**Symptoms and quality of life following hospitalisation for COVID-19 (Post COVID-19 Syndrome/Long COVID) in the ISARIC WHO Clinical Characterisation Protocol UK: preliminary results**

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**Executive summary**

- Half of participants reported feeling not fully recovered from COVID-19 (median follow-up 7 months).
- Three quarters experienced fatigue, half were more breathless compared to before and around a quarter had a new disability in sight, walking, memory, self-care and/or communication.
- Outcomes were worse in working age females than males. Females under 50 were over five times more likely to report incomplete recovery, over five times more likely to report a new disability, more likely to have severe fatigue, and more than six times more likely to report increased breathless than males under 50.
- Participants who had required invasive ventilation were four times more likely to report an incomplete recovery compared to those who had not required supplementary oxygen.

**Introduction**

The objectives of this study were to establish:

1) the long-term effects of COVID-19 in those who survived hospital admission

2) the impact of COVID-19 on patient reported outcome measures

3) demographic risk factors for developing long term COVID-19 sequelae

A syndrome is defined as a group of symptoms which consistently occur together, or a condition characterised by sets of commonly associated symptoms. Post COVID-19 Syndrome/ Long COVID has not so far been defined in a prospective cohort study. Our analysis identifies clusters of symptoms allowing the syndrome to begin to be described.

**Methods**

A multicentre, prospective cohort study with at least 3 months follow-up, from symptom onset to completion of case report form. All sites participating in Tier 1 or Tier 2 of the ISARIC WHO Clinical Characterisation Protocol in the United Kingdom (CCP-UK) were eligible to participate in this study. Participants who provided consent to do so during their initial hospital stay were contacted by the research team and asked to complete a structured questionnaire by post or via a telephone assessment. Each respondent only completed one questionnaire, so one response per participant with no paired measures.

The primary outcome was self-reported recovery at least 3 months after initial COVID-19 symptoms. Secondary outcomes included persistent symptoms, breathlessness (MRC Dyspnoea scale), new

disability (Washington group short scale), and quality of life (EQ5D5L). We compared these outcome measures across age, pre-existing comorbidity status and in-hospital COVID-19 severity to identify those at highest risk of developing long-term problems. Exact binomial 95% confidence intervals are reported on percentages. Multilevel logistic and linear regression models were used to adjust for the effects of patient age, sex, comorbidity and in-hospital severity and centre level risk factors on these outcomes.

**Results**

This is preliminary data from an ongoing study. In total, 325 participants admitted between 5th February 2020 and 4th October 2020, from 31 UK Hospitals responded to the follow-up questionnaire. This represents 15% (325/2682) of the surviving Tier 1 / 2 CCP-UK study population. 905 participants who consented to follow up have been contacted, 361 responded (40%). Thirty-six (4%) responded before 3 months of their symptom onset or returned incomplete questionnaires leaving 325 (36%) participants in the current analysis. The median follow-up time was 7 months ($25^{th}$ centile 6 months, $75^{th}$ centile 9 months) after COVID-19 symptom onset. The mean average age of the cohort was 59 years old (SD 14 years) and was predominantly male (59%, 192/325).

**Key findings**

- 54% 177/325, (Confidence interval (CI): 49-60%) respondents (54%, 103/192 men, 57%, 74/133 women) reported they did not feel fully recovered.
- Ongoing symptoms were reported by 93% (303/325, CI: 90-96%) of participants.
- Fatigue was the most common symptom (77%, 251/325, CI: 72-82%), followed by shortness of breath (54%, 175/325, CI: 48-59%). 49% (150/304, CI: 44-55%) of participants reported a fatigue level of 5 or higher and 56% (153/273, CI: 50-62%) reported an increase in MRC breathlessness grade of at least 1. New MRC breathlessness grade of 3 or higher was reported in 26% (72/273, CI: 21-32%) of participants. Fatigue and breathlessness commonly occurred together, along with other neurological and pain symptoms.
- New disability was reported in 24% (77/318, CI: 19-29%) of participants. There was a significant deterioration in sight, walking, memory, self-care and communication, but not in hearing.
- Overall, participants reported a drop in quality of life of around a tenth (0.1 out of 1.0) assessed by EQ5D-5L. Usual activities, anxiety and depression and pain were the domains most affected. In total, 35% (109/308, CI: 30-41%) reported new difficulties that were described as at least

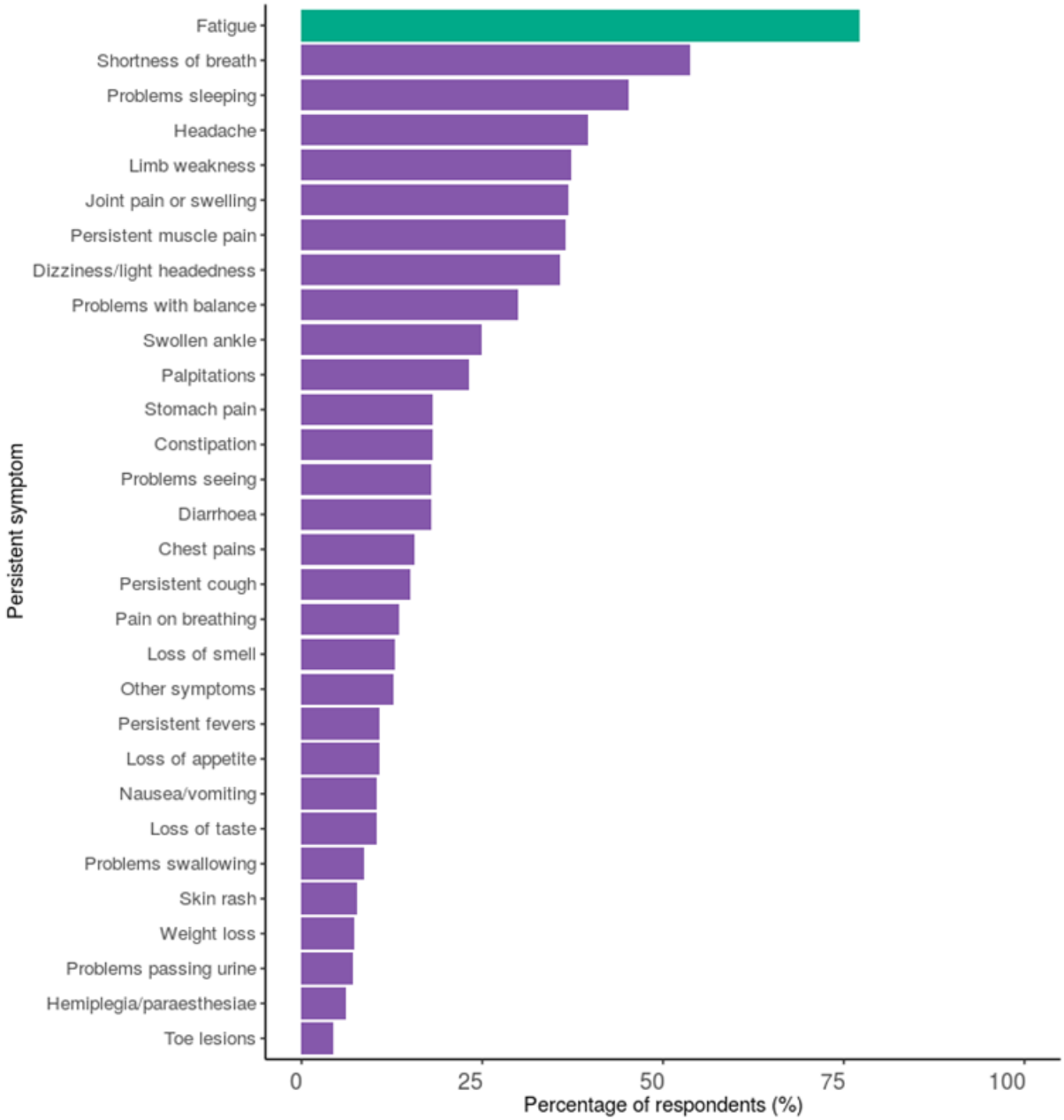
moderate, with pain and discomfort the most common (21%, 65/317, CI: 16-25%) followed by anxiety and depression (18%, 58/320, CI: 14-23%).

- Outcomes were worse in females versus males; Younger females (<50) were five times more likely to report both incomplete recovery (adjusted OR 5.29, 95% CI: 1.69 to 16.60) and greater disability (adjusted OR 5.27, 95% CI: 1.25 to 22.21), twice as likely to report worse fatigue (mean difference 2.03 points on 0 to 10 VAS scale, 95% CI:0.76 to 3.30) and six times more likely to become more breathless (adjusted OR 6.15, 95% CI:1.91 to 19.77).
- Overall recovery was worse in patients who had required invasive ventilation (adjusted OR 3.61, 95% CI:1.58 to 8.25) compared to those who had not required any form of supplemental oxygen.
- Persistent symptoms were not related to increasing age or number of comorbidities. In fact, younger participants were more likely to report persistent symptoms and ongoing difficulties.
- Commonly occurring symptoms were described in related clusters, confirming the existence of Post COVID-19 Syndrome and providing preliminary data about the sets of symptoms that define the syndrome. A) Fatigue, breathless on exertion, headache, dizziness, muscle pain, joint pain, disturbance of balance and limb weakness, B) muscle pain, joint pain, disturbance of balance and limb weakness (nested within cluster A), and C) loss of smell, taste, difficulty passing urine weight loss and disturbance of appetite.

**Limitations**

These are preliminary results form an ongoing study. People who experience symptoms may have been more likely to respond to a questionnaire. In this study, initial non-responders were contacted by telephone, and almost all were happy to participate. Nevertheless, responder bias is recognised in follow up studies and may explain the high rates of persistent symptoms and poor outcomes in this data. Individuals who participated in Tier 1 and Tier 2 of the CCP-UK study were more likely to be younger than the general COVID-19 hospitalised population, had fewer comorbidities (including those associated with extremely poor in-hospital prognosis such as dementia) and were more likely to be admitted to critical care. Therefore, the respondents to our questionnaire assessment are likely to over represent a healthier patient population and those who were likely to be escalated to critical care due to severe disease.

**Figure 1:** Specific symptoms reported. Ongoing symptoms were reported by 93% of participants. Fatigue was the most common symptom, followed by shortness of breath.




Fatigue is in green because it is derived from the percentage of participants reporting any fatigue on a 0-10 Visual Analogue Scale, rather than a yes/no answer. Erectile dysfunction affected 33% of men who responded to the question (45/136, CI: 25-42%, 56 chose not to respond).

**Figure 1B:** Heatmap dendrogram of co-occurring symptoms. Colour intensity represents the Jaccard index, where 0 (white) is no cooccurrence and 1 (red) is where a symptom always cooccurs. Fatigue and breathlessness were most commonly found together and with other neurological and pain symptoms. Three clusters are identified by visual inspection and by dendron: A) Fatigue, breathless on exertion, headache, dizziness, muscle pain, joint pain, disturbance of balance and limb weakness, B) muscle pain, joint pain, disturbance of balance and limb weakness, and C) loss of smell, taste, difficulty passing urine weight loss and disturbance of appetite.

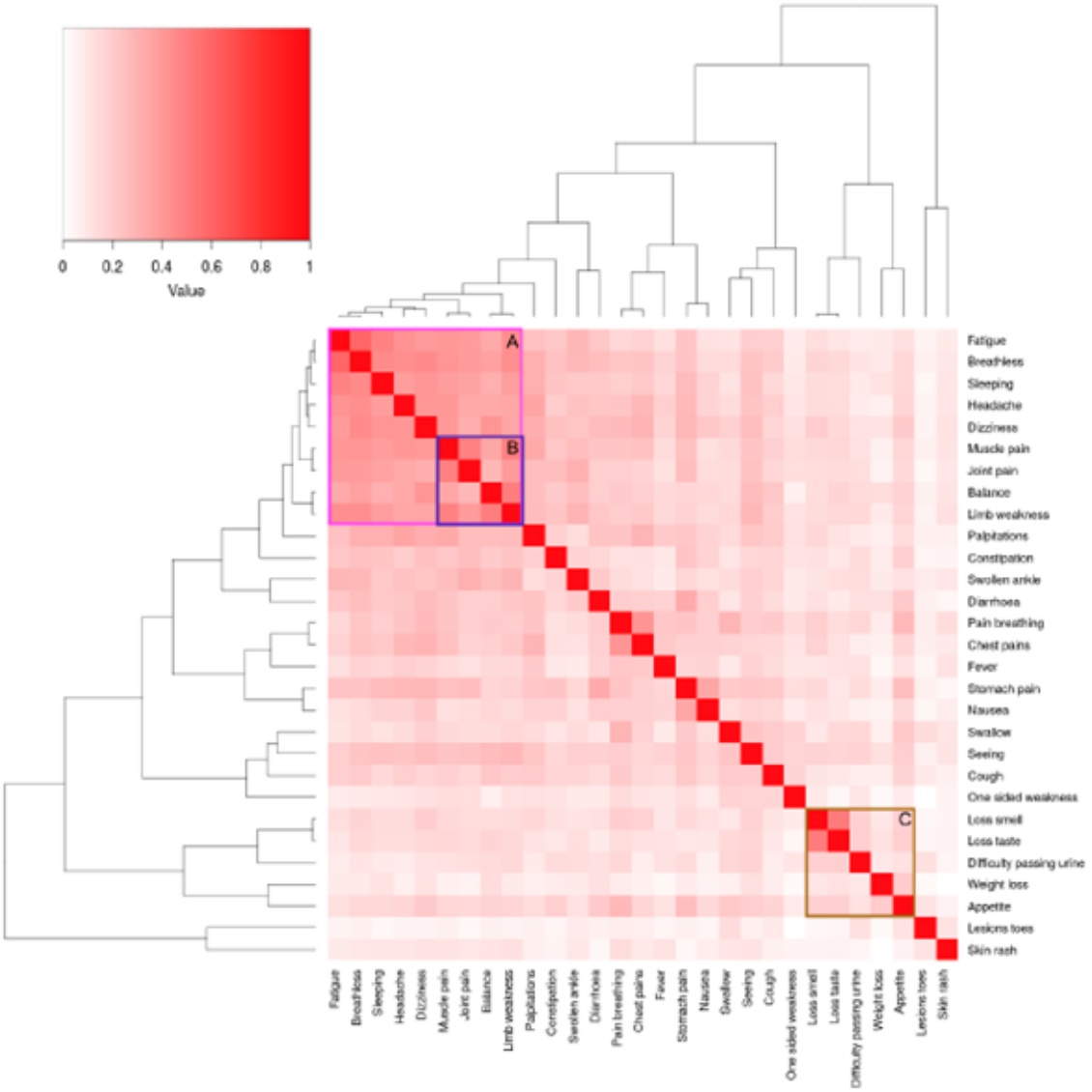


**Figure 2:** Self-reported level of Fatigue on a 0 to 10 visual analogue scale (VAS). 0 was no fatigue and 10 was the worst fatigue possible. Overall, 49% (150/304, CI:44-55%) participants reported a fatigue level of 5 or higher. Females tended to report fatigue of 5 or more (59%, 74/125 CI:50-68%) versus males (42%, 76/179 CI:35-50%).

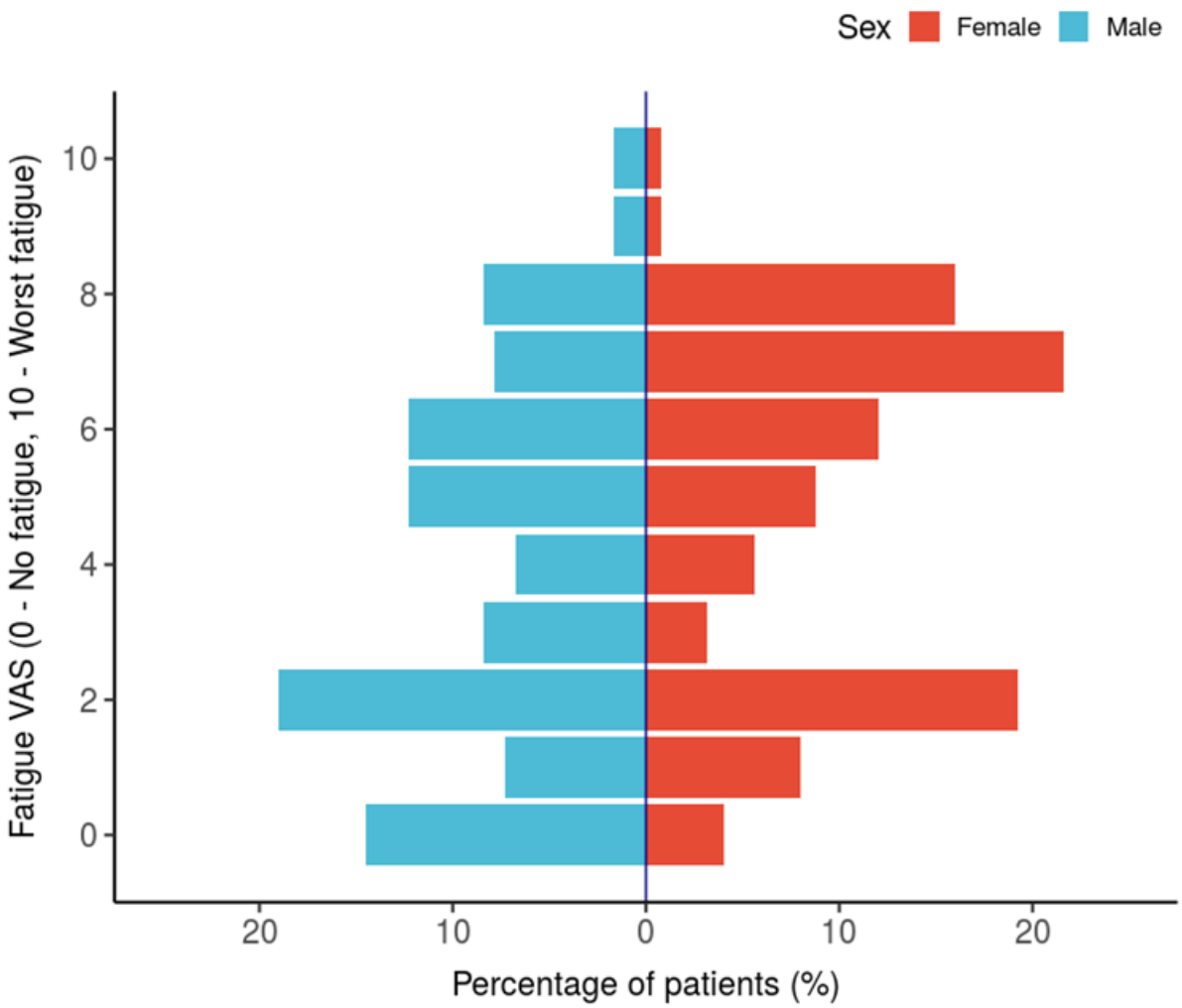
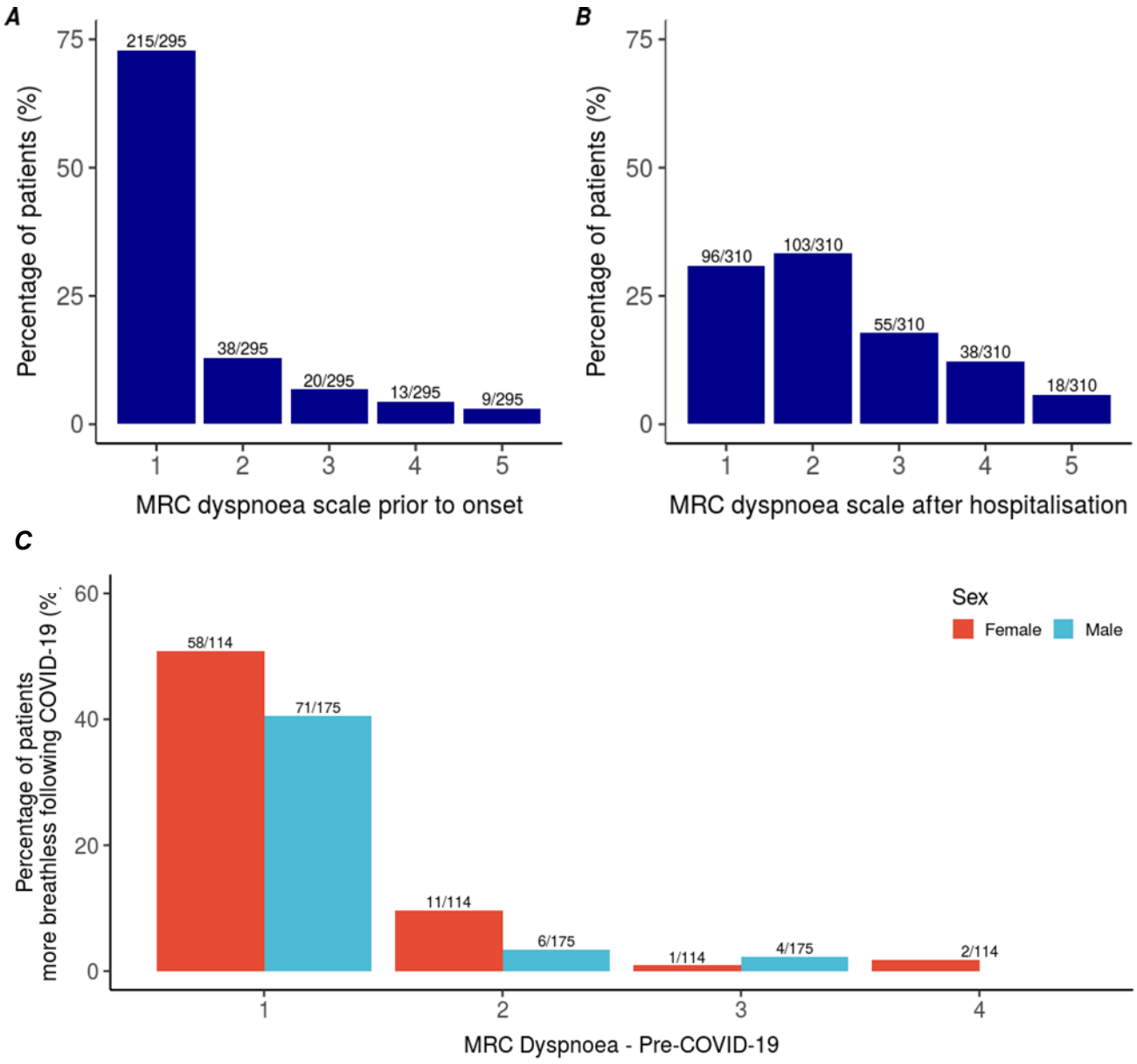


**Figure 3:** Overall MRC dyspnoea scale before symptom onset (A) and after hospital admission (B). Change in MRC dyspnoea scale by sex is shown in (C), showing women are affected most. (D): An alluvial plot showing change in MRC Dyspnea scale before vrs after COVID in males and females. (E) An alluvial plot showing change in MRC Dyspnea scale before vrs after COVID in <50 year olds, 50-69 year olds and > 70 year olds

MRC dyspnoea scale:

1 - Not troubled by breathless except on strenuous exercise,
2 - Short of breath when hurrying on a level or when walking up a slight hill,
3 - Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace,
4 - Stops for breath after walking 100 yards, or after a few minutes on level ground
5 - Too breathless to leave the house, or breathless when dressing/undressing.



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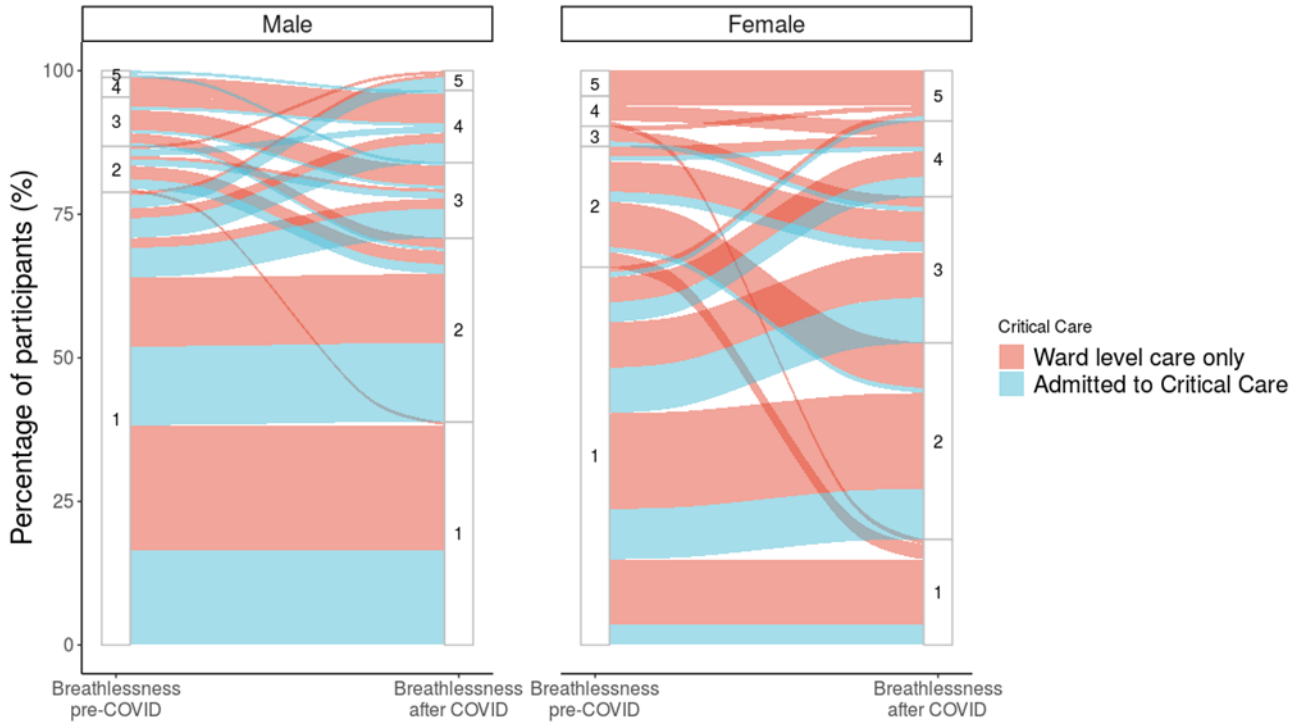

Male
Female
Percentage of participants (%)
100
75
50
25
0
5
4
3
2
1
Breathlessness pre-COVID
Breathlessness after COVID
Critical Care
Ward level care only
Admitted to Critical Care

**E**

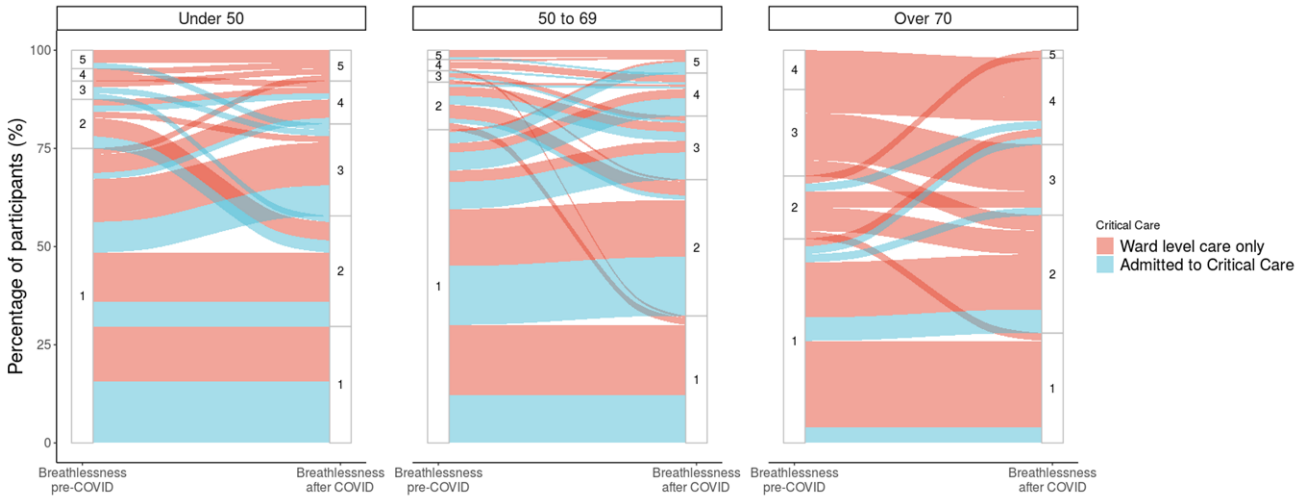

Under 50
50 to 69
Over 70
Percentage of participants (%)
100
75
50
25
0
Breathlessness pre-COVID
Breathlessness after COVID
Critical Care
Ward level care only
Admitted to Critical Care

**Table 1:** Percentage of participants reporting disability in each domain of the Washington Group short set functioning score (WG-SS): Significant deterioration in seeing, walking, remembering, washing and communicating (not including hearing).

| label | levels | After | Before | p |
|---|---|---|---|---|
| Total N (%) | | 325 (50) | 325 (50) | |
| Seeing | No - no difficulty | 229 (70) | 275 (85) | <0.001 |
| | Yes - some difficulty | 81 (25) | 41 (13) | |
| | Yes - a lot of difficulty | 12 (4) | 4 (1) | |
| | Cannot do at all | 0 (0) | 0 (0) | |
| | (Missing) | 3 (1) | 5 (2) | |
| Hearing | No - no difficulty | 228 (70) | 251 (77) | 0.070 |
| | Yes - some difficulty | 83 (26) | 65 (20) | |
| | Yes - a lot of difficulty | 10 (3) | 3 (1) | |
| | Cannot do at all | 1 (0) | 1 (0) | |
| | (Missing) | 3 (1) | 5 (2) | |
| Walking | No - no difficulty | 126 (39) | 228 (70) | <0.001 |
| | Yes - some difficulty | 135 (42) | 65 (20) | |
| | Yes - a lot of difficulty | 56 (17) | 23 (7) | |
| | Cannot do at all | 7 (2) | 4 (1) | |
| | (Missing) | 1 (0) | 5 (2) | |
| Remembering | No - no difficulty | 140 (43) | 247 (76) | <0.001 |
| | Yes - some difficulty | 127 (39) | 61 (19) | |
| | Yes - a lot of difficulty | 54 (17) | 13 (4) | |
| | Cannot do at all | 1 (0) | 0 (0) | |
| | (Missing) | 3 (1) | 4 (1) | |
| Washing | No - no difficulty | 250 (77) | 282 (87) | 0.005 |
| | Yes - some difficulty | 58 (18) | 34 (10) | |
| | Yes - a lot of difficulty | 13 (4) | 5 (2) | |
| | Cannot do at all | 3 (1) | 1 (0) | |
| | (Missing) | 1 (0) | 3 (1) | |
| Communicating | No - no difficulty | 255 (78) | 300 (92) | <0.001 |
| | Yes - some difficulty | 61 (19) | 16 (5) | |
| | Yes - a lot of difficulty | 7 (2) | 3 (1) | |
| | Cannot do at all | 1 (0) | 1 (0) | |
| | (Missing) | 1 (0) | 5 (2) | |

**Table 2:** Change in EQ5D-5L (pre onset versus post admission for COVID-19) by dimension (N = 325).

| Dimension | Change in EQ5D-5L | Number | Percent |
|---|---|---|---|
| Mobility | No change | 199 | 65 |
| | Improve | 3 | 1 |
| | Worsen | 106 | 34 |
| | Total | 308 | 100 |
| Self-care | No change | 256 | 83 |
| | Improve | 1 | 0 |
| | Worsen | 51 | 17 |
| | Total | 308 | 100 |
| Usual activities | No change | 184 | 60 |
| | Improve | 5 | 2 |
| | Worsen | 119 | 39 |
| | Total | 308 | 100 |
| Pain/discomfort | No change | 183 | 59 |
| | Improve | 10 | 3 |
| | Worsen | 115 | 37 |
| | Total | 308 | 100 |
| Anxiety/depression | No change | 178 | 58 |
| | Improve | 14 | 4 |
| | Worsen | 116 | 38 |
| | Total | 308 | 100 |

**Figure 4**: Quality of Life: EQ5D-5L by domain pre and post COVID-19

Deterioration seen in all five domains: Mobility, Self-care (washing or dressing), Usual Activities Pain or discomfort, Anxious or depressed.

Levels are: No problems, Slight problems, Moderate problems, Severe problems and unable to do domain activity.

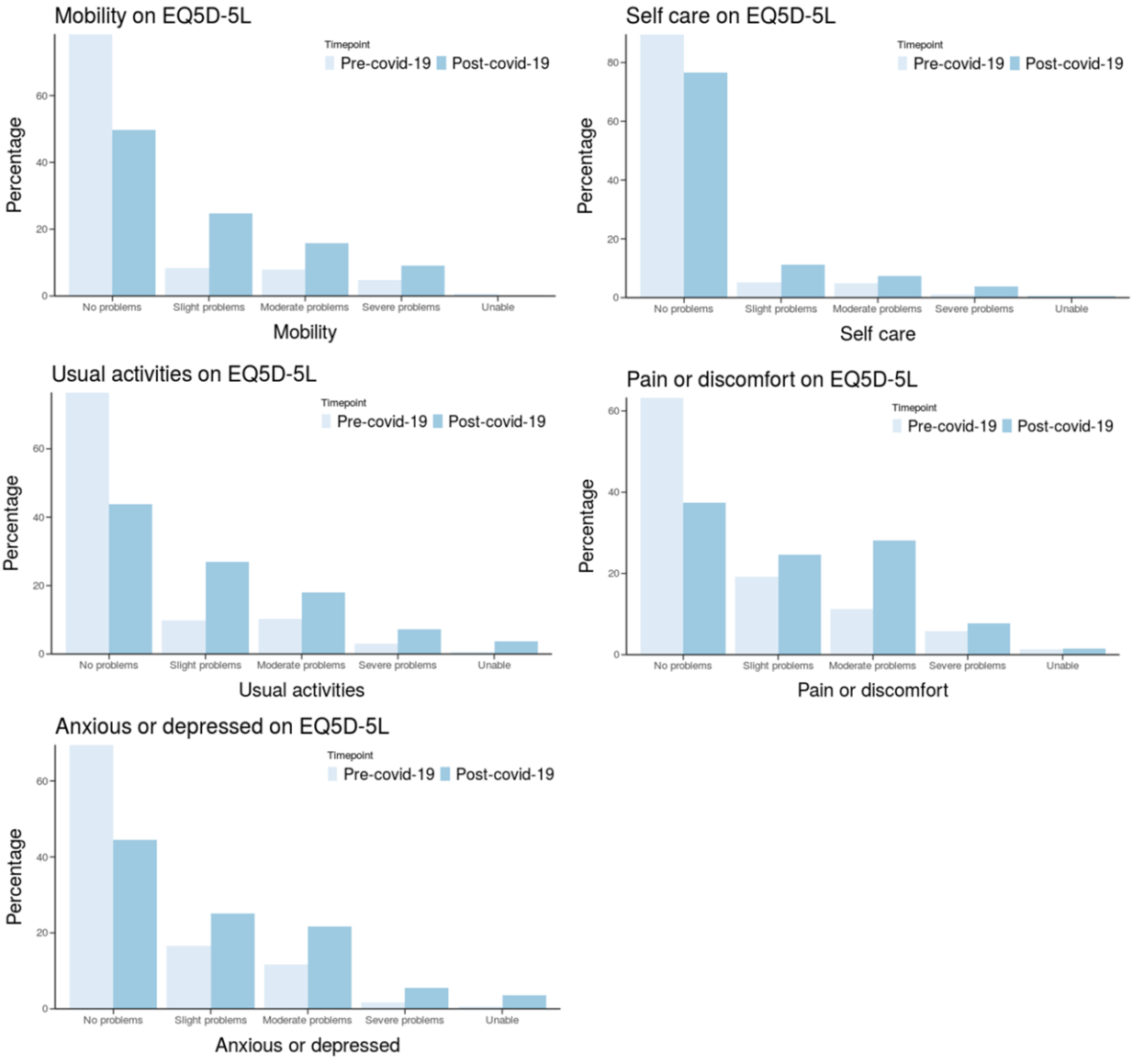
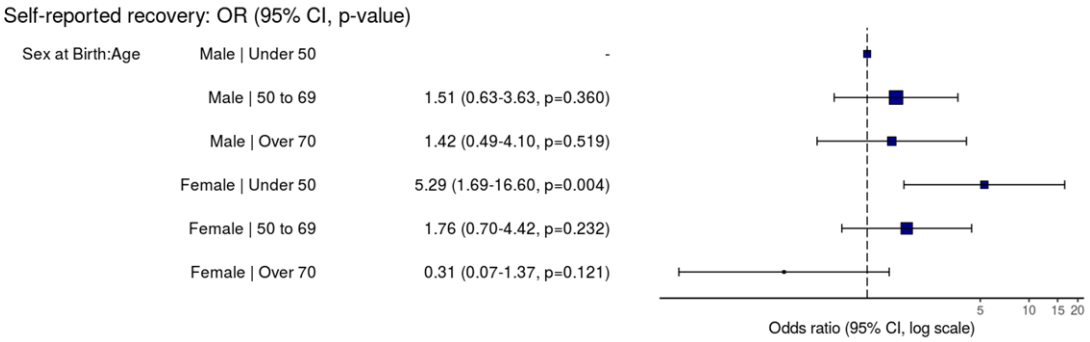
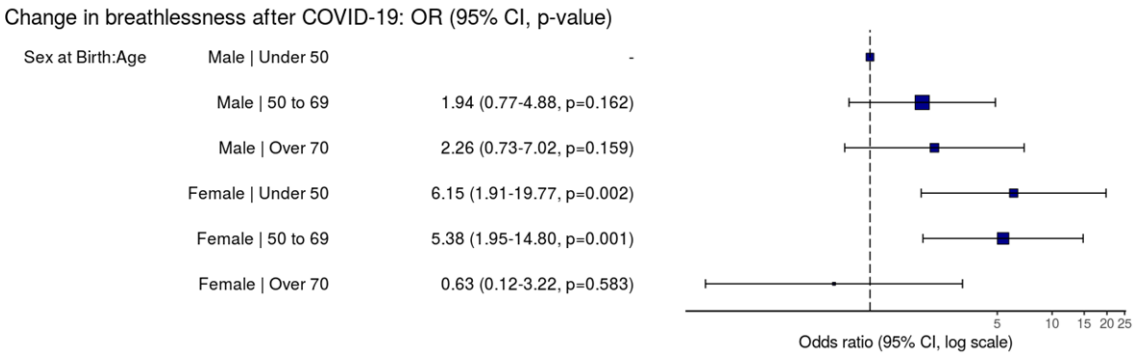
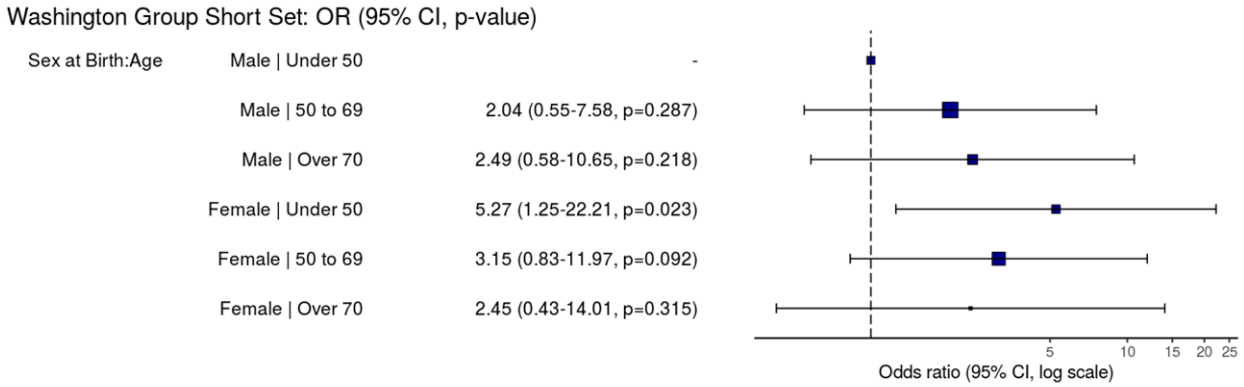


**Table 3:** Multivariable models for long-term outcomes of overall recovery, MRC dyspnoea scale, fatigue and Washington Short Set functioning score after hospitalisation with COVID-19. Outcomes were worse in females versus males, particularly in younger females. Females under 50 were more than five times most likely to report incomplete recovery, more than five times most likely to report a new disability, have increased fatigue, and six times more likely to report worse breathlessness compared to males under 50 years old.



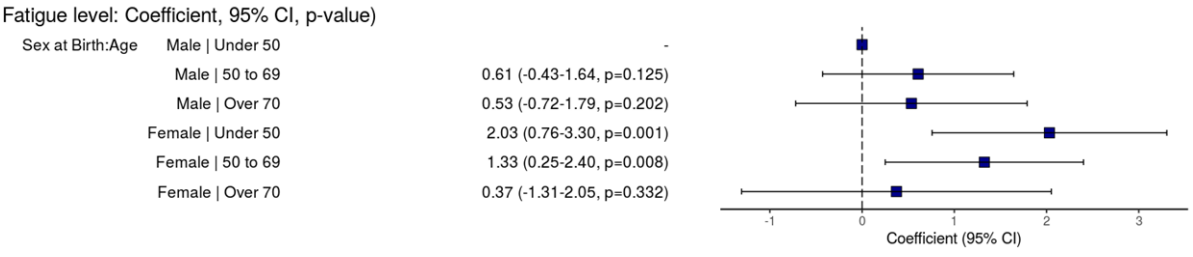



**Figure 5:** Outcomes by age and comorbidity status. No differences were seen in Long COVID symptoms reported in terms or pre-COVID comorbidity status.