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## Preliminary data: Long COVID and the ISARIC WHO Clinical Characterisation Protocol in the UK (CCP-UK)

Unpublished preliminary data from a UK multicentre, prospective cohort study of previously hospitalised COVID-19 patients with a minimum of 3 months of follow-up post symptom onset. At the point of reporting, 40% (361/905) of those approached had responded, with 325 (36%) providing eligible data.

Results: Primary outcome: 54% (95% CI 49-60%) reported not feeling fully recovered from COVID-19 (median follow-up 7months). Secondary outcomes: ongoing symptoms (93%), increased breathlessness (56%), new disability (24%) and drop in QOL of about a tenth (0.1 out of 1.0).

### How this supports the previous Advisory Group summary

- **Confirms that long COVID is a significant issue**

93% (n=303/325, 95% CI) in the ISARIC cohort had ongoing symptoms after 3 months (median follow-up 7mth, IQR 6-9mths). This is significant, and in fact higher than the 76% (1265/1655) of Huang et al's larger Wuhan hospitalised cohort (median follow-up 6mth, IQR 5.8-6.5)(1). It is worth nothing that although 93% had ongoing symptoms, a still sizeable, but much lower figure of 54% (95% CI 49-60%) said they were not feeling fully recovered from COVID-19.

All of these figures are much higher than data from populations where non-hospitalised patients were also included eg ONS (around 10%12wk)(2) and the Covid Symptoms Study app (2.3% for 12wk or more)(3).

- **Confirms that fatigue is the most commonly identified symptom**

77% experienced fatigue (95% CI 72-82%), with 49% describing a fatigue level of 5 or higher (0 is no fatigue, 10 is the worst fatigue). This supports the previous summary, which reported that all key primary studies concluded fatigue was the most common ongoing symptom(1–4).

- **Confirms that a diverse array of symptoms can be experienced**

29 specific symptoms were enquired about, plus an 'other symptoms' category. Following fatigue, the next two most common symptoms in the ISARIC paper were shortness of breath (54%) and problems sleeping (roughly 50%). This supports the previous advisory group summary, which found flagged shortness of breath and sleep difficulties as common.

### How it differs from the previous evidence in the Advisory Group summary

- **Higher prevalence of symptoms**

The most comparable cohort for ISARIC in the previous summary is Huang et al's study of hospitalised patients in Wuhan(1). Whilst eleven specific symptoms were each individually reported by 25% or more of the ISARIC cohort, only two symptoms in Huang's questionnaire were found in 25% or more of the cohort, with most surveyed symptoms being much less common. These two symptoms were also much more common in ISARIC than in Huang's Wuhan cohort:

- Fatigue: Wuhan: 63% (fatigue or muscle weakness) vs ISARIC: 77% (fatigue)

- Sleep difficulties: Wuhan: 26% vs ISARIC: ~50%

These higher percentages could potentially reflect a degree of responder bias. Whereas the Wuhan cohort represents 70% (1733/2469) of all COVID confirmed patients discharged from Jin Yin-tan Hospital, the ISARIC data, represents 15% of the total relevant ISARIC study population (325/2682) and 36% of those approached (325/905). The authors recognise the potential for responder bias leading to high rates of ongoing symptoms and poor outcomes. However, they also report that when contacted, almost all initial non-responders were happy to participate. These are only preliminary data and it will be important to see how the figures unfold as the research progresses.

## **What this study adds to the previous Advisory Group summary**

Two points briefly touched on in the previous summary rise in prominence based on the ISARIC data.

- **Provides more evidence to suggest being female and disease severity as risk factors**

The most consistent risk factor across studies was being female. In ISARIC, compared to males under 50, females under 50 were:

- Over five times more likely to report incomplete recovery (aOR 5.29, 1.69-16.60)
- Over 5 times more likely to report greater disability (aOR 5.27, 1.25-22.21)
- Over 6 times more likely to report increased breathlessness (aOR 6.15, 1.91-19.77)

The estimates of effect are imprecise, but the overall finding that being female was associated with worse outcomes is supported by the Wuhan study (eg fatigue or muscle weakness (aOR 1·33, 1·05–1·67))(1). The Covid Symptoms Study App also reported that women were significantly more likely to have symptoms beyond 56days (no OR provided)(3).

With regards severity, ISARIC found participants who had required invasive ventilation were 4x more likely to report an incomplete recovery compared to those who had not required supplementary oxygen (aOR 3.61, 1.58-8.25). Similarly, the Wuhan study found the risk of ongoing symptoms was higher in those requiring HFNC/NIV/IMV, than those who did not require oxygen (OR 2·42, 95% CI 1·15–5·08). However, further data are needed as the Wuhan study found that ongoing symptoms were actually *less* common in the intermediate group who received supplemental oxygen but not HFNC/NIV/IMV (OR 0.70, 0.52-0.96), when compared with those who received no oxygen.

- **Provides more evidence that more than one syndrome exists**

The ISARIC paper suggested three symptom clusters:

A) Fatigue, breathlessness 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 A)
C) Loss of smell, taste, difficulty passing urine, weight loss and disturbance of appetite

This clustering concept is supported by the Covid Symptoms Study app data. However more work is needed to delineate the clusters, as the nature of the symptom constellations varied between the studies. The app data proposed two alternative clusters: (A) fatigue, headache and upper respiratory B) those with additional multi-system complaints eg fever, GI symptoms.

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## Ongoing evidence needs

Long COVID has potentially massive long-term implications for the country, from employment to healthcare provision. As a UK based prospective cohort study, ISARIC is a key data source and it will be invaluable to have the full results in time. However, no single study will provide all the answers, and a co-ordinating consortium needs to be formed. Ongoing data needs are many, but include:

- A clear case definition
- Identification of whether there are multiple syndromes, and what their symptom profiles are
- Robust risk factor data
- Treatment options
- Prospective UK cohort data from beyond the hospital
- Physiological measurements of long COVID are needed, not solely self-reported data

**Bibliography**

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