.

Brown and Jason, 2020: **https://tinyurl.com/5emv8ru9**

- **Holtzman *et al.***, 2019 found that the highest reported triggers in addition to physical/cognitive exertion were emotional events (88.3%), noise (85.3%), sensory (83.6%), and visual overload (79.7%).

Holtzman *et al.*, 2019: **https://tinyurl.com/5n8yfza5**

- **Mateo *et al.***, 2020 showed that people with ME/CFS reported more symptoms during and after a two-day CPET with an extended recovery period being required. They discovered that the worsening of 2 key symptoms can indicate the occurrence of PEM which are cognitive dysfunction and a decrease in function.

Mateo *et al.*, 2020: **https://tinyurl.com/n46whwhs**

- The delayed recovery after exercise has been demonstrated in other studies (**Paul *et al.***, 2003; **Mateo *et al.***, 2020).

Paul *et al.*, 2003; **Mateo *et al.***, 2020: **https://tinyurl.com/ycyst639**

HOW CAN WE MEASURE PEM?

PEM has been historically measured in ME/CFS by using scaled questionnaires, which have not been validated. It is particularly difficult to assess PEM as it tends to be measured retrospectively, scoring is subjective, and the scales used have floor/ceiling effects (upper limit on a questionnaire with a larger percentage of respondents scoring on upper limit).

A team of researchers from America developed the DePaul Post-Exertional Malaise Questionnaire based on the input from hundreds of patients – although it is not widely used.

Jason *et al.*, 2021

- The Visual Analog Scale (VAS) is frequently used to assess PEM. This scale is designed to rate a person's intensity to certain sensations and feelings and is typically used as a pain rating scale. **Strussman *et al.***, 2023 found that VAS performed poorly at the peak of PEM and were unable to capture information correctly due to floor and ceiling effects.

Strussman *et al*: **https://tinyurl.com/nvrb4uyy**

Detail about this scale can be found here: **https://tinyurl.com/ya6czttx**

- Qualitative interviews (QI) can also be used to capture the onset, changes in PEM severity, trajectory and symptoms overtime (including the most bothersome), although data collected through this is hard to quantify. QIs are very useful to compliment the use of VAS and capture information correctly.

Neither VAS nor QIs have been validated to assess PEM in ME/CFS following cardiopulmonary exercise testing (CPET). Validation is needed as CPETs are the most common clinical and research method used to study PEM.

To address this, a team of researchers from America developed the DePaul Post-Exertional Malaise Questionnaire based on the input from hundreds of patients (**Jason *et al.***, 2021) – although it is not widely used.

Jason *et al.*, 2021: **https://tinyurl.com/yuxbxvxt**

WHAT IS CARDIOPULMONARY EXERCISE TESTING (CPET)?

Cardiopulmonary exercise testing (CPET) is frequently used in studies to induce PEM as it provides an exertional stressor. During CPET, the patient will perform maximum exertion exercise on an upright bicycle while breathing through a mouthpiece.

Typically, each breath will be measured to assess how the body is performing, which allows measurements of peak oxygen consumption (VO^2) for example. The capacity and strength of the lungs is measured before and during exercise, and the heart's electrical signal (ECG) will be recorded prior to, during, and after exercise.

A normal CPET provides physiological measures at rest and throughout exercise to determine energy producing capacity at metabolically relevant time points. But, in ME/CFS research, CPET is conducted on two consecutive days. This is because an additional exercise test can explore and record the post-exertional pathology.

In ME/CFS research, CPET is conducted on two consecutive days. This is because an additional exercise test can explore and record the post-exertional pathology.

A typical test protocol involves incrementally challenging energy production, so that the patient is able to complete at least 8 minutes but no more than 12 minutes of cycling. Workload increments of 10–15 W/minute, beginning at 0 watts (measure of power), is appropriate to achieve an 8–12 minute test to maximum effort duration. (More information of the protocols used can be found in **Stevens *et al.***, 2018.)

Stevens *et al*: **https://tinyurl.com/yns33p5s**

Inducing PEM in those with ME/CFS can present an ethical challenge, but CPET is arguably one of the few tests at this time that can be used to demonstrate not only PEM but also functional incapacity.

- A recent study by **Moore *et al.***, 2023 showed that those with ME/CFS take on average 2 weeks to recover from a 2-day CPET, whereas healthy controls only take 2 days.

Moore *et al.*, 2023 **https://tinyurl.com/yrrzxzn9**

- However, **Mateo *et al.***, 2020 found that half of their patients took a week or less to recover, with an average recovery time of 4.5 days (the other half had not recovered after 7 days), but found that no patients suffered permanent or protracted damage.

Mateo *et al.*, 2020 **https://tinyurl.com/n46whwhs**

Both of these studies demonstrate that well-informed consent is needed prior to CEPT in ME/CFS.

RESEARCH: PEM IN ME/CFS

Latest research

a. Germain A *et al*.

Plasma metabolomics reveals disrupted response and recovery following maximal exercise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. JCI Insight 7(9): e157621 | 09 May 2022

https://tinyurl.com/2ypbaw7r

Background:

Cornell University. Image by Kenneth C. Zirkel, courtesy of Wikipedia Commons

Researchers from Cornell University in America examined changes in plasma metabolomics (the study of metabolites (small molecules) in the blood) after exercise and demonstrated a disrupted response and recovery time. The study used a 2-day exercise event with 4 timepoints to explore the metabolic response.

Results:

The most significant findings showed that lipid and energy-related pathways differed between health individuals and people with ME/CFS 24 hours after an exercise challenge. Distinct to the ME/CFS cohort was that after the 24-hour recovery period, over ¼ of the pathways studied were shown to be statistically different, providing clues to metabolic disruption in PEM, i.e. disruption in the process of making energy and are detrimental to an appropriate response to physical effort. Many of the altered pathways are dependent on glutamate metabolism, which is crucial to organ homeostasis.

Interestingly, this study also showed that even at baseline, the metabolites present in the plasma in people with ME/CFS were significantly different to controls.

Insight:

This was a strong study with interesting findings that provide new insights into PEM. However, the study was limited by the sample size (60 ME/CFS, 45 controls), sex imbalanced (the authors expressed difficulty in recruiting male participants but took steps to minimise effect on results) but also pre-existing activity levels (controls were sedentary but that doesn't mean activity is equal to ME/CFS patients).

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This research looked into the effect of exercise and maximal exertion on metabolomes in urine (small molecules that are needed by or produced as a result of metabolism (the chemical reactions in the body's cells that change food into energy)).

b. Glass KA *et al*:

Urine Metabolomics Exposes Anomalous Recovery after Maximal Exertion in Female ME/CFS Patients. International Journal of Molecular Sciences 24(4): 3685 | 12 February 2023

https://tinyurl.com/2t3cxh2c

Background:

This research follows on from the previous study (the same research group), however this time examining urine composition. It looked into the effect of exercise and maximal exertion on metabolomes in urine (small molecules that are needed by or produced as a result of metabolism (the chemical reactions in the body's cells that change food into energy)).

This study used 10 ME/CFS patients and 8 sedentary controls. A urine sample was collected at baseline and 24 hours after exercise, with the aim of seeing the effect of CPET on metabolomes.

Results:

A significant number (1403) of metabolites were discovered (a 30-fold increase on any previous study). They included amino acids, carbohydrates, lipids, nucleotides, cofactors, vitamins, and xenobiotics.

The novel finding was the lack of any significant changes to the metabolome following exercise in ME/CFS patients compared to controls (i.e. the urine metabolome was not altered during recovery in ME/CFS, while changes were seen in controls). The results demonstrated a lack of adaptation to severe stress (exercise) in ME/CFS.

The findings are very comprehensive, and details are given of differences in specific metabolites in ME/CFS and controls, for example differences were seen in lipids (steroids, acyl carnitines and acyl glycine's) and amino acid sub pathways (cysteine, methionine, leucine, isoleucine, urea cycle, arginine and proline). In summary, other key findings were:

- No significant changes in any compound were found in ME/CFS following exercise and in the recovery period.
- Pathway analysis was used to discover what the metabolites were being used for, showing significant alteration in the pathways in controls but not in ME/CFS.

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The study compared results to previous research that used plasma. It showed a correlation between the metabolites present in urine and those present in plasma. This gives further evidence for metabolic dysregulation following exercise in ME/CFS.

- Predominantly lower metabolite concentrations were found in ME/CFS.
- The metabolites that changed differently during recovery in controls compared to ME/CFS are predominantly amino acids and lipids.
- Large-scale changes were found in the urine metabolome for the controls with 255 compounds being significantly altered following exercise. Of these, 250 compounds increased in concentration after exercise.
- 110 of the compounds had a significant relationship between disease status (with or without ME/CFS (control)) and time (baseline or post-exercise).

The study compared results to previous research that used plasma. It showed a correlation between the metabolites present in urine and those present in plasma. This gives further evidence for metabolic dysregulation following exercise in ME/CFS.

Insight:

Unfortunately, as with much research into ME/CFS, it was a small study. The authors say that it was a pilot study that produced more interesting results than were expected, so we must hope that it will be followed up.

The absence of metabolic changes following exercise in people with ME/CFS, clearly demonstrates a lack of adaptation to physical exercise in ME/CFS. These findings could further mean that insufficient energy is being produced to meet energy demands needed following exercise. Nevertheless, these findings could be the reasoning behind experiencing PEM and linked to exercise intolerance experienced.

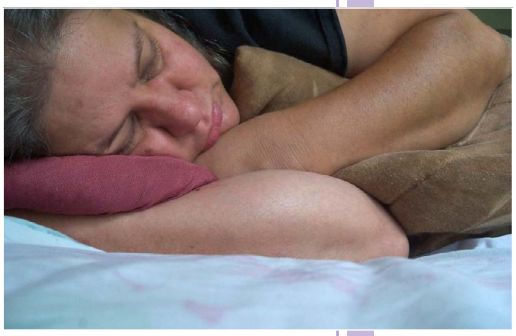
This study was limited by not controlling diet which can have a significant effect on urine metabolites. It also only collected urine at 2-time points. Increasing the number of time-points might better indicate if the delay in excretion of metabolites can be linked to the delay in relative symptom improvement. Finally, the study only used women, so we don't know if similar results would be found in men.

RESEARCH: PEM IN ME/CFS

c. Van Booven DJ *et al*.

Stress-Induced Transcriptomic Changes in Females with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Reveal Disrupted Immune Signatures. International Journal of Molecular Sciences 24(3): 2698 | 31 January 2023

https://tinyurl.com/yfw22yne



In this study, 20 women with ME/CFS were recruited alongside 20 matched healthy controls.

Background:

This study examined transcriptomic changes while undergoing exercise and involved international collaboration from America and Spain (the MEA Ramsay Research Fund supports Professor Elsa Oltra in Spain). Transcriptomics is the study of RNA molecules and how their expression changes i.e., it studies the gene expression of molecules which help to make proteins.

In this study, 20 women with ME/CFS were recruited alongside 20 matched healthy controls. The participants underwent an exercise challenge and blood samples were analysed at 3 time points: before the exercise challenge (T0), at maximal exertion (T1) and 4 hours after the exercise challenge (T2). The exercise challenge was a standard maximal graded exercise test which consisted of pedalling for 2 min at 60 W (watts, unit of power), followed by an increase of 30 W every 2 min until they reached their maximal exertion.

N.B. the researchers refer to exercise as “stress”.

Results:

The study yielded significant findings in a number of areas:

At maximal exertion (T1):

- no significant changes in gene expression were found in ME/CFS, but there were changes in healthy controls. 102 genes showed significant changes. In healthy controls these changes related to signalling and integral functions of their immune cells, such as those effecting natural killer cells.

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The results were fascinating and showed that in ME/CFS there was a different response to exercise than in healthy controls. ME/CFS participants were unable to facilitate the transcriptomic changes that are needed by the immune system to allow rapid recovery.

- no significant changes in cell type abundance, such as immune cell types were found in ME/CFS. Although in healthy controls CD4+ T cells were decreased, and natural killer cells (NK) were increased.

In the recovery period (T2):

- in ME/CFS there were 1277 genes expressed differently, compared to the 831 in healthy controls. Several pathways were significantly affected, dysregulated immune signalling pathways and dysfunctional cellular responses to stress, especially functions relating to cytokines. In healthy controls, leukocyte activation and immune response-regulating signalling were more significantly affected.

- a number of differences were seen in cell-type abundance, where the types of cells examined were all significantly different in healthy controls at T1 to T2.

These results were fascinating and showed that in ME/CFS there was a different response to exercise than in healthy controls. ME/CFS participants were unable to facilitate the transcriptomic changes that are needed by the immune system to allow rapid recovery.

Furthermore, after exercise and while in recovery, the ME/CFS participant's immune cells had dysfunctional cytokine signalling networks and were vulnerable to cell death due to poor defence systems and dysregulated epigenetic regulation of apoptotic pathways (programmed cell death). While healthy controls regulated their lymphocytes (a type of immune cell) and effectively inactivated the inflammatory response.

Insight:

- ME/CFS subjects met the 1996 CDC/Fukuda and 2003 Canadian Case definitions, which meant the diagnostic criteria was tighter than in other studies.

- Additional effects were minimised as all participants had a uniform breakfast, and a range of additional diseases were ruled out. Receiving a different breakfast than usual could induce changes, for example if on a Keto diet.

- Only women were enrolled, so we don't know if the results would vary in males.

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- The study reduced any potential menstrual impact as it ensured blood collection for the study happened during the first two weeks of a menstrual cycle.

- Matched controls were used, but there is no mention of them being sedentary (sedentary behaviour is defined as a mean of 6 hours or more of daytime sitting or lying down and is sometimes used to compare with long-term chronic illness), which might have made the comparisons more realistic.

- There are no details of illness duration (i.e. years since onset), so we don't know if illness duration would alter gene expression or if PEM changes over time, this therefore would have been a useful comparison to make.

- It is a great shame that there were no measurements taken 24 hours (or longer) after the exercise challenge, to discover if this further influenced gene expression, especially given that PEM tends to be delayed by 24-72 hours.

In conclusion, this study is neat and well performed, but its main limitation is the sample size.

- Most of the comparisons focused on changes between timepoints within the 2 groups and not between groups.

For example, when looking at cell type abundance this is presented as the change at T2 from T1 in ME/CFS, but the data does not tell us how at these timepoints ME/CFS participants differed from controls. Therefore, the abundance of cells in ME/CFS and controls could be similar (or different), just they change over time.

It is disappointing that there was no comparison between baseline data (T0) for ME/CFS participants and healthy controls showing how gene expression differs (or is similar) for this study group. This is an important comparison to make to establish whether exercise induced all the changes found or the differences were present pre-exercise and are part the disease aetiology (cause).

In conclusion, this study is neat and well performed, but its main limitation is the sample size. It would be interesting to see the authors revisit this topic with a much larger number of participants and with some changes (as above) to the methodology.

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Linked research

A similar study using transcriptome analysis looked to see if changes in immune dysregulation or virus reactivation could be detected after exercise:

Bouquet *et al*., 2019: **https://tinyurl.com/5n8v22xm**

The results showed that ME/CFS patients had 6 differentially expressed genes compared to controls, but none were related to immune signalling. Therefore, the findings did not support transcriptionally mediated immune cell dysregulation in response to exercise.

These findings are different from those reported by van Booven *et al*., 2023 – above – but this might be because Bouquet *et a*l., 2019 used whole blood, compared with the 2023 study which isolated cells from whole blood (peripheral blood mononuclear cells (PBMCs)).

Additionally, the 2019 study found there were no changes in the composition of viruses, so virus reactivation was not seen to be part of PEM (we have produced a Research Review on Virus Reactivation):

https://tinyurl.com/mrmbx6uj

A 2020 study (**Nepotchatykh *et al.***), examined the circulating microRNAs in severely ill people with ME/CFS before and after a stress challenge (a therapeutic massager with an inflatable cuff which was applied for 90 minutes). The study revealed 11 differentially expressed microRNAs that were associated with a physiological response to PEM. Furthermore, microRNA expression patterns were associated with specific symptom severities.

Nepotchatykh *et al*: https://tinyurl.com/38kwk8r4

Follow up research

The 2023 research group has conducted another study (**Gamer *et al.***,2023) which shows that transcriptional changes are sex-dependent (the process of copying a segment of DNA to RNA). Like their previous research, this study also used an exercise challenge to provoke PEM and used RNA-sequencing (i.e., investigating the gene expression for molecules which help to make proteins).

Gamer *et al*.,2023: **https://tinyurl.com/2sfmcpav**

The 2019 study found there were no changes in the composition of viruses, so virus reactivation was not seen to be part of PEM.

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The study provided an insight into sex-specific pathophysiology in ME/CFS, showing the importance of investigating sex-related differences.

The central finding of this study was that the pathways related to immune-cell signalling (such as IL-12 which defends against intracellular infection) and natural killer cell cytotoxicity were activated as a result of exertion in the male ME/CFS cohort, while females did not show significant changes in gene expression to meet the criteria for the differential expression.

During the recovery period male ME/CFS patients had distinct changes in the regulation of specific cytokine signals (such as IL-1β which is a key mediator in inflammatory response), but females had significant alterations in gene networks related to cell stress, response to herpes viruses, and NF-κβ signalling (plays a role in regulating the immune response to infection).

The study provided an insight into sex-specific pathophysiology in ME/CFS, showing the importance of investigating sex-related differences.

a. Cheng Y *et al*.

A unique circular RNA expression pattern in the peripheral blood of myalgic encephalomyelitis/chronic fatigue syndrome patients. Gene 877: 147568 | 15 August 2023

https://tinyurl.com/k5t52p4j

Background:

This study is the first of its kind to delve into circular RNAs (circRNAs) in ME/CFS, which have been shown to have a unique pattern in the disease.

- CircRNAs are single-stranded RNA molecules, which unlike a standard RNA molecule form a covalently (type of bond between two atoms) closed continuous loop.

- CircRNA are non-coding, and play a regulating role in gene expression, and an essential role in the process of biological development, including a critical role in disease diagnosis, which may enable them to potentially act as diagnostic biomarkers and therapeutic targets in ME/CFS.

- CircRNA research is still in its early stages and there is still more to be discovered about the biological functions they perform (a review on CircRNA can be found by **Zhou *et al.***, 2020):

Zhou *et al*., 2020: **https://tinyurl.com/25kk5y48**

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The study compared the expression profiles of CircRNAs in ME/CFS and sedentary controls before and after 2 sessions of CPET in a 7-day period. It used data collected by **Bouquet *et al.***, 2019, from 14 ME/CFS patients and 11 sedentary controls which formerly looked into transcriptome and virome analysis (using RNA sequencing).

Results:

Cheng Y *et al*. found a distinct CircRNA expression profile in ME/CFS:

- The number of detected CircRNAs was higher in ME/CFS compared to healthy controls, indicating potential differences in CircRNA expression associated with the disease.
- Human peripheral blood CircRNA profile changes in response to exercise.
- Healthy controls showed an increase in the number of CircRNAs after exercise testing, while no similar pattern was evident in ME/CFS, further highlighting physiological differences between the two groups.
- In ME/CFS, 14 CircRNAs were highly expressed but absent in controls.
- Of these 14 CircRNAs identified, significant enrichment of protein and gene regulative pathways were detected in five of them based on their predicted miRNA target genes. (The trends of specific circRNAs are discussed in the study.)
- The CircRNA expression patterns were shown to remain altered 5 days after the CPET.

Healthy controls showed an increase in the number of CircRNAs after exercise testing, while no similar pattern was evident in ME/CFS, further highlighting physiological differences between the two groups.

Insight:

A few points about this study:

- It is very small so larger samples sizes are needed for verification. The results may not represent a larger and more diverse sample.
- The sample was all women, so we don't know if the results vary in men with ME/CFS.

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- The study re-analysed previous data and relies on a correct diagnosis of ME/CFS, and robust protocols being performed by the previous researchers. Although, in this study, the authors knowledge of ME/CFS might be questioned.

- Sedentary controls were used, which is good, but this is still a huge step away from the activity levels of those with ME/CFS, so it would be useful to compare to other activity-limiting chronic illnesses.

In conclusion, this study is unique in its investigation into CircRNA, and results may be useful in leading us towards specific molecules which could be targeted to develop a diagnostic test.

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Earlier PEM Research

a. Neurology

- **Baraniuk *et al***. 2021 investigated patients with ME/CFS and Gulf War Illness (GWI) (plus controls) who underwent fMRI during cognitive tests performed before and after submaximal exercise. Before exercise, controls and GWI had greater activation in the part of the brain known as the left pedunculotegmental nucleus during cognition than ME/CFS. Postexercise ME/CFS had greater activation than GWI for the parts of the brain of midline periaqueductal gray, dorsal and median raphe, and right midbrain reticular formation, parabrachial complex and locus coeruleus. This study showed that exercise caused opposite effects on the brain in people with ME/CFS demonstrating different pathophysiological responses to exertion and disease mechanisms.

Baraniuk *et al*., 2021: **https://tinyurl.com/3rhjmap3**

- **Cook *et al***., 2017 looked into the neural consequences of submaximal exercise using functional brain imaging. They found that exercise exacerbated symptoms, impaired cognitive performances and affected brain function. Furthermore, providing evidence of the detrimental neurophysiological effects of PEM due the study linking symptom exacerbation to brain function.

Cook *et al*., 2017: **https://tinyurl.com/bdhuu7am**

- **Manca *et al***., 2021 investigate the effect of cognitive exertion and changes in functional connectivity in the two main brain networks. They found that PEM is associated with changes in the functional connectivity of the salience network (part of the brain which includes the anterior

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insula, anterior cingulate cortex and ventral striatum). They also found that increased right insular functional connectivity is associated with symptom worsening.

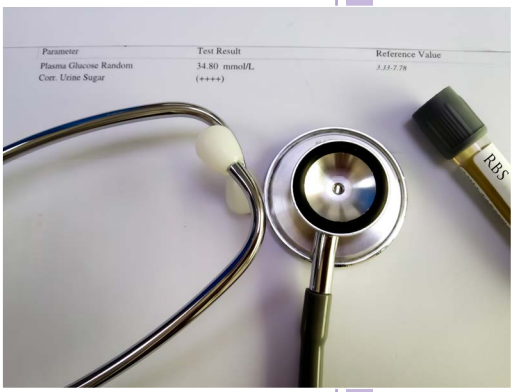
Manca *et al*., 2021: **https://tinyurl.com/3ndzxxp5**

■ **Rayhan and Baraniuk**, 2021 used submaximal bicycle stress testing follow-up with MRI blood oxygenation level dependent (BOLD) scans and symptoms assessment. Results showed striking exercise induced changes in the activity in the medial prefrontal cortex, which is an anterior node of the Default Mode Network (DMN). However, the region had decreased activity in controls. Results also suggested reduced cerebral flood flow in ME/CFS.

Rayhan and Baraniuk, 2021: **https://tinyurl.com/ykcyxu85**

■ **Renz-Polster *et al*.**, 2022 proposed that central nervous system dysfunction due to impaired neuroglia are the cause of the pathobiology in ME/CFS and bring about the key feature of PEM.

Renz-Polster *et al*., 2022: **https://tinyurl.com/26uhmmt6**



b. Biochemistry – More blood, plasma and urine abnormalities.

■ **Ghali *et al*.**, 2019 investigated elevated blood lactate at rest due to this being reported in some patients following exercise. Interesting they found that elevated blood lactate levels at rest may results in more severe PEM, which has implications for managing the condition.

Ghali *et al*., 2019: **https://tinyurl.com/y3kfu7mv**

■ **McGregor *et al*.**, 2019 looked at the changes in biochemistry with self-reported PEM (i.e. PEM was not induced in this research), with 35 patients out of 46 reporting PEM in the 7-day study period. The researchers analysed serum and urine metabolites, with the principal biochemical change relating to PEM showing a decrease the purine metabolite, hypoxanthine. This decrease correlated with alterations in the glucose:lactate ratio. They also found increased excretion of urine metabolites indicated a hypermetabolic event, which is an elevated resting energy expenditure. Increases in urine excretion of methylhistidine (muscle protein degradation), mannitol (intestinal barrier deregulation) and acetate were noted with the hypermetabolic event.

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The study showed that PEM is associated with changes in glycolysis and acetylation in ME/CFS, with wider implications in cellular enzyme activity.

McGregor *et al*., 2019: **https://tinyurl.com/4pv9pawj**

■ **Giloteaux *et al***., 2023 found a range of findings showing that there is dysregulation of the extracellular vesicle (EVs) protein cargo in females with ME/CFS following maximal exercise, and these changes were also correlated to symptom severity. These differences could also be found over different time points, with ME/CFS patients having a higher concentration of circulating EVs compared to controls. (A summary of the findings can be found in our weekly roundups.)

Giloteaux *et al*., 2023: **https://tinyurl.com/2s3w33xr**

Weekly roundups: https://tinyurl.com/5n7ex5au

Wang et al., 2023, have recently found a protein (WASF3) that is present in unusually high levels in the muscles of people with ME/CFS, this protein is found to disrupt mitochondria function.

■ **Wang *et al***., 2023 have recently found a protein (WASF3) that is present in unusually high levels in the muscles of people with ME/CFS, this protein is found to disrupt mitochondria function. This leads to decrease oxygen consumption, reduced the ability to generate energy in cells and exercise endurance. Removing the stress of this protein can restore mitochondrial function, showing the impair muscle bioenergetics and may be a target for treating fatigue. Coverage on this study can be found here:

https://tinyurl.com/3muu7m57

Wang *et al*., 2023: **https://tinyurl.com/3cdm47yx**

c. Cardiac function

■ **van Campen *et al***., 2021 studied the effect of tilt-tabling testing (which is used to diagnosis orthostatic intolerance) on PEM. They found that pain and fatigue significantly increased, and concentration decreased for seven days following tilt-table testing, showing that orthostatic stress is a significant stressor inducing PEM.

van Campen *et al*., 2021: **https://tinyurl.com/mr23nnhn**

RESEARCH: PEM IN ME/CFS

■ **Joseph *et al.***, 2022 findings suggest that neurovascular dysregulation underlies acute exercise intolerance in ME/CFS, their study showed that targeting this dysregulation with pharmaceutical drugs improves the exercise capacity in ME/CFS. (See more under "Treatment for PEM")

Joseph *et al.*, 2022 **https://tinyurl.com/fbywesdk**

d. Gut

■ **Uhde *et al.***, 2023 looked at whether observed immune responses to intestinal damage are affected by maximal exercise, which is known to increase intestinal permeability and gut microbial translocation. Their findings included showing significant increases in LBP and sCD14 in the control group (involved in the innate immune response to bacterial challenge) but this was lacking in ME/CFS, providing evidence for a downregulated acute-phase response in ME/CFS. During exercise, ME/CFS patients were also shown to have increased levels of IL-10. Following exercise, LBP were seen to rise in ME/CFS but not healthy control, giving evidence for insufficiency of acute-phase innate immune responses.

Following exercise, LBP were seen to rise in ME/CFS but not healthy control, giving evidence for insufficiency of acute-phase innate immune responses.

Uhde *et al.*, 2023: **https://tinyurl.com/mt52m5yd**

e. Miscellaneous

■ **Barhorst *et al.***, 2020 found that people with ME/CFS and fibromyalgia perceive aerobic exercise as more effort than healthy controls, although their meta-analysis did not relive any mechanisms which may cause this.

Barhorst *et a.*, 2020:**: https://tinyurl.com/vuk37wxt**

■ **Barhost *et al.***, 2022 conducted a systematic review to better characterise the pain component of PEM in ME/CFS and fibromyalgia. They found that there is small to moderate increases in pain following exercise and that pain is an important debilitating component of PEM.

Barhorst *et al.*, 2022 : **https://tinyurl.com/5n8exspt**

RESEARCH: PEM IN LONG COVID

■ Recent research by **Vernon *et al***., 2023 showed that PEM is also a hallmark symptom in Long Covid. In their research 99% of Long Covid patients experienced PEM, compared to 100% in the ME/CFS cohort. The study reported differences in the PEM experienced, however, this is more than likely due to the different illness durations. Other surveys have reported PEM to be experienced by 89.1% of a Long Covid Cohort (**Davis *et al***., 2021).

Vernon *et al*., 2023: **https://tinyurl.com/2em9zb3b**

Davis *et all*., 2021: **https://tinyurl.com/yzajj3e5**

■ Researchers have also stressed that we must look at the lessons learnt from ME/CFS when dealing with symptom exacerbation in Long Covid (**Davenport *et al***., 2022), with a personal approach being needed to prevent PEM (**Breedveld *et al***., 2023). One study using the STOP-REST-PACE technique has shown that PEM is persistent in two-thirds of patients despite adopting this approach (**Tanguay *et al***., 2023).

Davenport *et al*., 2022: **https://tinyurl.com/mu7cbp2m**

Breedveld *et al*., 2023: **https://tinyurl.com/2t5enmey**

Tanguay *et al*., 2023: **https://tinyurl.com/4xa6wnzp**

■ There have also been several studies which have used CPET to investigate PEM in Long Covid, with CPET being seen as a useful tool for assessing reducing exercise capacity (**Durnstenfeld *et al***., 2022). Due to the nature of Covid-19 these patients tend to be characterised by impaired system oxygen extraction- the body's ability to extract oxygen from the blood. However, **Gattoni *et al***., 2023 found no difference between variables assessed in a 2-day exercise test, concluding that CPET protocol may not be valued for assessing PEM in Long Covid.

Durnstenfeld *et al*., 2022: **https://tinyurl.com/ucs3jajs**

Gattoni *et al*., 2023: **https://tinyurl.com/5n87t3hm**

■ **Singh *et al***., 2023 used CPET to further investigate PEM, where long covid patients have their mildly or severely reduced oxygen extraction. They also investigated the blood proteomic profiling at peak exercise, finding differences between these two patient groups. Proteins in the severe group were involved in inflammatory and fibrotic processes, and in the mild group the proteins were associated with oxidative phosphorylation and glycogen metabolism were elevated. Results shows

that there are different phenotypes of Long Covid patients who suffer with impaired system oxygen extraction. News article on this study here:

https://tinyurl.com/33jzk3uf

Singh *et al.*, 2023: **https://tinyurl.com/mr3ycwtm**

STUDYING PEM AND ALTERNATIVES TO CPET

Pilot studies using a low burden exercise protocol (6-minute walk test followed by 30 seconds of squats on two-consecutive days) have so far proved disappointing, and not been able to prove that females have a slower recovery than males.

Unfortunately, there are a lack of alternatives to assessing PEM to the same extent than is available through CPET. Pilot studies using a low burden exercise protocol (6-minute walk test followed by 30 seconds of squats on two-consecutive days) have so far proved disappointing, and not been able to prove that females have a slower recovery than males.

The research demonstrated that more exertion-sensitive exercise testing is needed to detect biological changes (**Friedberg *et al.***, 2023). Six-minute walk tests and step tests are often used as alternatives to CPET in other conditions, such as evaluating heart failure, but assessing PEM is tricker (**Oliveira *et al.***, 2016).

Friedberg *et al.*, 2023: **https://tinyurl.com/jpkekmu6**

Oliveira *et al.*, 2016 **https://tinyurl.com/znum3e44**

A potential alternative is to use wearable sensor technology to monitor daily activity and symptoms. Technology in this field and what we can easily measure is increasing, although at the moment no biomarker exists which can identify PEM through wearables (such as changes in heart rate) and there are few studies in ME/CFS to support its use.

Several studies have been conducted that show potential although they have not specifically investigated PEM, e.g., **Clague-Baker *et al.***, 2023; **Sun *et al.***, 2023; **Rekeland *et al.***, 2022; **van Campen *et al.***, 2020.

Clague-Baker *et al.*, 2023: **https://tinyurl.com/3r4hkrdp**

Sun *et al.*, 2023: **https://tinyurl.com/3ume9bvf**

Rekeland *et al.*, 2022: **https://tinyurl.com/mstbeszh**

van Campen *et al.*, 2020: **https://tinyurl.com/2ue7nahf**

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PEM TREATMENTS

Until research such as this can be replicated in much larger studies, we continue to recommend energy management as the safest and most effective form of self-management and this is the recommendation of the 2021 NICE Guideline on ME/CFS as well.

Joseph *et al*., 2022 looked at neurovascular dysregulation and whether this contributes to exercise intolerance. In their small study, an oral dose of the drug pyridostigmine was given (n=23) or a placebo (n=22) after an intense exercise test.

Joseph *et al*., 2022: **https://tinyurl.com/yj8kkrer**

■ The drug pyridostigmine is used to improve muscle strength and is typically given to patients with muscle diseases. Pyridostigmine works by preventing the breakdown of the natural substance acetylcholine, which is needed for normal muscle function.

The study found an improvement when the drug was taken compared to the placebo, which led the authors to conclude that neurovascular dysregulation is treatable in ME/CFS where there is acute exercise intolerance.

They found that pyridostigmine improved maximal oxygen consumption (peak VO^2, the maximum amount of oxygen that an individual can utilise during intense exercise) in ME/CFS by increasing cardiac output and right ventricular filling pressures in the heart.

A more recent study looked at building on these findings, further showing an increase in oxygen uptake efficiency and pulmonary vascular capacitance (reflects the ability of the pulmonary vessels to dilate during systole and recoil during diastole, phases of the cardiac cycle) from taking pyridostigmine. However, again the sample size was very small with 37 in the treatment group and 16 controls, with very small effects seen (**Squires *et al***., 2023).

Squires *et al*., 2023: **https://tinyurl.com/4m552vnu**

Until research such as this can be replicated in much larger studies, we continue to recommend energy management as the safest and most effective form of self-management and this is the recommendation of the 2021 NICE Guideline on ME/CFS as well:

https://tinyurl.com/2n37hjht

■ We have produced a free booklet on **Pacing: Activity and Energy Management**:

https://meassociation.org.uk/h8qj

CONCLUSIONS

In this research review, we have shown that:

- Research has demonstrated that people with ME/CFS have a different response to exercise which effects their recovery. Some studies have shown, that energy demands are not to not met during this time, leading to PEM experienced.
- Studies show there are clear biological changes which occur during PEM, meaning the presence of PEM cannot be disputed. Changes can be found in the brain, cardiac function, gut, and biochemical changes in the blood, plasma and urine, showed by changes in lactic acid levels, metabolites present and gene expression changes.
- CPET can objectively confirm the presence of PEM, it is an objective marker for PEM, however, the use of CPET as a diagnostic test is ethically questionable.
- Research has shown that PEM cannot be due to inactivity or deconditioning.

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"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

me

HOW WE CAN HELP

■ **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. 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. We will provide you with a regular ME Essential magazine which is simply the best magazine available. It will keep you informed of developments, it shares personal stories and the latest medical information, with an Ask the Doctor feature in every issue.

To become a member, please click the following link:
https://meassociation.org.uk/nmrs

■ **SUPPORT:** Support is available from ME Connect, our telephone helpline, email, and social media private messaging service. It can be very helpful to speak with a trained member of the team at a time when you need it most. We can find the most relevant information for your situation and we are available 365 days a year.

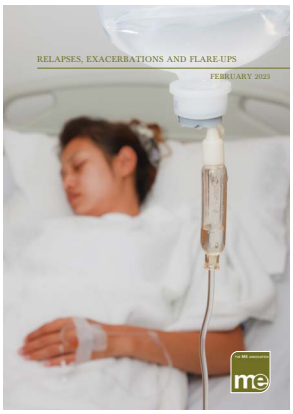
■ **INFORMATION:** We produce reliable and timely information written by topic experts and have the largest range of literature covering all aspects of life with ME/CFS and Long Covid. We can show you how to recognise and manage symptoms, to get an accurate diagnosis, a referral to specialists, and to 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.

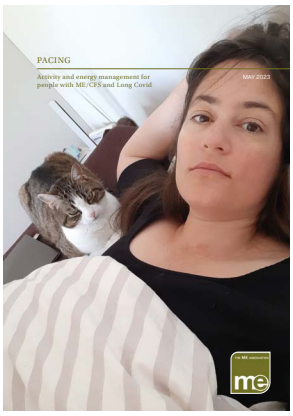
■ **RESEARCH:** We fund biomedical research through our dedicated Ramsay Research Fund, which has invested over £1m in recent years. We support the UK ME/CFS Biobank and we are funding post-mortem tissue research and the Manchester Brain Bank.

■ **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 from the 2021 NICE Clinical Guideline on ME/CFS – the successful result of 14 years lobbying and hard work.

■ **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

"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."





HOW WE CAN HELP

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.

THE ME ASSOCIATION LITERATURE

The ME Association has the largest selection of literature on ME/CFS and Long Covid in the UK. We cover:

Awareness and Fundraising
Benefits
Carers and Social Care
Diagnosis
Diet and Nutrition
Education and Employment
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Mental Health
Symptoms
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https://meassociation.org.uk/shop

THE ME ASSOCIATION

ME CONNECT

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

Contact ME Connect by phone, email or social media private message

0344 576 5326

10am-12 noon, 2pm-4pm, 7pm-9pm every day of the year

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