



Llywodraeth Cymru  
Welsh Government

# Long COVID Update

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Science Evidence Advice (SEA)

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Providing evidence and advice for Health and Social Services  
Group on behalf of the Chief Scientific Advisor for Health

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## Background

In October 2022, the Science Evidence Advice team published a report titled Long Covid Update (SEA 2022)<sup>1</sup>. This report forms an extension of that original report, to provide a further update on developments in Wales two years later (May 2024). This was requested by the Head of Long Covid, Stroke, Neurological conditions and Frailty Quality & Nursing Directorate of the Health Social Care and Early Years (HSCEY) Group in Welsh Government. UK Government have recently published a Research Briefing titled “Coronavirus: Long Covid”<sup>2</sup> which gives an overview of current NHS guidance and services, diagnosis and treatment, research on Long COVID and the impact of it in the UK. The aim of this report is to contextualise this for Wales, through an updated representation of the statistics and picture of Long COVID in Wales.

## Summary

- Updated prevalence figures for Wales are challenging to obtain since the end of the Office for National Statistics (ONS) infection survey in March 2023. The most recent data available shows there could be **approximately 94,000 people in Wales** suffering from Long COVID. The survey results also suggested there is an increased prevalence of self-reported Long COVID among women and in the 50-69 years age range.
- Long COVID may be having a significant ongoing impact on the labour market in Wales, the impact of which could be the equivalent **of 4,948 people being off sick on any given day**.
- The cost of primary care consultations in Wales for Long COVID could be as high as **£2 million per year**.
- There is ongoing research into the area of treatments for Long COVID and results from several larger scale studies internationally are yet to be published. The published trials so far are of variable methodological quality but focus mainly on symptom alleviation and individualised rehabilitation. There are trials ongoing within Wales.
- Referral pathways have been developed across all health boards to support those in Wales living with Long COVID.

## Introduction

Long COVID is the term used to describe symptoms of COVID-19 which are persistent after 4 weeks. This can be further divided into ‘Ongoing Symptomatic Covid-19’ for symptoms for 4-12 weeks and ‘Post-Covid Syndrome’, where symptoms continue for more than 12 weeks and not explained by an alternative diagnosis. The symptoms can affect multiple systems throughout the body and can fluctuate over time, lasting

<sup>1</sup> [Science Evidence Advice: Long COVID update October 2022 \(gov.wales\)](https://gov.wales/science-evidence-advice/long-covid-update-october-2022)

<sup>2</sup> [CBP-9112.pdf \(parliament.uk\)](https://parliament.uk/cbp-9112.pdf)

weeks, months or years<sup>3</sup>. This definition has remained the same since the previous SEA paper<sup>1</sup>.

The National Institute for Health and Care Excellence (NICE) describe that the signs and symptoms of Long COVID are highly variable and exacerbations can be triggered by physical or mental stress. Symptoms are divided into ‘Generalised’, Cardiovascular, dermatological, ear nose and throat, gastrointestinal, musculoskeletal, neurological, psychological and respiratory<sup>4</sup>. The NICE guidelines were updated in January 2024, but the recommendations are unchanged since November 2021<sup>5</sup>.

When the ONS infection survey ended in March 2023, there was an estimated 1.7 million people living with symptoms of Long COVID in the UK. Approximately a third of these had their first COVID-19 infection in 2020 and 40% had their first infection over 2 years prior to reporting Long COVID symptoms in the survey<sup>5</sup>.

### Subtypes and proposed pathophysiology of Long COVID

It is acknowledged that Long COVID is likely a single multisystemic disease and its presentation has a high degree of variability between people. Another hypothesis is that it is a group of conditions with distinct pathophysiological mechanisms which present similarly<sup>6</sup>.

There are several suggested mechanisms to describe why and how the symptoms may present. These may coexist and impact one another.

One theory is viral persistence, whereby ‘pockets’ of the virus are ongoing and cause inflammation and or reactivate pre-existing but previously dormant viruses.

Immune dysregulation is another proposed mechanism whereby there is an excessive immune response.

Some symptoms are suggested to be linked to imbalance of ‘good’ and ‘bad’ bacteria within the gut, which is known as microbiome dysbiosis.

There is also a theory that with severe Long COVID, inflammation of the inner surface of blood vessels (endothelium) leads to microscopic blood clots, leading to insufficient oxygenation of certain tissues and organs.

Nerve damage and inflammation is also proposed to contribute to Long COVID symptoms as well as mitochondrial dysfunction. If mitochondria are dysfunctional, muscles may not produce enough energy to meet the body’s demands. This might give insight into reduced exercise capacity in people with Long COVID<sup>7</sup>.

<sup>3</sup> [Long COVID or Post-COVID Conditions | CDC](#)

<sup>4</sup> [9 Common symptoms | COVID-19 rapid guideline: managing the long-term effects of COVID-19 | Guidance | NICE](#)

<sup>5</sup> [Update information | COVID-19 rapid guideline: managing the long-term effects of COVID-19 | Guidance | NICE](#)

<sup>6</sup> [Long COVID: a clinical update - The Lancet](#)

<sup>7</sup> [Solving the puzzle of Long Covid | Science](#)

Risk factors associated with being more likely to develop Long COVID and less likely to recover include: pre-existing conditions, deprivation level, multisymptomatic initial illness, ability to rest during initial illness, antiviral treatment and reinfection with COVID-19 amongst others. People who have had symptoms between 6 months and 2 years are said to be less likely to recover, although there is a paucity in research of people whose symptoms have persisted past 2 years. Recovery time varies and can follow a relapsing-remitting pattern<sup>8</sup>.

### Impact of Long-COVID in Wales

ONS data on the prevalence of ongoing symptoms following COVID-19 infection in the UK was recorded until 20 March 2023. The infection survey data covered the four weeks leading up to 5 March 2023<sup>9</sup>. For Wales, the data shows that of the approximately 94,000 reported cases of Long COVID, there was increased prevalence of self-reported Long COVID in females and the highest number of people reporting Long COVID were 50-69 years of age.

There is a discrepancy between estimated figures for Long COVID and Long COVID diagnostic coding in Primary Care. It has been suggested that this may be due to lack of presentation or recognition<sup>10</sup>. Abbasizanjani et al (2023) completed a cohort study of 3.5 million people using linked health and demographic data in Wales which reported that only 0.2% of residents had a clinical diagnosis of Long COVID but 30.9% of primary care practices had not used the Long COVID diagnosis codes at all. These figures are inconsistent with the surveys by the Office of National Statistics (ONS) data, which reported a prevalence of 2.9%<sup>11</sup>. There may be a lack of presentation or recording which makes updated monitoring an accurate estimate of prevalence challenging<sup>12</sup>. There may also be some challenges in terms of awareness of Long COVID and hesitancy to engage with healthcare services. This may be due to being unsure whether their symptoms are caused by Long COVID, a perception that there is not any help available, not wanting to add burden to the NHS and the nature of multisystem and fluctuating nature of symptoms. There are also reports of experiences of gender and age discrimination with female participants reporting that their symptoms were being attributed to mental health and experiences of feeling belittled by healthcare professionals. Anticipated stigma and fear of judgement due to past experiences was also identified as a barrier to accessing healthcare<sup>13</sup>. It has also been

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<sup>8</sup> [Long COVID: a clinical update - The Lancet](#)

<sup>9</sup> [Prevalence of ongoing symptoms following coronavirus \(COVID-19\) infection in the UK - Office for National Statistics \(ons.gov.uk\)](#)<sup>9</sup>

<sup>10</sup> [Long covid—an update for primary care | The BMJ](#)

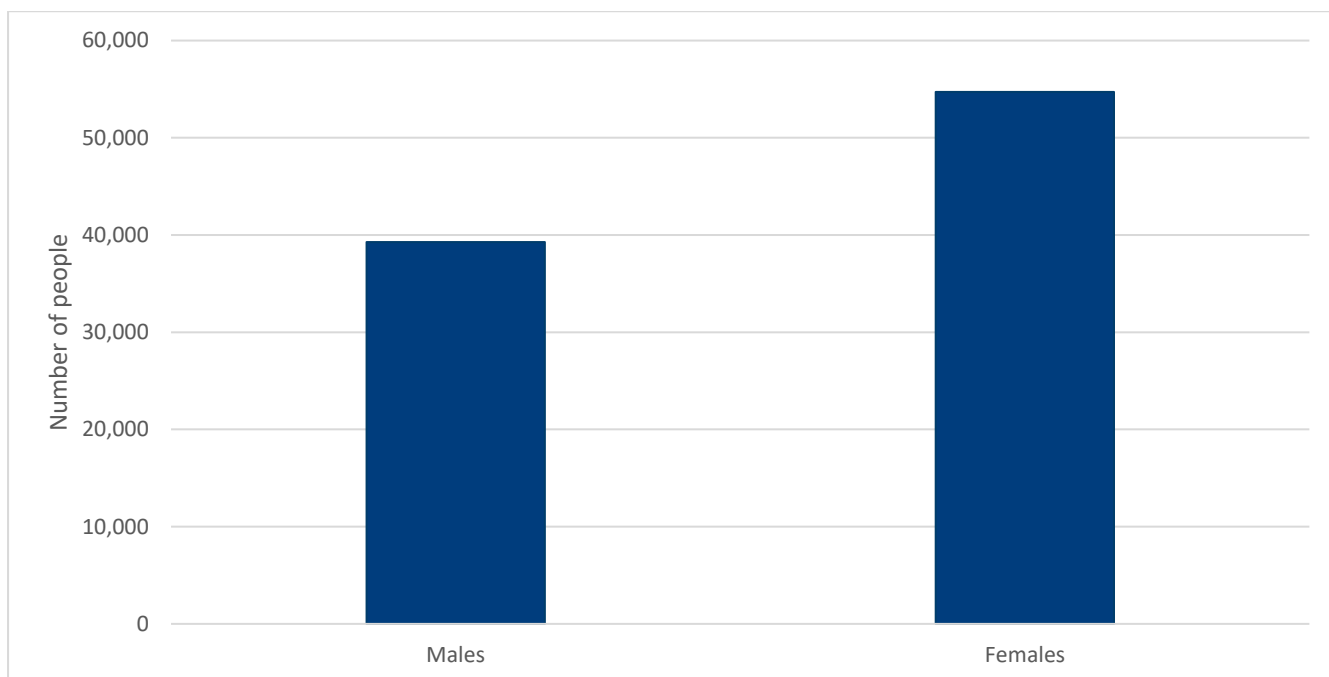
<sup>11</sup> [Prevalence of ongoing symptoms following coronavirus \(COVID-19\) infection in the UK - Office for National Statistics \(ons.gov.uk\)](#)

<sup>12</sup> [Clinical coding of long Covid in Wales: A cohort study of 3.5 million people using linked health and demographic data - PMC \(nih.gov\)](#)

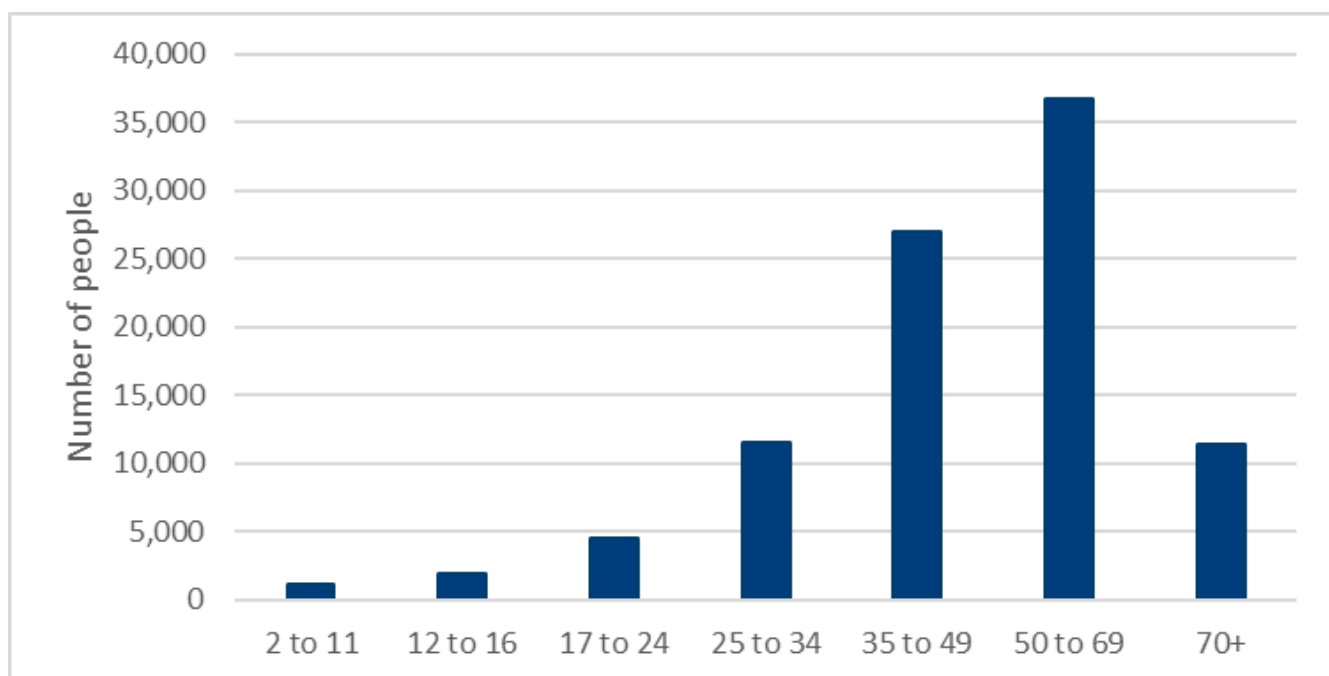
<sup>13</sup> [Barriers to healthcare access and experiences of stigma: Findings from a coproduced Long Covid case-finding study - Clutterbuck - 2024 - Health Expectations - Wiley Online Library](#)

identified that healthcare workers are underrepresented in studies relating to Long COVID, potentially limiting the relevance and effectiveness of such studies.<sup>14</sup>

**Figure 1a and 1b: Estimated number of people living in private households with self-reported Long COVID of any duration, Wales by sex and age group, four-week period ending 05 March 2023 [Note 1] [Note 2]**



Source: ONS and SEA calculations



Source: ONS and SEA calculations

<sup>14</sup> [Healthcare workers must be included in long covid research in the UK | The BMJ](#)

## Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK on ONS

[Note 1] There are no current comparable updated figures since the ONS infection survey ended.

[Note 2] Figures 1a and 1b have been calculated taking a Welsh proportion of the UK data.

### Primary Care Consultations

In November 2023, researchers at the University of Birmingham published a modelling study that estimated that primary care consultations in relation to Long COVID could cost over £23 million each year<sup>15</sup>. Taking the population proportion for Wales this would be an estimated £2 million.

In the absence of well-established and evidenced pharmaceutical treatments, there is an issue around people with Long COVID turning to alternatives such as over-the-counter medicines, remedies, supplements and off label prescriptions which are sometimes purchased in an unregulated manner overseas. There are reports<sup>16</sup> of people seeking private care for Long COVID and being offered treatments which do not have a strong evidence base. This may lead to expensive, invasive and ineffective interventions being carried out without sufficient checks that the treatment is suitable and safe and without sufficient follow up care. It may also contribute to challenges in Primary Care, where patients expect a GP to adhere and prescribe according to protocols which are not supported by the current body of evidence and NICE guidelines<sup>15</sup>.

There are risks associated as well as ethical considerations around treatments which do not have proven efficacy. A lack of more official support can also lead to misinformation and self-medication. It is important that any off-label prescriptions are effectively monitored within the usual UK safety standards and guidelines followed as well as potential drug-drug interactions, side effects and evidence of effectiveness<sup>17</sup>.

### Long COVID and the labour market

A July 2022 report from the Institute for Fiscal Studies think tank said the impact of Long COVID was equivalent to 110,000 workers being off sick on any given day<sup>18</sup>. Taking the population proportion for Wales this would be an estimated 5,060 per day.

<sup>15</sup> [The cost of primary care consultations associated with long COVID in non-hospitalised adults: a retrospective cohort study using UK primary care data | BMC Primary Care | Full Text \(biomedcentral.com\)](#)

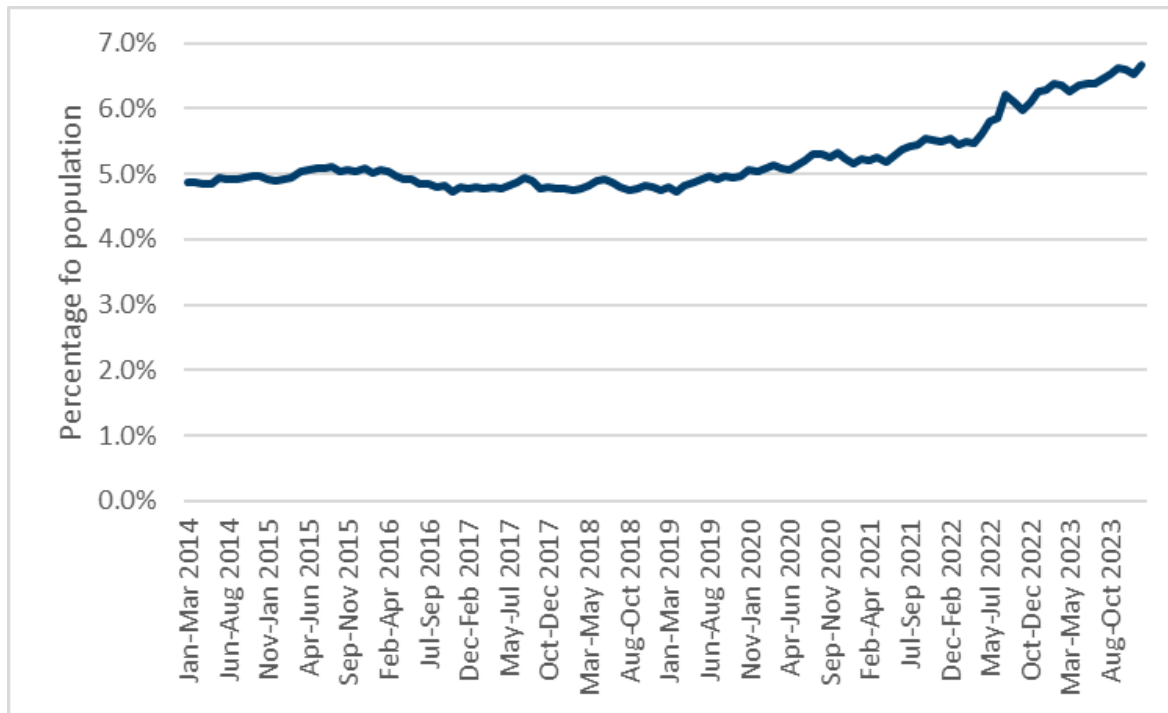
<sup>16</sup> [Long covid patients travel abroad for expensive and experimental “blood washing” | The BMJ](#)

<sup>17</sup> [Long COVID and self-management - The Lancet](#)

<sup>18</sup> [Long COVID and the labour market | Institute for Fiscal Studies \(ifs.org.uk\)](#)



## Percentage of the UK population aged 16 to 64 years who were classed as inactive and gave reason as Long-term sick, January-March 2014 to November 2023-January 2024 [Note 1]



Source: ONS and SEA calculations

### INAC01 SA: Economic inactivity by reason (seasonally adjusted)

[Note 1] 2023 UK population calculated using Wales proportions for 2022 mid-year population estimates

The percentage of the population aged 16 to 64 years on long term sick was relatively stable (between 4.7% and 5.1%) from January-March 2014 to May-July 2020. Since then, the trend has been steadily increasing and reached 6.7% in December 2023-February 2024. Analysis by the ONS shows that for in the three months to March 2023, the most common cause of economic inactivity due to long term sickness (as an individual's main or secondary health condition) was "depression, bad nerves or anxiety"<sup>19</sup>. However, the category "Other health problems or disabilities" has increased 53% since 2019. Due to the difficulty in diagnosing and categorising Long COVID, it may be the case that some of this increase is caused by those off sick due to Long COVID. Likewise, a large increase can be seen in days of sickness absence among working people due to "Other" health problems between 2019 and 2022, which may include those suffering from Long COVID<sup>20</sup>.

<sup>19</sup>

<https://www.ons.gov.uk/employmentandlabourmarket/peoplenotinwork/economicinactivity/datasets/risingillhealthandeconomicinactivitybecauseoflongtermsicknessuk2019to2023>

<sup>20</sup>

<https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/employmentandemployeetypes/datasets/sicknessabsenceinthelabourmarket>



Although it is not possible to quantify the extent to which increased sickness absence is due to Long COVID, it is likely to be a contributing factor. Other factors such as waiting list backlogs as a direct or indirect result of the pandemic may also be contributing, and the cumulative stresses of the pandemic, national lockdowns, and the cost-of-living crisis may explain an increase in mental ill-health.

In terms of economic impact on the UK, Cambridge econometrics completed a study on the impact of Long COVID using their E3ME macroeconomic model to stimulate a Long COVID future. The results suggest that Long COVID may have macroeconomic costs of £1.5 billion per year & predict that if Long COVID cases were to increase to around 4 million by 2030 the impact could be £2.7 billion every year in GDP. The main driver of this result is the way Long COVID reduces people ability to work leading to lower household incomes and lower economic growth. Lower employment of around 138,000 by 2030 follows as a consequence. Higher health costs of around £4 billion each year could also be seen, which would place the impact of Long COVID somewhere between COPD and cardiovascular disease<sup>21</sup>.

Around half of people studied with Long COVID reduced their working hours and many of them needed informal care from friends and family. Work lost to Long COVID cost each participant on average £10,929 and informal care costs have been estimated to be worth £8726 per person. This care is often provided at the expense of their own wellbeing and finances. 23% of the informal carers worked fewer hours to accommodate caregiving. Employment loss from Long COVID is said to be similar to that of Multiple Sclerosis and non-metastatic breast cancer. Schemes which support returning to work may be beneficial. These authors estimate that across the UK monetary values of productivity losses could be as high as £5.7 billion and £4.8 billion from informal caregiving costs<sup>22</sup>. Support and adaptations may also be needed to assist children with Long COVID to return to school<sup>23</sup>

## Research Update

UK Government have highlighted ongoing trials on Long COVID by the National Institute for Health Research and UK Research and Innovation. Some of them are focused on understanding the experiences of Long COVID, exploring the definition of Long COVID and others are looking at assessing current care pathways and models of care for patients with Long COVID with the aim of developing a 'gold standard' for managing it. They also direct to research evidence summaries on living with COVID-19 and research worldwide including the European Commission and studies which have been launched in the USA such as testing the effectiveness of antiviral

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<sup>21</sup>[The economic burden of Long Covid in the UK \(camecon.com\)](https://camecon.com)

<sup>22</sup>[Impact of Long COVID on productivity and informal caregiving | The European Journal of Health Economics \(springer.com\)](https://www.springer.com)

<sup>23</sup>[Impact of Long Covid on the school experiences of children and young people: a qualitative study | BMJ](https://www.bmj.com)  
[Open](#)

medication for Long COVID. The Evidence for Policy and Practice Centre (EPPI) are also highlighted as a source of research evidence summaries on Long COVID<sup>2</sup>.

There are a number of research projects ongoing such as the Post-Hospitalisation COVID-19 (PHOSP-COVID) trial which looked at the phenotypes of patients who were hospitalised with COVID-19, which would miss a proportion of the people with Long COVID who had a milder initial infection. It does however demonstrate the ongoing burden of Long COVID-19 with psychological, functional and organ related impairments. They found that the severity of the initial infection and the persistence and severity of ongoing symptoms were not linked except for lung function tests and walking performance. They also identify risk factors for lack of recovery and cluster modelling for recovery trajectory. The factors described however are correlations as opposed to having a causal link established<sup>24</sup>.

In terms of large randomised controlled trials (RCTs), there are a couple which address the treatment of Long COVID. One randomised, double blind, placebo controlled trial looked at a symbiotic preparation based in Hong Kong with 463 participants (RECOVERY)<sup>25</sup>. They demonstrate that it may have some potential in the treatment of some Long COVID symptoms and improved gut microbiota composition but did not show a significant difference in quality of life or physical activity.

Another group carried out a multicentre RCT<sup>26</sup> investigating the clinical effectiveness of an online supervised group physical and mental health rehabilitation programme for adults with post COVID-19 condition (REGAIN study). This was carried out in England and Wales and included 585 adults and included weekly home based, live, supervised group exercise and psychological support sessions over 8 weeks. They found that their intervention led to improvements in health-related quality of life at 3 months and effects were sustained at twelve months. This highlights the potential role of rehabilitative interventions.

There are a number of smaller studies which may be useful to consider as preliminary evidence but are in need of further research. A smaller Phase 2 pilot RCT with 60 participants has looked at the efficacy and tolerability of an endogenous metabolic modulator (EMM) (AXA1125) in fatigue-predominant Long COVID. EMMs are a group of molecules produced in the body which play crucial roles in regulating metabolism and have been identified as a potential therapeutic agent for complex diseases<sup>27</sup>. It

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<sup>24</sup> [Cohort Profile: Post-Hospitalisation COVID-19 \(PHOSP-COVID\) study | International Journal of Epidemiology | Oxford Academic \(oup.com\)](#)

<sup>25</sup> [A synbiotic preparation \(SIM01\) for post-acute COVID-19 syndrome in Hong Kong \(RECOVERY\): a randomised, double-blind, placebo-controlled trial - The Lancet Infectious Diseases](#)

<sup>26</sup> [Clinical effectiveness of an online supervised group physical and mental health rehabilitation programme for adults with post-covid-19 condition \(REGAIN study\): multicentre randomised controlled trial - PubMed \(nih.gov\)](#)

<sup>27</sup> [Endogenous Metabolic Modulators: Emerging Therapeutic Potential of Amino Acids \(cell.com\)](#)

was associated with improved fatigue scores, but more research is needed to confirm these findings.<sup>28</sup>

A small, randomised sham-control double blind trial has investigated hyperbaric oxygen therapy (HBOT) which was shown to improve global cognitive function, attention and executive function, energy, sleep and psychiatric symptoms. They also report improvement in brain MRI perfusion and structural changes to the brain which they state shows that HBOT can create changes to the neural pathways in the areas of the brain associated with cognitive and emotional roles in patients with post-COVID-19 symptoms. Larger scale RCTs would also be needed to add validity to these results.<sup>29</sup>

In terms of prevention of Long COVID, there are a few areas of interest. A multicentre, randomised, quadruple blind, parallel group phase 3 trial in the US concluded that outpatient treatment with metformin, a common drug used in the treatment of diabetes, reduced the incidence of Long COVID by about 41% compared to placebo for overweight or obese adults when administered shortly after the onset of COVID-19 symptoms (and positive test)<sup>30</sup>. The variant of covid infection also appears to have an impact on the likelihood of developing Long COVID, with Delta and Omicron variants causing less Long COVID symptoms compared to the wild-type variant (Wuhan)<sup>31</sup>. Catala et al (2024) report that vaccines have a preventative effect on the development of Long COVID, the vaccinated group being 29-52% less likely to develop Long COVID than the unvaccinated group<sup>32</sup>. Marra et al (2023) also support vaccination as a preventative measure, reporting that the pooled prevalence of post COVID conditions was 11.8% in people who had not been vaccinated compared to 5.3% of people who were. There is variable reported effect of vaccination on people who already have Long COVID however Greenhalgh et al (2024) recommend it on the basis of reducing the effect of recurrent infections. Antivirals in the acute stages are also said to potentially reduce the risk of developing Long COVID alongside measures which reduce people's risk of catching COVID-19, such as mask requirements and air quality measures<sup>33</sup>.

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<sup>28</sup> [Efficacy and tolerability of an endogenous metabolic modulator \(AXA1125\) in fatigue-predominant long COVID: a single-centre, double-blind, randomised controlled phase 2a pilot study - eClinicalMedicine \(thelancet.com\)](#)

<sup>29</sup> [Hyperbaric oxygen therapy improves neurocognitive functions and symptoms of post-COVID condition: randomized controlled trial | Scientific Reports \(nature.com\)](#)

<sup>30</sup> [Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months \(COVID-OUT\): a multicentre, randomised, quadruple-blind, parallel-group, phase 3 trial - The Lancet Infectious Diseases](#)

<sup>31</sup> [The effectiveness of COVID-19 vaccine in the prevention of post-COVID conditions: a systematic literature review and meta-analysis of the latest research \(cambridge.org\)](#)

<sup>32</sup> [The effectiveness of COVID-19 vaccines to prevent long COVID symptoms: staggered cohort study of data from the UK, Spain, and Estonia - PubMed \(nih.gov\)](#)

<sup>33</sup> [Long COVID: a clinical update - The Lancet](#)

In terms of rehabilitation, one of the ongoing programmes which is also collecting research data is being run by Nuffield Health<sup>34</sup>. They published findings in 2023 of their own programme and used outcome measures for breathlessness, functional capacity, physical fitness, mental wellbeing, health status and disease burden. They report positive results in breathlessness, functional capacity, wellbeing, and health related quality of life on completion of the programme with a reduced number of GP appointments, sick days and outpatient admissions compared to the three months before. However, there was no control group so it cannot be ruled out that such improvements might have happened over time, or have been a placebo. There was a lack of diversity in the participants in the trial, comprising 77.4% females and 88.6% white British ethnicity, which reduces its external validity. Since the research was being carried out by employees of Nuffield about their own programme, there is also risk of bias. Furthermore, it would be useful to see a repeat of those measures after a longer period of time post intervention to determine whether these effects were maintained. It does however demonstrate a possible structure and feasibility for rehabilitation programmes.

There are also a number of other non-randomised trials which carry a high risk of bias. An extensive literature search and critical appraisal is outside the scope of this report therefore some research which may be relevant may not have been included.

NICE advice currently focuses on self-management and supported self-management, multidisciplinary rehabilitation and additional support.

A holistic assessment is advised which includes realistic goal setting, signposting for support, social prescribing, and trusted online resources such as [NHS Inform](#). It is not known whether over the counter vitamins and supplements are helpful, harmful or have no effect. In terms of multidisciplinary rehabilitation, it should include physical psychological and psychiatric management and patient safety should be considered first, taking into consideration that symptoms may fluctuate. Use of tracking apps to monitor goals, recovery and symptoms is encouraged. Rehabilitation which is paced according to the patient's symptoms rather than a set progressive structure is likely to be the best balance to increase activity levels and quality of life whilst reducing the risk of exacerbating symptoms<sup>35</sup>. Additional support for those who are vulnerable or have complex needs, such as short-term care packages, advance care planning and support with social isolation, loneliness and bereavement is also discussed<sup>36</sup>.

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<sup>34</sup> [Frontiers | Improved clinical outcomes in response to a 12-week blended digital and community-based long-COVID-19 rehabilitation programme \(frontiersin.org\)](#)

<sup>35</sup> [Long COVID: a clinical update - The Lancet](#)

<sup>36</sup> [5 Management | COVID-19 rapid guideline: managing the long-term effects of COVID-19 | Guidance | NICE](#)

## Systematic Reviews for Treatment of Long COVID

Since it was identified as a priority, a summary of secondary evidence was completed looking at treatments for Long COVID ([Appendix 1](#)). There were consistent issues with study quality and methodological limitations highlighted which high risk of bias and poor generalisability. Treatments were divided into ‘Pharmaceutical’ and ‘Rehabilitative’. Due to the high variability in Long COVID presentation, the treatments studied were mainly focused on symptom alleviation. There was low quality evidence for rehabilitation and telerehabilitation interventions however caution is advised when managing post exertional malaise, where exercise can be contraindicated.

COVID-19 Vaccines are reported to have a protective function for Long COVID but no conclusions can be drawn for effectiveness on existing Long COVID symptoms ([Appendix 1](#)). This is consistent with the findings of the previous 2022 SEA Long COVID paper<sup>1</sup>.

### Long COVID Services in Wales

Welsh Government published [an All Wales Community Pathway for Long COVID](#) in 2021<sup>37</sup> which provides a framework for health boards and promote consistency in the development of local pathways for Long COVID. There is also a Welsh Government funded programme called Adferiad, which provides advice for primary care and GPs regarding referrals and diagnostics and aims to support individuals with their recovery<sup>38</sup>. All health boards in Wales have developed multidisciplinary recovery services which people can be referred to after screening for other conditions has taken place. They all have a comprehensive assessment tool to ensure patients are treated holistically and individually. The NHS Wales Recovery app is also available for people with mild symptoms.

### Long COVID Research in Wales

Wales is involved in a UK study called ‘The Post Hospitalisation Covid-19 Study’, which focuses on assessing the long-term effects of COVID-19 on patient health and recovery<sup>i</sup>.

In terms of treatment specifically, Swansea University is involved in several Long COVID projects, one being the LISTEN project, which aims to develop and evaluate personalised rehabilitation programmes for patients with Long COVID. The other area they are researching is inspiratory muscle training, which is hoped to strengthen and

<sup>37</sup> [All Wales Community Pathway For Long COVID | GOV.WALES](#)

<sup>38</sup> [Adferiad \(Recovery\) long COVID programme \[HTML\] | GOV.WALES](#)

rehabilitate the respiratory muscles. They report that their initial findings are ‘extremely promising’<sup>39</sup>.

Cardiff University are also undertaking primary research that concentrates on overactivation of the immune system and circulation of inflammatory proteins as a key factor in Long COVID. It is hoped that this research will assist in understanding the causes of Long COVID, potentially assist in formal diagnosis and guide treatment options<sup>40</sup>.

There are two other trials currently open which are taking place in Wales: one looking at a brain training app for cognition in people with Long COVID (BEACON) which is being run by the University of Exeter but open at Cardiff and Vale (awaiting recruitment)<sup>41</sup>. Another also open at Cardiff and Vale with 327 recruits is a ‘Coronavirus Immunological Analysis’ by the University of Birmingham<sup>42</sup>.

### Ongoing Long COVID Research

There is further work being carried out worldwide such as the National Institutes of Health (NIH) funded work on antivirals such as Paxlovid<sup>43</sup>. Clinical trials looking at modafinil, solriamfetol and melatonin to address sleep disturbances are also planned alongside trials involving cardiopulmonary rehabilitation and structured pacing as part of the NIH RECOVER initiative<sup>44</sup>. There are also protocols for brain training and stimulation interventions as well as those targeting autonomic features of Long COVID. A further protocol is also being developed to investigate exercise intolerance and fatigue<sup>45</sup>. For more information on trials ongoing by NIH see [NIH launches Long COVID clinical trials through RECOVER Initiative, opening enrolment | National Institutes of Health \(NIH\)](#).

A multicentre randomised, placebo controlled clinical trial is in Phase 3 and is looking at the use of immunomodulation with Baricitinib for Long COVID<sup>46</sup>. Another ongoing trial from the University of Leicester is a phase 2a double blind randomised placebo controlled trial, investigating the use of Tocilizumab on health related quality of life in adults with Long COVID by means of reducing inflammation<sup>47</sup>. There is also a protocol from STIMULATE-ICP for a multi-centre cluster randomised trial which is looking at

<sup>39</sup> [Inspiration for the future – rehabilitation for sufferers of long covid - Swansea University](#)

<sup>40</sup> [Targeting inflammation to tackle long covid - News - Cardiff University](#)

<sup>41</sup> [Study will test use of brain training games for better brain health in long Covid - Exeter Biomedical Research Centre \(nhr.ac.uk\)](#)

<sup>42</sup> [Coronavirus Immunological Analysis \(CIA\) \[COVID-19\] \[UPH\] - Health Research Authority \(hra.nhs.uk\)](#)

<sup>43</sup> [RECOVER Clinical Trials | VITAL \(recovercovid.org\)](#)

<sup>44</sup> [NIH to open long COVID clinical trials to study sleep disturbances, exercise intolerance, and post exertional malaise | National Institutes of Health \(NIH\)](#)

<sup>45</sup> [NIH Launches Clinical Trials for Long COVID Treatments | NIH COVID-19 Research](#)

<sup>46</sup> [REVERSE-Long COVID: A Multicenter Randomized, Placebo-Controlled Clinical Trial of Immunomodulation \(With Baricitinib\) for Long COVID Related Cognitive Impairment and ADRD \(Alzheimer's Disease and Related Dementias\) - AdisInsight \(springer.com\)](#)

<sup>47</sup> [PHOSP](#)



rehabilitation interventions as well as medications such as loratadine, rivaroxaban and colchicine<sup>48</sup>.

There is ongoing research into autoimmunity, some is in preprint at the time of writing<sup>4950</sup>. There is a need for high quality RCTs for any potential treatments.

This list is not extensive and there is further research ongoing worldwide.

## COVID link with ME/Post Viral Fatigue Syndromes

It has been suggested that there are similarities between Long COVID and Myalgic Encephalopathy (ME)/Chronic Fatigue Syndrome/Fibromyalgia and other post viral fatigue (PVF) syndromes and whether services could provide support to these conditions concurrently<sup>51</sup>.

Similarities between Long COVID and PVF syndromes include fatigue which is exacerbated by exercise and not relieved by rest, pain, malaise, cognitive dysfunction, dysautonomia, sleep disturbance, headaches, poor temperature regulation and paraesthesiae (pins and needle type sensations)<sup>52</sup>.

Long COVID is known to affect other body systems such as the lungs, cardiovascular system, liver, kidneys, gastrointestinal tract and nervous system. Contrasting those with ME, Long COVID sufferers can have ongoing problems with breathlessness, chest pain, disturbances to heart rhythm, periodic fevers, change in taste or smell, “post COVID irritable bowel syndrome”<sup>53</sup>, skin rashes and hair loss. Some have symptoms more linked to fatigue and ME and fibromyalgia type symptoms, whilst others experience symptoms that may be linked to the organs damaged by the initial Covid infection<sup>54</sup>.

Long COVID services therefore, may have elements that are appropriate to guide management for ME/CFS type conditions, but the assessment and management for both may vary in some respects, depending on presentation and systems affected.

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<sup>48</sup> [STIMULATE-ICP: A pragmatic, multi-centre, cluster randomised trial of an integrated care pathway with a nested, Phase III, open label, adaptive platform randomised drug trial in individuals with Long COVID: A structured protocol - PMC \(nih.gov\)](#)

<sup>49</sup> [Transfer of IgG from Long COVID patients induces symptomology in mice | bioRxiv](#)

<sup>50</sup> [A causal link between autoantibodies and neurological symptoms in long COVID | medRxiv](#)

<sup>51</sup> [Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome \(ME/CFS\)-A Systemic Review and Comparison of Clinical Presentation and Symptomatology - PubMed \(nih.gov\)](#)

<sup>52</sup> [Frontiers | ME/CFS and Long COVID share similar symptoms and biological abnormalities: road map to the literature \(frontiersin.org\)](#)

<sup>53</sup> [COVID-19 infection causing residual gastrointestinal symptoms – a single UK centre case series | RCP Journals](#)

<sup>54</sup> [Signs and symptoms of long COVID | Long-term effects of COVID-19 \(nhsinform.scot\)](#)



## Conclusion

The clinical and economic impact of Long COVID in Wales is significant and further research is ongoing in this area within Wales and internationally. Long COVID services have been established across all health boards. Accessing recent prevalence data is challenging since the end of the ONS survey in March 2023. There is some symptom overlap between Long COVID and ME type conditions so if they are treated within the same clinics it is important to differentiate between the two as management according to individual presentation may vary. Primary research is progressing but in terms of treatments, more large scale RCTs and secondary evidence of better-quality studies are needed.

## Future Research

The efficacy and cost effectiveness of multidisciplinary Long COVID clinics on patients' recovery or ability to self-manage Long COVID compared to single discipline services

Investigations of biological mechanisms as well as trials to test existing and development of new potential drug treatments

## Policy Implications

### *Vaccines*

There is increasing evidence that Covid-19 vaccines have a preventative effect on Long COVID and post COVID thromboembolic and cardiovascular complications<sup>55</sup>. It is also reported that repeated Covid-19 infections increase the risk of developing Long COVID. There is a lack of quality evidence around the effect of vaccination on those who already have Long COVID at present<sup>56</sup>. Many vaccine policies worldwide restrict vaccine availability to high-risk groups, considering risks of death and hospitalisation specifically in the acute phase of the disease and do not take more Long-term impacts such as Long COVID into account. Ziyad et al (2024) recommend including Long COVID patients within ongoing covid vaccination programmes on the basis that reinfection can trigger de novo Long COVID or exacerbate the severity of Long COVID<sup>57</sup>.

### *Off label prescribing*

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<sup>55</sup> [Effectiveness of COVID-19 vaccines to prevent long COVID: data from Norway - The Lancet Respiratory Medicine](#)

<sup>56</sup> [Effect of covid-19 vaccination on long covid: systematic review | BMJ Medicine](#)

<sup>57</sup> [Long COVID science, research and policy | Nature Medicine](#)

In the UK, no medicines are authorised by the Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of Long COVID. However, some clinicians may be prescribing medicines “off label” for some patients.

Where clinicians prescribe a licensed medicine off-label, they must follow professional guidance. This includes taking responsibility for prescribing the medicine and for overseeing the patient’s ongoing care. The prescriber must also be satisfied that there is a sufficient evidence base and/or experience of using the medicine to show its safety and efficacy, and that prescribing an alternative, appropriately licensed medicine would not meet the patient’s needs.

Advice for healthcare professionals about off label prescribing is available in [Prescribing Dilemmas: A Guide for Prescribers](#) produced by the All Wales Medicines Strategy Group and at [Off-label or unlicensed use of medicines: prescribers’ responsibilities - GOV.UK \(www.gov.uk\)](#).

The evidence for efficacy of medicines for the treatment of long COVID is in general limited to individual non controlled case studies. Such studies are not of sufficient quality to demonstrate the efficacy of potential treatments. Well-designed randomised controlled trials are needed demonstrate improvements experienced by some patients are not the result of chance and the natural history of long COVID. Randomisation and blinding which are not present in the current studies also help to reduce bias. Robust trials of potential medications would be of much greater value to the evidence base and further research on biological mechanisms underpinning long COVID may support progress in this area.

Where a clinician is considering off label prescribing for long COVID they should do so only as part of a formal clinical trial.

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## Appendix

### Summary of Systematic Reviews about the Treatments of Long COVID

#### **Background**

The research briefing “Coronavirus: Long COVID” (UK Gov, 2024) outlines what is currently understood about the management and rehabilitation of Long COVID. This document sets out that there is no cure at present, but that there are several areas of ongoing study. NICE guidelines are also referred to which offers available options concerning support services and managing symptoms (NICE, 2024). UK Gov (2024) highlights a range of studies being carried out by the National Institute for Health Research (NIHR) and UK Research and Innovation (UKRI) which are ongoing, as well

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as an article which provides further information on ongoing and completed studies on Long COVID in addition to two research evidence summaries (NIHR, 2024).

## **Methodology**

When looking at the body of published research concerning Long COVID, it can be divided into two main groups: pharmaceutical interventions and rehabilitative interventions. There are several challenges faced when looking at the currently available and published body of evidence which will be discussed in this section with a view to guiding further research.

A brief literature search was performed using PubMed and the search terms “Pharmac\* AND Long COVID”, “Rehab\* AND Long COVID\* and “Manag\* AND Long COVID”. These search terms were not extensive, only included systematic reviews and in one database. Primary research and grey literature was not included so it is possible that some evidence has been missed. Full text analysis and critical appraisal was not carried out. The searches returned 1274 results and the titles of the first 10 pages of each search term were reviewed and refined for relevance. This resulted in 7 studies for “Manag\* AND Long COVID”, 20 studies for “Rehab\* AND Long COVID” and 24 studies for “Pharmac\* AND Long COVID”. The abstracts were then reviewed. Following this, two systematic reviews were finally included for pharmaceutical treatments and 14 for rehabilitative. Relevant quotes from the abstracts were collected in a table (Appendix 1).

## **Evidence Summaries**

### *Pharmaceutical Treatments*

The systematic review by Chee et al (2023) highlights that due to the broad and multisystem nature of the symptoms associated with Long COVID, trials have focused largely on treating and dealing with these individual symptoms classified by either cardiovascular, respiratory and functional capacity, neurological and psychological, fatigue and olfactory dysfunction. Chee et al (2023) highlight that the quality of the published trials limits their internal and external validity. This means that there is uncertainty as to whether the intervention being measured was reliable and whether results can be generalised to the wider population. This is often due to issues such as sample sizes, risk of bias and lack of homogeneity in the research. For example, the definition of Long COVID differs between papers varies. They report that the longitudinal data emerging raises concerns regarding atrophy in the memory and cognitive processing areas of the brain and the potential implications that could have on the associated risk of developing neurodegenerative diseases such as dementia.

(Fawzy, 2023) also discussed pharmaceutical interventions, encountering 76 trials of pharmacological agents, most commonly colchicine. They also reviewed rehabilitative, psychotherapeutic and educational interventions as well as electrotherapy modalities such as transcranial direct current stimulation, transcutaneous auricular vagus nerve stimulation, general electrical stimulation, cranial electrotherapy stimulation, stem cell

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investigations and oxygen therapy. They conclude that most studies aim for alleviation of symptoms but encountered methodological issues in terms of standardisation of outcomes. Internal and external validity was again an issue.

A review of expert opinions by Ora et al (2023) summarises that pharmacological research is ongoing and specifically targeting reducing or modulating systemic inflammation as well as looking at drugs used in similar pathologies. They also state that at present, rehabilitation appears to be the safest treatment to offer in the meantime pending further results from the trials currently in progress. Improving understanding of the condition itself at a cellular level will also assist in development of pharmaceutical treatments.

### **Vaccines and Long COVID**

Ceban (2023) and Notarte (2022) did systematic reviews looking at the effects of COVID-19 vaccination on the risk of developing Long COVID and conclude that the current evidence supports vaccination for the prevention of Long COVID. In their studies, low level evidence suggested that at least one vaccination was protective against Long COVID. The picture is less clear on its impact on those who already have Long COVID, with some symptom change reported but most reporting no change (Ceban 2023; Notarte 2022). Catala et al (2024) is the first international study to show that COVID-19 vaccines reduce the risk of Long COVID at a population level. They evaluated data from the UK, Estonia and Spain and found that the vaccinated group were 29-52% less likely to develop Long COVID than the unvaccinated group. The findings were consistent across the countries and databases analysed (Catala, 2024).

### **Rehabilitation for Long COVID**

Fugazzaro et al (2022) did a systematic review which included five RCTs. Two of these had a low risk of bias and three had 'some concerns'. They report that rehabilitation improved outcomes such as dyspnea, anxiety, kinesiophobia, muscle strength, walking capacity, sit to stand performance and quality of life. Pulmonary function results were more inconsistent.

Chen et al (2024) also reported beneficial effects on dyspnea, fatigue and depression, walking capacity, one measure of pulmonary function (forced expiratory volume in 1 second) and quality of life. They identify physical exercise based rehabilitation as a potential therapeutic strategy but highlight that this should be customised on an individual basis.

Pouliopoulou (2023) identified the most common interventions included in their systematic review, which were breathing exercises (either alone or concurrent with resistance and/or aerobic training), Strengthening and aerobic exercises without a breathing exercise component and aerobic exercise only. Similarly to the other systematic reviews identified, they agree that rehabilitation interventions are

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associated with improvements in functional exercise capacity, dyspnoea and quality of life but low for other outcomes. They also highlight that there is a concern around safety outcomes of exercise in people with Long COVID. There was high risk of bias as blinding was a significant problem in these studies.

Torres and Gradidge (2023) did a systematic review and meta-analysis on the quality and pattern of rehabilitation interventions prescribed for post COVID-19 infection patients and highlighted many of the recurrent issues found with the studies currently available. They agree that the evidence so far suggests that rehabilitation can improve cardiorespiratory fitness and pulmonary function however the small sample sizes, bias, poor external validity and reliability in terms of determining cause and effect relationships due to lack of control groups, limits the applicability of the evidence base. They suggest encouraging further research on the effectiveness and long-term effects of individualised rehabilitation. Torres and Gradidge (2023) recommend use of the 22 item Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist be used to enhance the quality of future observational studies. This is not something which any of the studies they identified used but would improve their scientific rigor.

### *Pulmonary Rehabilitation*

Chen et al (2022) identified that impaired respiratory function has an impact on activities of daily living and quality of life in people with COVID-19 after discharge from hospital. They describe that the intervention details varied between studies but that the three studied they included used respiratory muscle training with or without endurance training. They also describe some studies which used device-based threshold positive expiratory pressure (threshold PEP) to increase airway diameter and enhance mucus clearance. One of the studies also implemented lower limb strength exercises and another focused on posture and flexibility. All three used interval training. The assessment tools varied as did the risk of bias. There were other methodological flaws in terms of their randomisation process and lack of blinding which reduce their validity and reliability. The results in terms of pulmonary function were inconsistent and contradictory. Nevertheless, they concluded that pulmonary rehabilitation may improve exercise capacity among patients with mild to moderate lung impairment associated with COVID-19.

Similarly, Oliva-Melendez et al (2023) report improvements on dyspnoea, physical function, quality of life and depressive symptoms compared to usual care but no differences to fatigue or anxiety levels with pulmonary rehabilitation.

A systematic review and meta-analysis by Martines-Pozas et al (2024) reports that dyspnoea, physical function, quality of life, anxiety and depression were improved with pulmonary rehabilitation. The effect on fatigue was not significant. They highlight the challenged in the research relating to bias and lack of comparability in the data. Face to face and telerehabilitation had positive outcomes, with only the physical domain of

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quality of life outperforming in the face to face group. They identify that out of only 6 RCTs available, 4 of them had a low risk of bias. Most of the observational studies (8/10) had a serious risk of bias. They also highlight that although guidelines exist concerning the components to include for pulmonary rehabilitation (aerobic and resistance training, respiratory training, psychological therapy, dietary interventions, not all of them included respiratory training, fewer included psychological counselling and none included dietary intervention including patients with a BMI >25. They identify a need for future research to include these elements to aid in standardisation of the interventions as well as extending the length of interventions and follow up evaluations. Larger sample sizes and reducing bias should also be a priority in future research.

Pollini et al (2024) offer less confidence and simply conclude that the evidence for the effect of pulmonary rehabilitation is very uncertain.

### *Telerehabilitation*

Calvache-Mateo et al (2023) completed a meta-analysis which found favourable outcomes relating to dyspnea, respiratory muscle strength, functional capacity and lower limb strength with respiratory telerehabilitation without significant difference to adverse events. No significant difference was found in lung function, anxiety and depression. They suggest that telerehabilitation therefore may be a useful method for those with Long COVID.

Pescaru et al (2023) also looked at telerehabilitation programmes which varied between 4 and 10 weeks via a mobile app or video connection. They used a combination of aerobic and strength training, breathing exercises and functional activities. They found that pulmonary rehabilitation via telemedicine approaches improved physical health (step test scores, 6 minute walking distance), mental health (BPAQ, SF-12 and PHQ-4 questionnaires), quality of life (SF-12, SGRQ and CAT scores) and some parameters of lung function (mMRC, STST and MVV) in Long COVID patients.

Bernal-Utrera et al (2022) were positive in their outlook on telerehabilitation, particularly regarding the results in cardiorespiratory measures and physical tests, identifying mixed protocols of aerobic, respiratory and low load strength exercises as appearing effective and safe for the recovery of short and long term post-COVID sequelae.

### **Limitations**

The themes appear consistent across the systematic reviews however they were all done within a short period of time (2022-2024) so it is likely that there is crossover in the studies included within the systematic reviews. The number of systematic reviews agreeing on the same principles therefore is not an indication of the strength of the evidence. They report similar methodological limitations throughout. Many of the trials included in the systematic reviews published so far have high risks of bias and poor

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generalisability. Only one database was searched for this summary therefore the literature search was not extensive. Primary research and grey literature was not included. The intention of this section is to give an 'update' summary of the current published systematic reviews concerning the treatment of Long COVID without repeating information which has already previously been published by UKGov (UK Gov, 2024) and SEA (SEA, 2022).

## **Conclusions**

As a multisystem pathology with significant variation in presentation between individuals, pharmaceutical treatment appears mainly focused on managing the symptoms of Long COVID. Due to the methodological flaws in many of the studies currently published and used in these systematic reviews, that there is insufficient data to make any broader recommendations at present. Higher quality studies are needed in this area.

The number of studies relating to rehabilitative interventions far outweigh pharmaceutical but similar challenges in terms of comparability of results between studies due to lack of standardised definition, interventions and outcomes were noted. Some systematic reviews focused on respiratory rehabilitation, others on exercise and others on the effectiveness of telerehabilitation. Many of the papers report positive outcomes however in some where they discuss post exertional malaise, exercise for example is contraindicated. It is likely that the rehabilitative approach required depends on the individual symptoms and presentation.

## **Policy Implications**

Due to the assortment of Long COVID symptoms and presentations, research in this area is challenging and management largely focuses on symptoms alleviation. Further research concentrating on treatment of subsets of Long COVID (e.g. pharmaceutical interventions for cardiovascular effects of Long COVID or rehabilitation for respiratory dysfunction in Long COVID) might produce more valid results. Scientifically sound research in this area would assist in providing a clearer picture. Another direction would be to design and test to a high standard, targeted and individualised multifactorial rehabilitative programmes.

There have been some trials published and ongoing concerning pharmaceutical and rehabilitative interventions but management at this time should continue be taken on a case-by-case basis, according to the individuals presentation. There are currently some optimistic results concerning rehabilitation and a potential role for telerehabilitation, but safety concerns have been raised regarding the role of exercise in people with post exertional malaise, so this also may need to be taken on an individual basis, and evidence of safety would be required.



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## Secondary Evidence Tables

### [Secondary Evidence Table: Pharmaceutical](#)

### [Secondary Evidence Table: Rehabilitation](#)

