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Prolonged Symptoms Attributable to Infection with COVID-19

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Background

During the initial stage of the global COVID-19 pandemic, attention was largely focused on the acute health impacts of SARS-CoV-2 infection (Leung et al 2020). Early observations suggested that most patients presented with and recovered from 'mild' infections within two weeks and from more serious disease within three weeks. As the pandemic progressed, accumulating evidence showed that some individuals may present with a prolonged and complicated hospital stay (National Institute for Health Research 2020). Over time, it has become clear that for some people COVID-19 can lead to persistent illness, with ongoing and often debilitating symptoms. Infection with SARS-CoV-2 can trigger health effects that can continue well after the resolution of the initial acute COVID-19 illness. These effects can manifest in most organ systems (Ito et al 2024; Kitsios et al 2024), and in some cases be disabling and have profound effects on quality of life. Most commonly referred to as long COVID, the constellation of symptoms after COVID-19 infection has multiple definitions with varied timeframes (Appendix A). This lack of a consensus definition of long COVID poses several problems, including achieving an accurate diagnosis, prevalence measurements and development of appropriate clinical guidelines (Appendix B). As such, the term 'long COVID' has been used sparingly in the brief.[1]

International evidence to date provides a broad range of prevalence estimates for long COVID, ranging from 45 to 80% (Lopez-Leon et al 2021; O'Mahoney et al 2023). However, the accuracy of these estimates is limited given the lack of universal definition of long COVID, non-specificity of some of the reported long COVID symptoms, the impact of pre-existing health disorders and the wider psychosocial, socioeconomic effects of the pandemic (Amin-Chowdhury et al 2021).

Further, in the absence of robust prevalence studies in New Zealand and lack of a formal long COVID registry, the potential burden of long COVID in New Zealand remains unknown. This is particularly significant as New Zealand had a high vaccination rate at the time of community spread, and Omicron was the predominant variant among those infected.

Thus, the aim of this brief was to understand the overall prevalence of prolonged symptoms (three months and beyond) that may be attributable to COVID-19 infection.

[1] Where the term long COVID has been used; it has been defined according to the World Health Organization's definition of long COVID.

Methodology

The literature search strategy initially encompassed 12 evidence questions, of which questions one and two, related to definition and prevalence, are addressed in this first evidence brief. Detailed methodology and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) across the 12 questions is presented elsewhere.[2]

Study selection

Studies that met the following criteria were included in the brief:

- published between September 2023 and August 2024
- involving human participants
- published in the English language and available in full text
- looking at symptoms from three months and longer.

Studies that met the following criteria were excluded from the brief:

- looking at symptoms less than three months
- beyond the scope of the evidence questions
- published in other languages
- conference proceedings
- abstracts only
- animal studies.

A total of 232 records were considered eligible for all 12 evidence questions. Of these, 14 studies were included in this brief to determine population prevalence where non-COVID-19 controls were used.

Data extraction and analysis

The Covidence online tool[3] was used to extract all relevant data. Extraction was performed by a single reviewer. Findings presented are not a meta-analysis; rather, they are general themes presented in a systematic manner.

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[2] Cover letter detailing the 12 original evidence questions is found here: cover letter.

[3] Covidence is an online tool designed to manage and streamline the writing of systematic reviews. **https://www.covidence.org/**

Results

The 14 studies included in this brief comprised three systematic reviews and meta-analyses, three case control studies, three cross-sectional studies, four cohort studies and one observational study.

Systematic reviews and meta-analyses

Two of the three studies we looked at for this brief included symptoms reported less than three months after infection, but sub-analysis of symptoms greater than three months was possible. The studies were heterogeneous in their control groups and measure of prevalence. However, the overall findings were similar.

Luo et al's meta-analysis included symptoms at any time interval after infection (not exclusively after three months) (Luo et al 2024). However, it was possible to extract the data for those symptoms at 3–6, 6–12 and >12 months. These results are presented as follows. In the time intervals of interest (3–6 months, 6–12 months and >12 months respectively, expressed as risk ratio (RR)), three symptoms were statistically significantly more prevalent in those individuals that had been infected with COVID-19: fatigue (2.6; 2.24–3.33), dyspnoea (2.78; 3.10–3.57), sore throat (1.76; 2.97–5.82) and loss of taste (ageusia) or smell (anosmia) (9.37; 5.10–39.99). In addition, depression and diarrhoea also appeared to be more prevalent at 3–6 months and 6–12 months, but not >12 months (see Luo et al study details in Appendix C).

Marjenberg et al's systematic review and meta-analysis from 2023 also investigated symptoms in COVID-19-infected individuals compared to non-COVID-19 controls (Marjenberg et al 2023).[4] This study included symptoms longer than four weeks, with sensitivity analysis of a subgroup of studies limited to symptoms after 12 weeks. This subgroup sensitivity analysis found similar relative risks compared with longer than four weeks. The review concluded that COVID-19 infection results in a significantly raised risk of fatigue (1.72-fold) and shortness of breath (2.60-fold) post infection when compared to a non-COVID-19 control group. There was also an increased risk of neurological symptoms found in this post-infection period; the risk of memory problems increased by 1.44-fold, and the risk of concentration problems increased by 2.53-fold (see Marjenberg et al study details in Appendix C).

[4] The studies used in this systematic review overlapped with several of the studies in Luo et al's systematic review and several other larger studies.

The third systematic review and meta-analysis was authored by Azzam et al (2024). This study examined the prevalence of prolonged symptoms in both hospitalised and non-hospitalised groups, including non-COVID-19 controls. The first group focused on studies that compared the prevalence of symptoms in patients hospitalised with COVID-19 versus those hospitalised with other conditions. The second group compared non-hospitalised COVID-19 patients and healthy population controls.[5] The study found that non-hospitalised patients with COVID-19 appeared to have a stronger association with certain symptoms compared to controls with no history of COVID-19. These included anosmia (loss of smell), ageusia (loss of taste), dyspnoea, fatigue and brain fog or confusion, all with pooled odds ratios greater than 1. Anosmia had the highest odds ratio (11.27), followed by ageusia (9.76). Some symptoms, such as chest pain, dizziness, skin conditions, myalgia/arthralgia and ear problems, showed slightly elevated odds ratios (1.9, 1.37, 1.42, 1.25, and 1.35 respectively ($p<0.05$)).

After adjusting for comorbidities, the pooled odds ratios for certain symptoms changed. Patients with COVID-19 were found to be at significantly higher odds of presenting with anosmia, ageusia, dyspnoea, fatigue and brain fog even after adjusting for comorbidities (4.91, 2.29, 2.2 and 2.91 respectively ($p<0.05$)). However, chest pain, skin conditions, myalgia/arthralgia and ear problems no longer showed a significant association (see Azzam et al study details in Appendix C). In a subgroup analysis of studies on children, when matched for comorbidities, anosmia and fatigue were found to be significantly associated with COVID-19 infection (see Azzam et al children study details in Appendix C). A subgroup of studies that focused on hospitalised COVID-19 patients compared to non-COVID-19 hospitalised controls did not find statistically significant differences in the prevalence of fatigue, brain fog, headache, anxiety or sleep disorders.

[5] Azzam's meta-analysis included three studies in common with Luo et al and Marjenberg et al. Several of the studies excluded by Azzam but included in the other two meta-analyses were excluded because they did not stratify their results based on hospitalised versus non-hospitalised groups.

Larger single studies with non-COVID-19 controls

Four large single studies were deemed eligible for inclusion in this evidence brief. The first is a cohort study from the United Kingdom that involved Scottish adults over 16 years of age, with polymerase chain reaction (PCR) test results, in the National Health Service Scotland Platform (Hastie et al 2023). In the study, 98,666 positive individuals were matched with 99,430 PCR-negative individuals. Although prevalence was not broken down by symptom, the overall prevalence of >1 symptom (out of 25) was 6.6%, 6.5% and 10.3% at 6, 12 and 18 months respectively.

The second study, Shen et al 2023, is a large cohort study of 64,888 individuals across Iceland, Sweden, Norway and Denmark. Of these individuals, 22,382 were COVID-19-positive. The study investigated the relationship between prolonged symptoms and symptom severity in infected and uninfected individuals. The researchers used the PHQ-15 scoring system (Kroenke et al 2002)[6] to assess physical symptoms in both groups. It is important to note that loss of smell or taste is not one of the symptoms included in that system. Scoring was based on self-reported symptoms severity: 'not bothered', 'bothered a little' and 'bothered a lot'. A score of 15 or higher out of 30 was considered 'severe'. The authors found that the overall adjusted prevalence ratio (aPR)[7] for a PHQ-15 score of >15 was 1.37. This was an aggregate measure of symptoms from 0–27 months from infection compared to those who reported no previous infection. When stratified by symptom, shortness of breath, headaches, chest pain, dizziness and low energy/fatigue were the only individual symptoms with a statistically significant aPR (see Shen et al study details in Appendix C).

On sub-analysis at later time intervals (three months or longer), the results were broken down into two groups, depending on how many days the person had been bedridden, if at all, during infection. For those not bedridden at all, there was no significant difference in PHQ-15 score between infected and non-infected individuals. For those bedridden for 1–6 days, an aPR of 1.6, 1.4 and 1.2 for 3–5 months, 6–9 months and 10–27 months respectively was observed in the infected group compared to the non-infected group. For those bedridden for >7 days, aPR of 2.5, 2.6 and 2.4 at 3–5 months, 6–9 months and 10–27 months respectively was observed.

A subsequent prospective analysis of 398 individuals was undertaken to determine the PHQ-15 score before and after infection. Individuals with pre-COVID-19 symptoms were used as the control group. The authors reported a statistically significant increase in fatigue and headache over the period of 0–27 months (fatigue aPR 1.36 and headache aPR 2.03) (see Shen et al study details in Appendix C).

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6 A list of 15 somatic complaints (see PHQ-15 in Appendix C).

7 Adjusted model controlling for age, gender, average monthly income, residency, relationship status, BMI, current smoking, habitual drinking, previous diagnosis of psychiatric disorder, pre-existing somatic comorbidity and response period.

Kostka et al is another large study from 2023 that aimed to assess the burden of 'post-acute COVID-19 symptoms' in a cohort analysis of databases in the United Kingdom (Clinical Practice Research Datalink (CPRD))[8] and Spain (SIDIAP)[9] (Kostka et al 2023). This study included 929,262 COVID-19-positive adult individuals and 4,800,280 negative controls. Participants were asked about the 25 symptoms chosen by World Health Organization (WHO) Delphi consensus to represent the most likely post-COVID-19 symptoms. Although symptoms were assessed at both 28 days and 90 days, the 3–6-month symptom data was extracted manually for the purposes of this report. The analysis showed that only loss of smell (anosmia), fatigue, and shortness of breath were statistically significantly more prevalent in those who had suffered from COVID-19 infection. Anosmia had an RR of 4.91 and 2.67 for the two different national databases. Fatigue had an RR of 1.06 (only the United Kingdom database was statistically significant). Shortness of breath had an RR of 1.12 (only the Spanish database was statistically significant) (see Kostka et al study details in Appendix C). Kostka's study was also able to demonstrate that the unadjusted prevalence of all symptoms increased after re-infection, compared to first infection.

The last of the larger studies included in this review is a 2024 three-year long-term study of United States veterans investigating three-year outcomes of 'post-acute sequelae' of COVID-19 (Cai et al 2024). It studied 114,864 COVID-positive non-hospitalised veterans and 19,297 hospitalised veterans. There were 5,206,835 individuals in the non-infected veteran control group. Of 80 possible symptoms, researchers identified nine symptoms that were statistically significantly more prevalent in infected veterans compared to non-infected at three years: fatigue, dyspnoea, sleep disturbance, myalgia, joint pains, cough, change in smell, diarrhoea and abdominal pain. Headache was more prevalent at year two than year three.

Smaller single studies with non-COVID-19 controls

Several smaller studies were reviewed for this report (Takamatsu et al 2024; de Bruijn et al 2024; Pagen et al 2023; Montoy et al 2023). In all four studies, shortness of breath and cognitive changes were more prevalent in positive individuals compared to negative controls at three or more months after infection. Fatigue and change in smell or taste were also more prevalent, but to varying degrees in the four studies.

[8] Clinical Practice Research Datalink (CPRD) collects anonymised patient data from a network of general practices across the United Kingdom.

[9] The Information System for Research in Primary Care (SIDIAP) is a database of population-wide primary care electronic health records.

Studies of children and adolescents with non-COVID-19 controls

Two controlled prevalence studies of children and adolescents were identified in the literature search. Hosozawa et al (2024) aimed to determine the prevalence and risk factors associated with post-COVID-19 symptoms among children and adolescents from ages 5 to 17 years in Japan. Of the 16 symptoms investigated, at three months or more after infection, they found only fatigue, decreased concentration, cough, headache and change in smell or taste were more prevalent compared to non-infected population matched controls (see Hosozawa et al study details in Appendix C).

The second controlled study of children and adolescents is a 2022 study of adolescents aged 11–17 years investigating physical and mental health three months after COVID infection in England (Stephenson et al 2022). The study used data from the CLoCK study in 2021 (Stephenson et al 2021). The analysis showed that 12 symptoms had a statistically significantly higher prevalence in COVID-19-positive adolescents compared with COVID-19-negative controls: fatigue, shortness of breath, cognitive difficulty, myalgia, headache, sore throat, chest pain, dizziness, loss of smell, skin complaint, gastrointestinal difficulty, earache, chills and eye pain. This study used latent class analysis to define two subgroups of clustering physical symptoms: class 1 was defined as 'few symptoms' (fewer than three symptoms) and class 2 was defined as 'many symptoms' (three or more). For those in class 1, COVID-19 positives had the same prevalence of symptoms as class 1 negatives. However, class 2 positives had a risk ratio of 1.53 compared to class 2 negatives. Latent class analysis helps us understand that on an individual basis, those with few symptoms are less likely to be able to attribute their symptoms to COVID-19 infection. Those that suffer from a multitude of symptoms may point to infection as the aetiology. This study also performed a qualitative assessment. The researchers used the Strength and Difficulties Questionnaire (SDQ)) to measure behavioural and emotional difficulties. They also used the Short Warwick-Edinburgh Mental Wellbeing Scale (SWEMWBS) score to measure mental wellbeing. A higher SDQ total difficulties score indicates more severe behavioural and emotional difficulties, and a higher SWEMWBS score indicates better mental wellbeing. Quality of life and functioning was measured using the EQ-5D-Y[10], and fatigue was measured by the 11-item Chalder Fatigue Questionnaire. SWEMWBS scores and SDQ scores were similar between the infected and control groups (mean 21.5 vs 21.4). Mean fatigue scores were similar (mean 13.3 vs 12.5). In terms of quality-of-life measures, EQ-5D-Y scores were higher for mobility problems, problems with usual activities and pain/discomfort in infected people compared to the control group. Regardless of test status, those with multiple physical symptoms at three months after the test reported concurrent poor mental health, reflecting the acknowledged close relationship between physical and mental health. Despite EQ-5D-Y scores being equivalent, the authors highlight that scores for worry/sadness/unhappiness were high in 40% of individuals in both groups, which is consistent with surveys of young people during the pandemic and is commonly attributed to lockdowns, school closures and social isolation.

[10] EQ-5D-Y is a youth-adapted version of the commonly used EQ-5D. The EQ-5D is a widely used standardised generic measure of Health Related Quality of Life (HRQOL) (Willie et al, 2010).

Discussion

Fatigue, poor concentration/memory, shortness of breath and loss of taste or smell are the most prevalent symptoms following COVID-19 infection in adults when compared with non-COVID-19 infected controls (either population controls or those with infective symptoms but testing negative for COVID-19). Children and adolescents present with similar symptoms to adults, but may also include cough and headache. Given the heterogeneity of evidence to date, and in the absence of high-powered, robust studies, a meta-analysis could not be undertaken to accurately determine the overall prevalence of one or more of these symptoms three or more months after infection with COVID-19. While a precise measurement of symptom prevalence remains a challenge, the knowledge that a narrower subset of symptoms can be confidently attributed to infection with COVID-19 has important implications. In the absence of definitive diagnostic criteria, this subset can inform a refined, iterative definition of long COVID-19, both internationally and in New Zealand. The finding that four symptoms appear to be attributable to infection with COVID-19 will enable focused attention on these symptoms. This will facilitate accurate surveillance and targeted resourcing for clinical and wellbeing support where it is most needed.

The studies focusing on children and adolescents also highlight the link between physical and mental wellbeing. Hosozawa et al found that 20% of children and adolescents had experienced moderate disruption of their daily life, and 10% severe disruption. Given the qualitative analysis did not include non-COVID-19 controls, determining disruption compared to non-COVID-19 individuals is difficult and needs further investigation in larger, controlled studies. However, this is one of the largest studies focusing exclusively on children, and it highlights the need for controlled studies investigating the impacts of persistent symptoms on quality of life. Stephenson et al (2021 and 2022) also found a correlation between the pandemic and reduced mental wellbeing in all individuals (infected and non-infected).

It is important to note that the studies included in this brief have several overarching limitations: first, the heterogeneous population and challenges with comparability between groups; second, lack of uniformity of time interval used to measure duration of symptoms. Some subgroup analysis of those symptoms present at greater than three months was possible, but this was not universally so, and this limits our ability to accurately define prevalence. Third, there was variation in the measures used to determine and report prevalence, such as odds ratio, hazard ratio and risk ratio, among others. This limits comparability across studies and prevents accurate determination of prevalence. Fourth, all studies have a risk of recall bias, given the reliance on individual recollection of symptoms prior to the pandemic.

There are also specific limitations on studies included in this brief that should be noted. Two of the large single studies (Hastie et al 2023 ; Shen et al 2023) report difficulty in determining the correlation between severity of acute illness and prolonged symptoms. Hastie et al concluded that the crude prevalence of prolonged symptoms was higher following severe infection compared with mild infection. However, the study was unable to calculate adjusted attributable prevalence stratified by infection severity. Population attributable risk could also not be calculated by severity, because it is a detailed version of the exposure variable (test status), meaning that severity and test status are strongly correlated. The authors note that future work should explore other indicators of severity and alternative methods for understanding the correlation between illness and prolonged symptoms. Shen et al point out that those patients bedridden for more than seven days (which could act as a surrogate measure of illness severity) had a higher prevalence of prolonged symptoms compared with non-infected people; however, this study was limited by the inclusion of symptoms starting at zero months, up to 27 months, without the ability for subgroup analysis at later time intervals.

One of the largest single studies (Cai et al 2024) also had significant limitations. It was a very large study and was able to discern symptoms from a robust database, ensuring symptoms were not present prior to infection rather than depending on recall. Its limitations were significant, however. The aim of the study was to investigate 'post-acute sequelae' in the form of medical events and disability-adjusted life years (DALYs) categorised by organ system. So it is not possible to ascertain if certain symptoms were related to diagnosable non-COVID-19 medical conditions or otherwise medically unexplained and therefore likely attributable to post-COVID-19 condition. Another notable limitation is that the study population was roughly 90% male, older, and ethnically less diverse than the general American population, and therefore less generalisable. The two studies in this review focused on children and adolescents are limited by the low absolute numbers of individuals with symptoms; especially in the case of Hosazawa's study, where several of the symptoms were only present in two or three individuals.

Conclusions

The symptoms most commonly attributable to prior COVID-19 infection in adults are fatigue, poor concentration/memory, shortness of breath and loss of taste or smell. In children and adolescents, the symptoms are similar but may also include cough and headache. While these are the symptoms most likely attributable to infection with COVID-19, it is clear from the literature that a significant proportion of the population suffers from additional unexplained symptoms that they did not experience prior to the pandemic. Regardless of cause, these symptoms deserve acknowledgement, attention, and dedication of health care resources.

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Appendices

Appendix A: Definitions

- **Long COVID: WHO (International):**

  The continuation or development of new symptoms three months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least two months with no other explanation (World Health Organization 2021). The WHO Delphi consensus on long COVID lists 24 symptoms spanning all organ systems.

- **Long COVID: US Centers for Disease Control and Prevention (United States):**

  Long COVID, also known as 'Post-COVID Conditions', is an infection-associated chronic condition that can occur after SARS-CoV-2 infection, the virus that causes COVID-19, and is present for at least three months as a continuous, relapsing and remitting or progressive disease state that affects one or more organ systems (CDC 2024).

- **Post-COVID-19 syndrome: National Institute for Health and Care Excellence (United Kingdom):**
  - **Ongoing symptomatic COVID-19:**

    Signs and symptoms of COVID-19 from 4 weeks up to 12 weeks.
  - **Post-COVID-19 syndrome**

    Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body. Post-COVID--19 syndrome may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed.

    In addition to the clinical case definitions, the term 'long COVID' is commonly used to describe signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more) (National Institute for Health and Care Excellence 2024).

- **Long COVID: National Academies of Sciences, Engineering and Medicine (United States):**

  The National Academies has taken a lengthier approach to a definition of long COVID. The definition is as follows:

  - Long COVID is an infection-associated chronic condition (IACC) that occurs after
    SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems. Long COVID manifests in multiple ways. A complete enumeration of possible signs, symptoms, and diagnosable conditions of Long COVID would have hundreds of entries. Any organ system can be involved, and Long COVID patients can present with:
    - single or multiple symptoms, such as shortness of breath, cough, persistent fatigue, post-exertional malaise, difficulty concentrating, memory changes, recurring headache, lightheadedness, fast heart rate, sleep disturbance, problems with taste or smell, bloating, constipation, and diarrhea.
    - single or multiple diagnosable conditions, such as interstitial lung disease and hypoxemia, cardiovascular disease and arrhythmias, cognitive impairment, mood disorders, anxiety, migraine, stroke, blood clots, chronic kidney disease, postural orthostatic tachycardia syndrome (POTS) and other forms of dysautonomia, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), mast cell activation syndrome (MCAS), fibromyalgia, connective tissue diseases, hyperlipidemia, diabetes, and autoimmune disorders such as lupus, rheumatoid arthritis, and Sjogren's syndrome (National Academies of Sciences, Engineering and Medicine 2024).

- **SARS-Cov-2:**

  Strain of the species of severe-acute-respiratory-syndrome-related-coronavirus. (Gorbalenya, 2022).

- **COVID-19:**
  Infectious disease caused by the SARS-CoV-2 virus[11]

- **Omicron variant:**

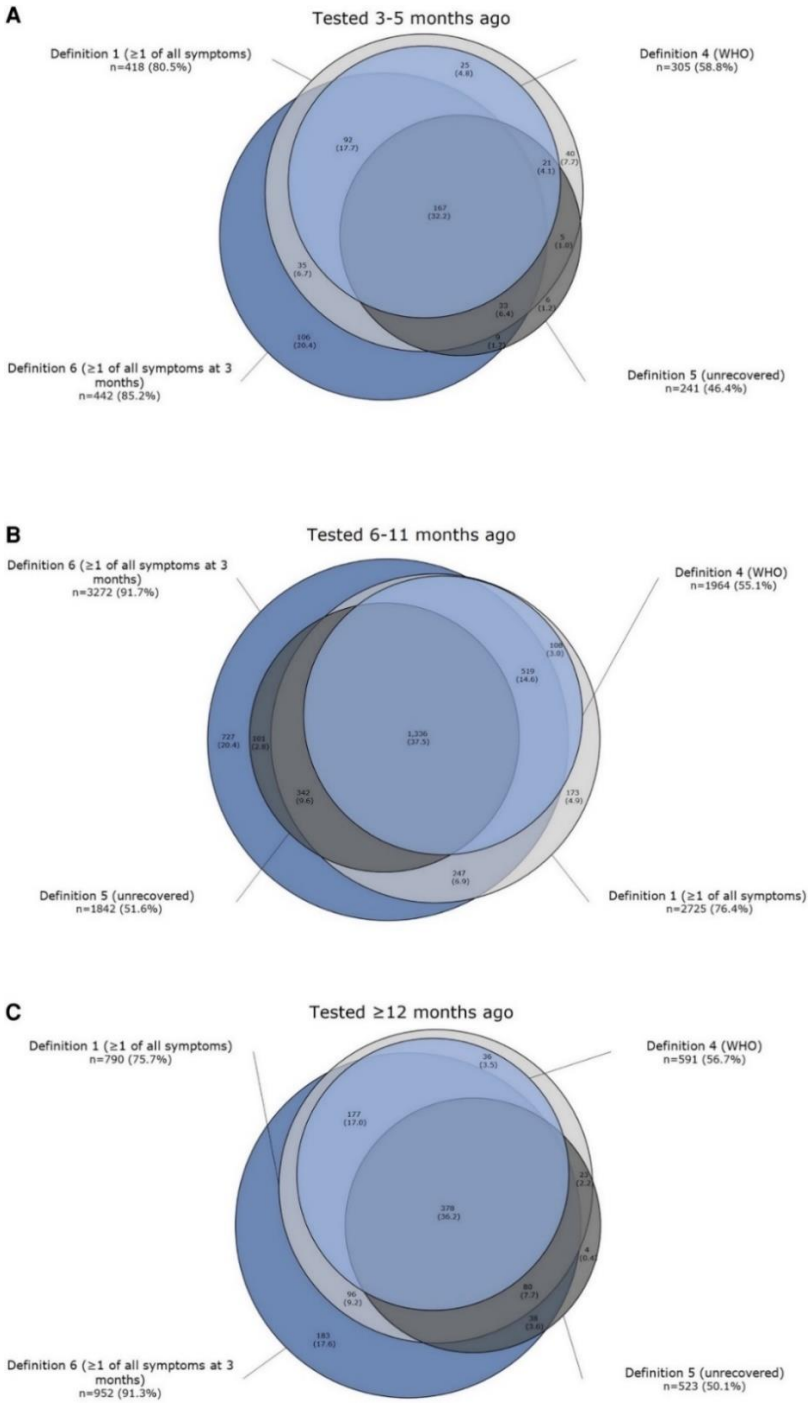
  Viral variant of SARS-CoV-2 first identified in mid-November 2021 and first detected in New Zealand on 10 December 2021 (Ministry of Health 2024).

[11] As defined by the World Health Organisation. **https://www.who.int/health-topics/coronavirus#tab=tab_1**..

Appendix B: Link between definition and prevalence challenges

In Pagen's 2023 study looking at prevalence of prolonged symptoms, the problem of inconsistency in long COVID definition is nicely illustrated (Pagen et al 2023). The researchers used six different definitions of long COVID to highlight the difference in prevalence depending on the definition used. Using definitions that do *not* include test negative controls, the researchers created Venn diagrams that show how inextricably linked definition and prevalence are. They also illustrate how important it is to define a core set of symptoms and use COVID-negative controls.

Figure A1: Venn diagrams of four Long COVID definitions



Venn diagrams of four long-term symptom definitions in positively tested participants, stratified for time since PCR test. A: tested 3–5 months ago. B: tested 6–11 months ago. C: Tested ≥12 months ago. Definition 1. Currently reporting ≥1 of the 44 prelisted symptoms. Definition 4. Meeting the WHO definition. Definition 5. Currently feeling unrecovered since PCR test. Definition 6. Reporting ≥1 of the 44 prelisted symptoms three months after testing. Percentages represent the proportion of participants meeting the definitions compared with all positives who met at least one of the definitions (n = 519 for participants tested 3–5 months ago, n = 3,567 for participants tested 6–11 months ago, and n = 1,043 for participants tested ≥12 months ago).

Appendix C: Study details

Luo et al study details

Luo et al included 28 studies that had non-COVID control groups and performed subgroup analysis of symptoms at 0–3 months, 3–6 months, 6–12 months and >12 months. It then performed a meta-analysis of the 25 symptoms that were reported by more than five studies.

Of the 28 studies, 17 were considered to be of high quality, having a Newcastle-Ottawa Score (NOS)[12] of 7 or higher. The remaining 11 studies were of moderate quality, all of them scoring zero for comparability. The authors addressed this in the discussion section of the paper, noting that differences in the measurement tools used to define long COVID were very variable. This limitation was addressed by comparing the prevalence of individual symptoms rather than of long COVID as a definable condition.

Luo's meta-analysis included a total of 13,368,074 participants, comprising 3,474,987 COVID-19 patients and 9,893,087 non-COVID individuals. Non-COVID individuals had a negative COVID-19 PCR, including healthy controls, symptomatic hospitalised patients, matched influenza patients and matched individuals. The meta-analysis included symptoms at time interval 0–3 months, which is not a focus of this present scoping review. It was possible, however, to extract the data for those symptoms at only 3–6, 6–12 and >12 months. That data is as follows:

[12] Newcastle Ottawa Scale (NOS) is a scale developed for assessing the quality of nonrandomized studies

Table A1: Long COVID symptoms at 3–6, 6–12 and >12 months as reported in Luo et al

	Duration (months)	COVID-19-positive (n=)	Controls (n=)	Risk ratio	95% CI
Fatigue	3–6	601,371	2,065,243	2.60	1.93–3.52
	6–12	256,847	4,498,463	2.24	1.41–3.58
	>12	17,302	89,767	3.33	1.97–5.56
Dyspnoea	3–6	600,023	2,063,359	2.78	1.80–4.30
	6–12	256,847	4,498,463	3.10	2.34–4.10
	>12	16,080	88,640	3.57	1.24–10.27
Depression	3–6	594,075	2,053,042	1.26	1.05–1.52
	6–12	181,384	4,397,509	1.82	1.77–1.88
	>12	N/A			
Sore throat	3–6	600,023	2,063,359	1.76	1.08–2.89
	6–12	1,022	24,888	2.97	1.90–4.66
	>12	1,192	1,127	5.82	5.82–24.41
Loss of smell or taste	3–6	489,214	1,948,319	9.37	4.29–20.51
	6–12	181,384	4,397,509	5.10	4.55–5.72
	>12	16,075	16,361	39.99	8.57–18.6
Diarrhoea	3–6	3,065	3,739	4.94	3.52–6.93
	6–12	182,406	4,422,397	1.89	1.10–3.22
	>12	N/A			

CI= Confidence Interval

Marjenberg et al study details

Table A2: Long COVID symptoms as reported in Marjenberg et al

Symptom	COVID-19 positive (n=)	Control (n=)	OR, hazard ratio, RR, or IRR*	95% CI
Fatigue	**Hospitalised**			
	Al-Aly 2022: 3,667	4,983,491	Hazard ratio 4.49	3.88–5.19
	Castro 2022: 6,619	6,342	OR 0.98	0.84–1.15
	Chevinsky 2021: 44,489	44,489	OR 1.1	0.90–1.4
	Desgranges 2022: 418	89	OR 2.14	1.04–4.41
	Rivera-Izquierdo 2022: 453	453	OR 0.57	0.36–0.90
	Roessler 2021: 145,185 children, 11,950 adults	3,106,010 children, 288,815 adults	IRR 1.97 children IRR 2.28 adults	1.89–2.06 1.71–3.06
	All COVID-19			
	Al-Aly 2022: 33,940	4,983,491	Hazard ratio 2.0	1.82–2.21
	Amin-Chowdhury 2021: 140	1160	OR 2.27	1.82–4.07
	Kuodi 2022: 294	2,437	RR 0.64	0.46–0.89
	Caspersen 2022: 29	2,222	RR 4.8	3.5–6.7
	Noviello 2022: 164	183	RR 2.24	1.48–3.37
	Sorenson 2022: 61,000	91,878	Risk difference 0.08	0.08–0.09
	Xie 2021: 181,384	181,384	Hazard ratio 1.75	1.68–1.81
	Compared to flu			
	Al-Aly 2022: 33,940	5,785,273	Hazard ratio 1.46	1.21–1.76
Dyspnoea	**Hospitalised**			
	Al-Aly 2022: 3,667	4,983,491	Hazard ratio3.54	3.13–4.00
	Rivera-Izquierdo 2022: 453	453	OR 1.13	0.76–1.68
	Desgranges 2022: 418	89	OR 2.81	1.10–7.16
	Roessler 2021: 145,184	3,106,010	IRR 2.88	2.74–3.02
	All COVID-19			
	Al-Aly 2022: 33,940	4,983,491	Hazard ratio 2.08	1.95–2.21
	Amin-Chowdhury 2021: 140	1,160	OR 3.51	1.68–7.32
	Caspersen 2022: 19	963	RR 8.7	5.7–13.3
	Kuodi 2022: 294	2,437	RR 1.52	0.87–2.65
	Petersen 2022: 443	1,328	OR 1.10	0.68–1.79
	Sorenson 2022: 61,002	91,878	Risk difference 0.05	0.05–0.05

Symptom	COVID-19 positive (n=)	Control (n=)	OR, hazard ratio, RR, or IRR*	95% CI
Cognitive dysfunction	**Hospitalised**			
	Al-Aly 2022: 3,667	4,983,491	Hazard ratio 3.06	2.47–3.79
	Desgranges 2022: 418	89	OR 5.71	1.53–21.3
	Liu 2022: 1,178	438	OR 9.10	5.61–14.75
	Rivera-Izquiero 2022: 453	453	OR 1.83	0.74–4.81
	All COVID-19			
	Al-Aly 2022: 33,940	4,983,491	Hazard ratio 1.7	1.54–1.88
	Amin-Chowdhury 2021: 140	1,160	OR 2.82	1.81–4.38
	Kuodi 2022: 294	2,437	RR 1.22	0.69–2.15
	Sorenson 2022: 61,002	91,878	risk difference 0.28	0.28–0.29
	Compared to flu			
	Al-Aly 2022: 33,940	5,785,273	Hazard ratio 1.35	1.15-1.87

* OR = odds ratio RR = risk ratio (RR) IRR = incident rate ratio

Azzam et al study details

Table A3 shows pooled odds ratio by symptom, matched for comorbidities.

Table A3: Long COVID symptoms as reported in Azzam et al

Sign/symptom/condition	Overall			Matched comorbidity		
	Studies No	Pooled odds ratio (95% CI)	I^2%	Studies No	Pooled odds ratio (95% CI)	I^2%
Abdominal pain	7	0.96 (0.76–1.23)	87.4	–	–	–
Diarrhea	5	1.14 (0.9–1.42)	63.1	–	–	–
Nausea/Vomiting	5	0.95 (0.81–1.12)	51.7	3	0.89 (0.8–0.99)	9.8
Heartburn/Stomachache	3	1.02 (0.9–1.16)	0	–	–	–
Sore throat	9	0.85 (0.67–1.08)	90.5	4	1.04 (0.95–1.14)	0
Fatigue	11	1.7 (1.51–1.93)	68.5	5	2.2 (1.6–3.03)	21.7
Headache	11	1.13 (0.89–1.42)	95.3	4	1 (0.83–1.21)	60.9
Fever	7	1.02 (0.82–1.26)	35.8	–	–	–
Dizziness	6	1.37 (1.08–1.75)	90.03	3	1.13 (1.05–1.2)	0
Anosmia	6	11.27 (9.59–13.24)	0	3	4.91 (1.48–16.3)	0
Ageusia	3	9.76 (5.49–17.36)	0	–	–	
Congested or runny Nose	4	0.89 (0.78–1.02)	0	3	0.89 (0.78–1.02)	0
Cough	10	0.95 (0.8–1.12)	78.3	4	0.98 (0.94–1.03)	0
Dyspnea	11	2.19 (1.63–2.96)	95.9	6	2.52 (1.41–4.52)	90.4
Anxiety	3	1.09 (0.98–1.21)	0	–	–	–
Sleep disorders	6	1.08 (0.95–1.22)	23.1	–	–	–
Depression	6	0.91 (0.72–1.16)	67.3	–	–	
Brain fog	18	1.85 (1.58–2.16)	79	10	2.91 (2.05–4.15)	80.3
Tachycardia/palpitation	4	1.46 (1.06–2.03)	90.8	–	–	–
Chest pain	8	1.9 (1.28–2.82)	97.3	4	1.74 (0.85–3.56)	87.2
Myalgia/Arthralgia	12	1.25 (1.07–1.45)	90.8	4	1.1 (0.97–1.23)	75.6
Skin conditions	4	1.42 (0.85–2.4)	74.9	–	–	–
Ear problems	5	1.35 (1.24–1.46)	0	3	1.06 (0.74–1.51)	0

No. number, *CI* Confidence interval

Azzam et al children study details

Table A4 shows pooled odds ratio by symptom for studies with subgroup analysis of children.

Table A4: Long COVID symptoms in children as reported in Azzam et al

Sign/symptom/condition	Hospitalized COVID-19 versus hospitalized for other indications		
	Studies (No.)	Pooled odds ratio (95% CI)	I^2%
Fatigue	4	0.94 (0.65–1.36)	57.2
Brain fog	3	1.19 (0.51–2.76)	62
Headache	3	0.86 (0.77–0.96)	0
Anxiety	4	1.04 (0.51–2.10)	78.2
Sleep disorders	3	0.89 (0.8–0.98)	0

Vs. versus, *No.* number, *CI* confidence interval

PHQ-15 scoring system

The following graphic, from Kroenke et al 2002, reproduces the questionnaire put to COVID-19 patients under the PHQ-15 scoring system.

Figure A2: PHQ-15 scoring system example

During the past 4 weeks, how much have you been bothered by any of the following problems?	Not bothered at all [0]	Bothered a little [1]	Bothered a lot [2]
a. Stomach pain	☐	☐	☐
b. Back pain	☐	☐	☐
c. Pain in your arms, legs, or joints (knees, hips, etc.)	☐	☐	☐
d. Menstrual cramps or other problems with your periods [***Women only***]	☐	☐	☐
e. Headaches	☐	☐	☐
f. Chest pain	☐	☐	☐
g. Dizziness	☐	☐	☐
h. Fainting spells	☐	☐	☐
i. Feeling your heart pound or race	☐	☐	☐
j. Shortness of breath	☐	☐	☐
k. Pain or problems during sexual intercourse	☐	☐	☐
l. Constipation, loose bowels, or diarrhea	☐	☐	☐
m. Nausea, gas, or indigestion	☐	☐	☐
n. Feeling tired or having low energy	☐	☐	☐
o. Trouble sleeping	☐	☐	☐

Shen et al study details

Figure A3 shows the prevalence ratio (95% confidence interval) of individual physical symptom severity among people with COVID-19 compared with those not diagnosed with COVID-19, by symptom. It presents a COVID-19-to-non-COVID-19 cross-sectional comparison (all cohorts).

Figure A3: Prevalence ratio of symptom severity among people with COVID-19 compared to those not diagnosed with COVID-19 as reported in Shen et al

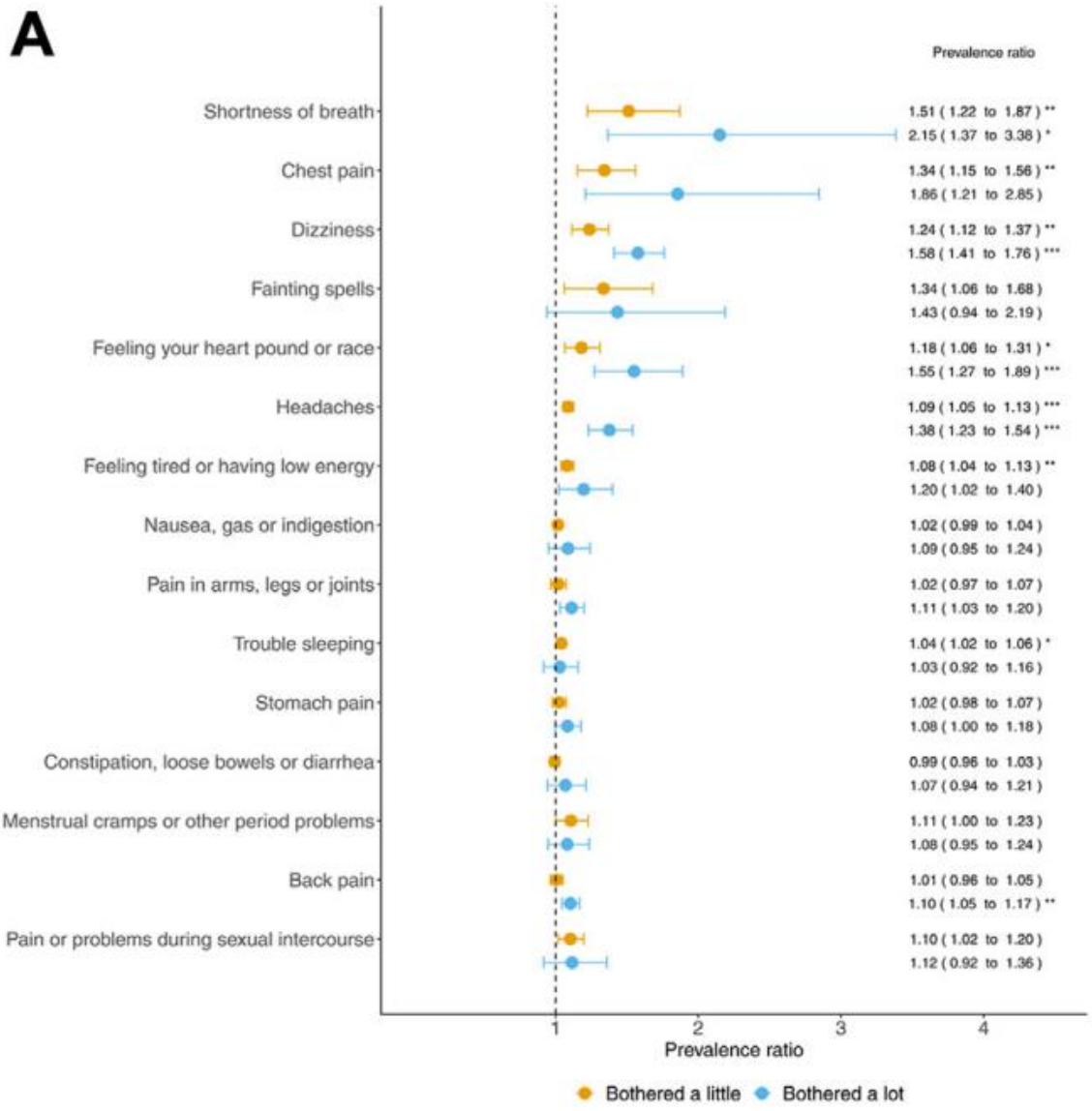
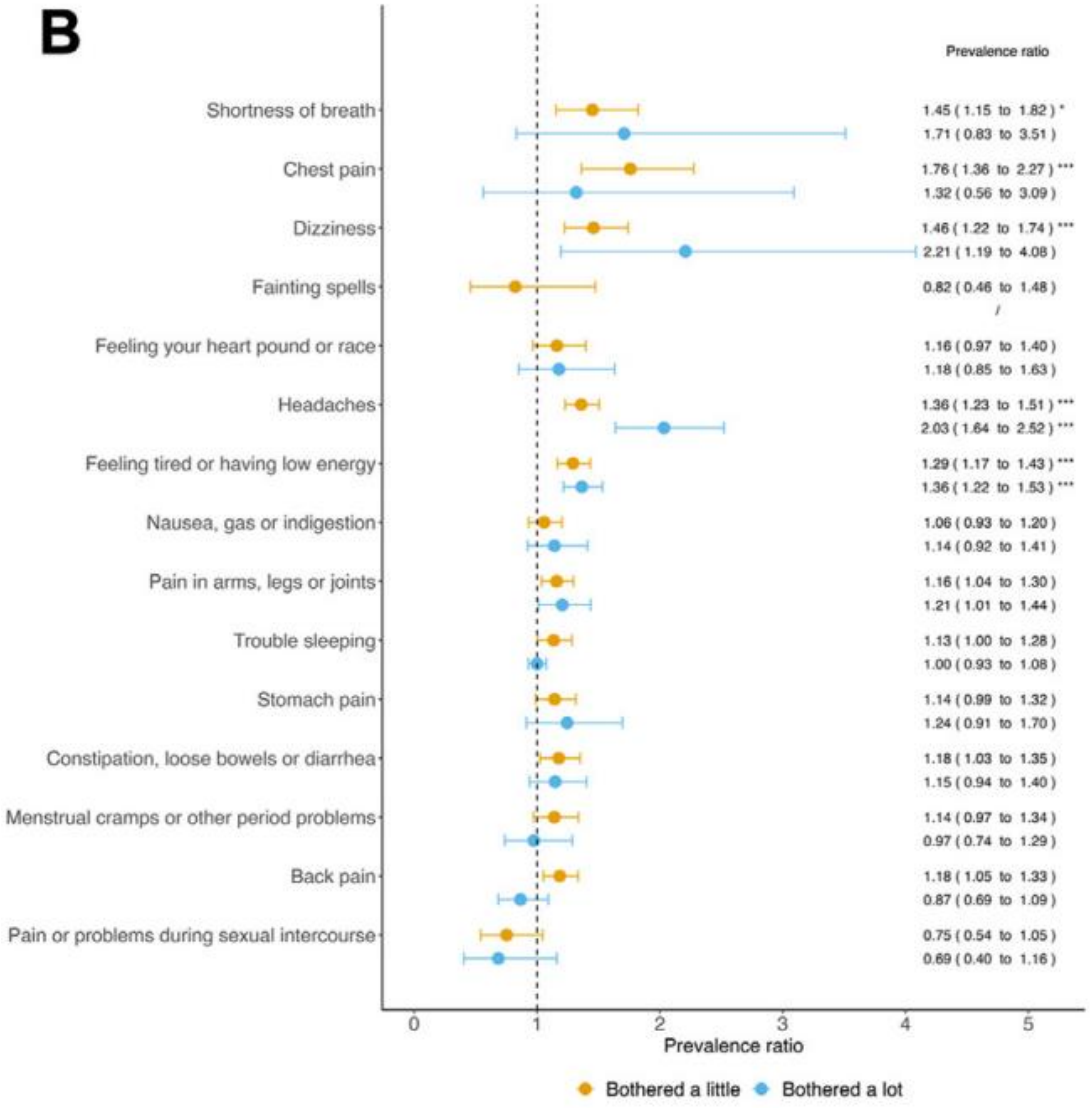


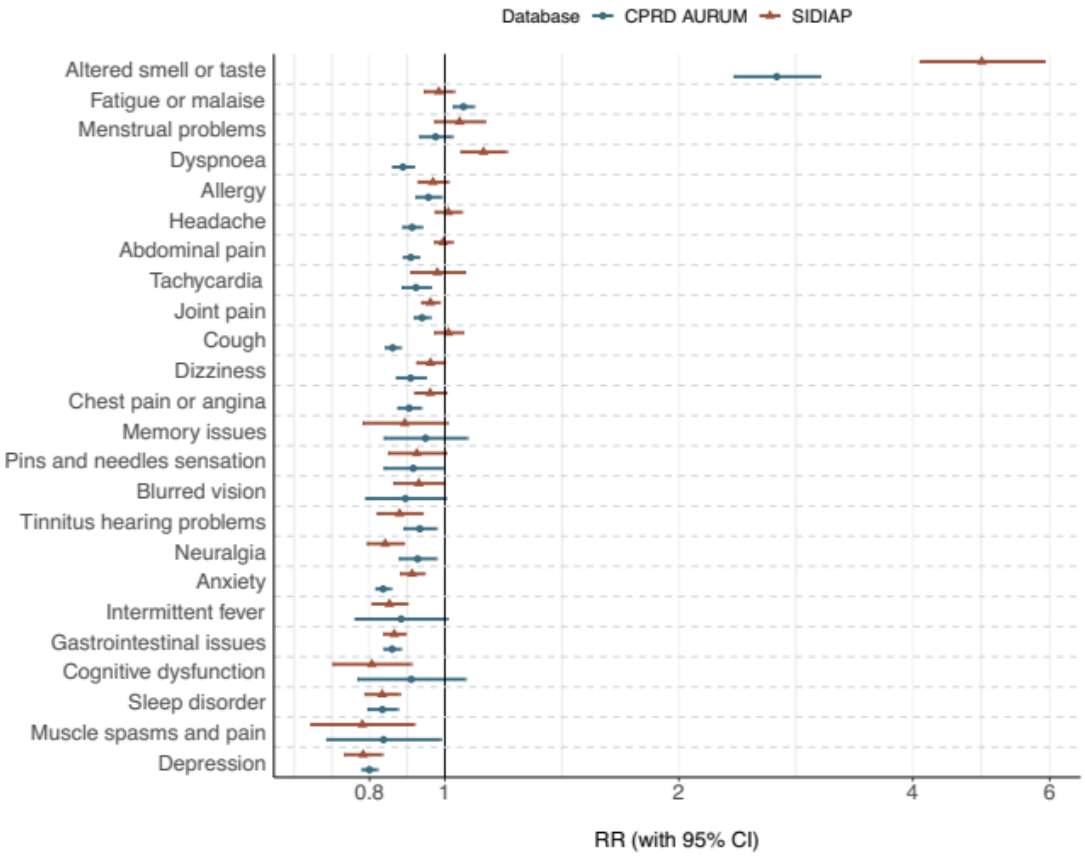
Figure A4 shows the prevalence ratio (95% confidence interval) of individual physical symptom severity, making a post-to-pre-COVID-19 longitudinal comparison (n = 398).

Figure A4: Prevalence ratio of symptom severity: post-to-pre-COVID-19 longitudinal comparison as reported in Shen et al



Kostka et al study details

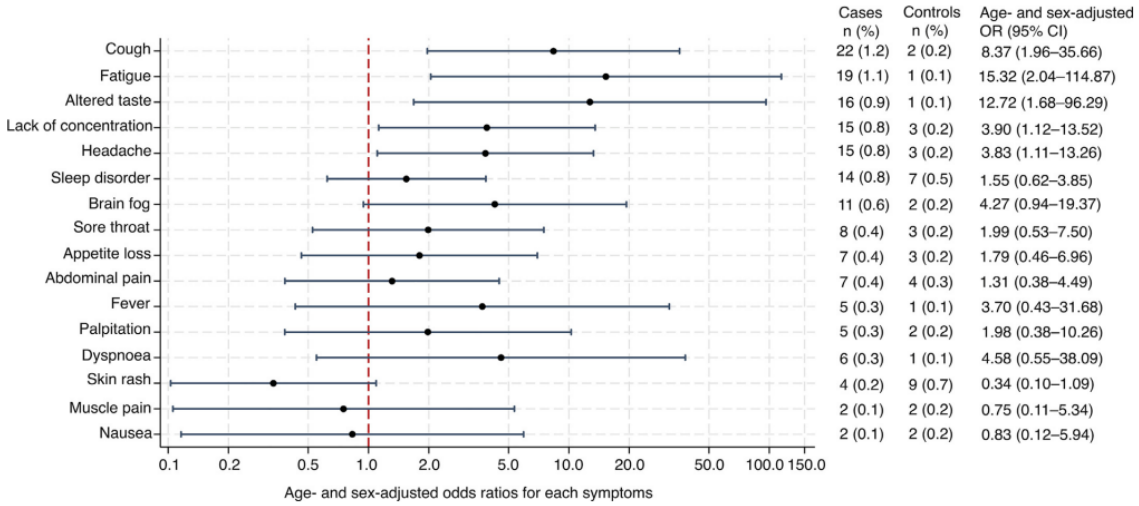
Figure A5: Risk ratio by symptom and database as reported in Kostka et al



Hosozawa et al study details

Among 8,167 invited individuals, 3,141 (1,800 cases, mean age: 10.4 years, 46.1% females; 1,341 controls, mean age 10.5 years, 47.1% females) participated in Hosozawa et al's study. Patients had elapsed an average of 273 (185-605) days from infection, and 1,708 (94.9%) experienced mild acute symptoms. Patients had higher odds of having persistent symptoms than did controls (6.3% vs 2.2%, adjusted odds ratio (aOR): 3.15, 95% confidence interval: 2.08–4.77). Age and sex-adjusted odds ratio by symptom expressed in figure below:

Figure A6: Age- and sex-adjusted odds ratios by symptom as reported in Hosozawa et al



Appendix D: Search strategy

Database:

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to April 26, 2024>, adapted for Scopus, Embase, Cochrane

Search Strategy:

1 ("2019-ncov" or "ncov19" or "ncov-19" or "2019-novel CoV" or "sars-cov2" or "sars-cov-2" or "sarscov2" or "sarscov-2" or "Sars-cORonavirus2" or "Sars-cORonavirus-2" or "SARS-like cORonavirus*" or "cORonavirus-19" or "covid19" or "covid-19" or "covid 2019" or "novel coronavirus" or COVID*).mp.

2 (long-covid or "long covid" or longcovid* or long-haul* or longhaul* or sequelae).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]

3 1 and 2

4 Post-Acute COVID-19 Syndrome/

5 3 or 4

6 ((social or financ* or economic* or societal or society or psychosocial or psych* or "mental health") adj2 (impact* or challeng* or consequenc* or implication* or effect*)).mp.

7 (work or employment or "reduce* income*").m_titl.

8 6 or 7

9 5 and 8

10 ((prevent* or protect* or reduce or lessen or effective*) adj5 vaccin*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]

11 5 and 10

12 ((variant* or "risk factor*") adj5 (long-covid or "long covid" or longcovid* or long-haul* or longhaul* or sequelae)).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]

13 5 and 12

14 ((long-covid or "long covid" or longcovid* or long-haul* or longhaul*) adj3 (Therapeutic* or treatment*)).mp.

15 ((long-term or longterm or post-intensive or postintensive or post-covid or postcovid or post-discharge or postdischarge or prolonged or persistent or long-lasting or permanent or lasting or pervasive or post-acute or postacute or aftereffect*) adj3 (Therapeutic* or treatment*)).mp.

16 14 or 15

17 5 and 16

18 (SNG001 or "interferon-beta1a" or "anti-histamin*" or "anti histamine*" or "dietary supplement*" or Paxlovid).mp.

19 5 and 18

20 ((supportive or model* or pathway*) adj3 care).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]

21 5 and 20

22 (guideline* or (policy adj3 response)).mp. or National Health Programs/ or health policy/ or public policy/ [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]

23 Practice Guideline/ or Guideline/

24 22 or 23

25 5 and 24

26 ((trajectory or recovery) adj5 (long-covid or "long covid" or longcovid* or long-haul* or longhaul* or postacute or post-acute)).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]

27 5 and 26

28 (definition* or (defin* adj3 (long-covid or "long covid" or longcovid* or long-haul* or longhaul or "post-acute covid syndrome" or "postacute covid syndrome"))).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]

29 5 and 28

30 Prevalence/

31 prevalence.ti.

32 5 and (30 or 31)

33 ((biomarker* or bio-marker* or pathophys* or patho-phys*) adj5 (long-covid or "long covid" or longcovid* or long-haul* or longhaul*)).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]

34 exp *Biomarkers/

35 33 or 34

36 5 and 35

37 (zealand or aotearoa or maori).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]

38 5 and 37

39 ((long term or longterm) adj5 ("health implications" or sequelae or "health complication*" or "health effect*" or "ongoing symptom*")).mp.

40 5 and 39

41 9 or 11 or 13 or 17 or 19 or 21 or 25 or 27 or 29 or 32 or 36 or 38 or 40

42 limit 41 to dt=20230801-20240426

Medline = 679 Embase = 796 Scopus = 650 Cochrane =0

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