# Response to "Was the rate of Long Covid as high as 45%-a scary report with flaw"

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We would like to thank Dr Yao and colleagues for their interest in our systematic review and for taking the time to express their concerns, which were listed in four key questions.

In relation to point one, the concern related to the calculation of a different and lower prevalence estimate than reported in our systematic review based on recalculation of data presented in the supplementary material (Table S3). As stated in the methods section of our paper, symptom prevalence data from individual studies were pooled and meta-analysed using a random effects model. When calculating an average this method weights the pooled estimate by study size, and therefore different prevalence estimates will be attained by simply totalling numbers across studies to calculate a simple percentage (as per the data provided by Yao and colleagues). When calculating a pooled effect size, random effects meta-analysis assigns larger studies with more precise effect size estimates greater weight than smaller studies with less reliable estimates.1 The formula for random effects models can be found in full in a 2010 paper by Borenstein et al.<sup>2</sup> When we report in our study "With an average study follow-up time of 126 days, the pooled prevalence of COVID-19 survivors experiencing at least one unresolved symptom, regardless of hospitalisation status, was 45%"? We have used random effects meta-analyses to calculate the pooled prevalence of experiencing at least one resolved symptom across all studies, and then we have calculated the mean follow-up time across all studies.

In addition to this, the data used as the basis of Yao and colleagues' re-analysis – 'at least one or more symptom' was not presented in Table S3. When creating this descriptive table, we provided symptom specific data in the table. Following their comment, we have amended Table S3 to remove this column to avoid any confusion. To provide further clarity we have presented the data extracted and used in our review (i.e. study values) for the three exemplar studies identified by Yao and colleagues (Table 1). Two of the three papers (O'Keefe et al. and Tessitore et al.) did not report 'at least one symptom at follow up' the data presented by Yao and colleagues in their Table 1 relates to individual symptoms by the corresponding studies and therefore would not have been extracted. We would like to thank the authors for highlighting that Venturelli et al., did report data for 'At Least 1 Symptom at Follow-up' (i.e., "51.4% still complained of symptoms). This symptom was not extracted in our original analysis. Adding this data point did not change the associated pooled estimates, but the CI changed marginally; 52.6 (95% CI: 43.5, 61.6) to 52.6 (95% CI: 43.6 to 61.5). We would like to take this opportunity to highlight that a 10% random sample of the extracted data was cross-checked by a second reviewer.

We would also like to note that although Dr Yao and colleagues suggest our prevalence estimates differ from a credible recent publication, the publication that they reference is not a meta-analysis. When compared to other meta-analyses, our prevalence estimates are similar.<sup>3,4</sup> Specifically, the study by Chen and colleagues found a pooled prevalence of 49% at 120 days which very similar to our finding of 45% at a mean follow-up 126 days.<sup>3</sup> Additionally, as the authors acknowledge in their paper, a key limitation of the study referred to is that coded symptom data in primary records is likely to underrepresent the true symptom burden experienced by individuals with persistent symptoms. Moreover, the authors explicitly state that "the symptom data we used for the study thus cannot be used to make inferences about the absolute prevalence of these symptoms", as has been done by Yao and colleagues.

In point two, Yao and colleagues discussed the impact of follow-up duration on prevalence estimates. As stated above, a meta-analysis was used which weights study estimates depending on sample size. A simple percentage based on total numbers of patients across studies will result in a different estimate. In addition, the prevalence estimates presented in our paper relate to the average follow-up time of all studies. We did not

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Author	Total	With symptom	Males (%)	Age	Hospital status	Time to FU	FU time point	Continent	Symptom
O'Keefe (A) <sup>a</sup>	304	16	31.8	45.7	Non-hospitalised	≥30	Symptom Onset	North America	Cough
O'Keefe (A)	304	7	31.8	45.7	Non-hospitalised	≥30	Symptom Onset	North America	Headache/Migraine
O'Keefe (A)	304	10	31.8	45.7	Non-hospitalised	≥30	Symptom Onset	North America	Exertional Breathlessness
O'Keefe (A)	304	4	31.8	45.7	Non-hospitalised	≥30	Symptom Onset	North America	Sore Throat
O'Keefe (A)	304	7	31.8	45.7	Non-hospitalised	≥30	Symptom Onset	North America	Chest Pain/Tightness
O'Keefe (A)	304	4	31.8	45.7	Non-hospitalised	≥30	Symptom Onset	North America	Abdominal Pain
O'Keefe (A)	304	7	31.8	45.7	Non-hospitalised	≥30	Symptom Onset	North America	Joint Pain
O'Keefe (A)	304	10	31.8	45.7	Non-hospitalised	≥30	Symptom Onset	North America	Nasal Symptoms
Tessitore	165	10	62	58	Hospitalised	365	Discharge	Europe	Muscles Weakness/Pain
Tessitore	165	1	62	58	Hospitalised	365	Discharge	Europe	Fever
Tessitore	165	4	62	58	Hospitalised	365	Discharge	Europe	Gastro-intestinal Problems
Tessitore	165	45	62	58	Hospitalised	365	Discharge	Europe	Fatigue
Tessitore	165	1	62	58	Hospitalised	365	Discharge	Europe	Sputum
Tessitore	165	8	62	58	Hospitalised	365	Discharge	Europe	Headache/Migraine
Tessitore	165	23	62	58	Hospitalised	365	Discharge	Europe	Breathlessness
Tessitore	165	1	62	58	Hospitalised	365	Discharge	Europe	Nasal Symptoms
Tessitore	165	5	62	58	Hospitalised	365	Discharge	Europe	Cough
Venturelli	767	395	67.1	63	Hospitalised	81	Discharge	Europe	At Least 1 Symptom at Follow-up <sup>b</sup>
Venturelli	767	39	67.1	63	Hospitalised	81	Discharge	Europe	Arrhythmia
Venturelli	767	23	67.1	63	Hospitalised	81	Discharge	Europe	Cough
Venturelli	767	24	67.1	63	Hospitalised	81	Discharge	Europe	Chest Pain/Tightness
Venturelli	767	16	67.1	63	Hospitalised	81	Discharge	Europe	Impaired Kidney Function
Venturelli	767	4	67.1	63	Hospitalised	81	Discharge	Europe	Headache/Migraine
Venturelli	767	33	67.1	63	Hospitalised	81	Discharge	Europe	Depression
Venturelli	767	222	67.1	63	Hospitalised	81	Discharge	Europe	PTSD
Venturelli	767	4	67.1	63	Hospitalised	81	Discharge	Europe	Fever
Venturelli	767	2	67.1	63	Hospitalised	81	Discharge	Europe	Cognitive Dysfunction
Venturelli	767	121	67.1	63	Hospitalised	81	Discharge	Europe	Impaired Usual Activity
Venturelli	767	228	67.1	63	Hospitalised	81	Discharge	Europe	Breathlessness
Venturelli	767	30	67.1	63	Hospitalised	81	Discharge	Europe	Palpitations
Venturelli	767	186	67.1	63	Hospitalised	81	Discharge	Europe	Fatigue
Venturelli	767	23	67.1	63	Hospitalised	81	Discharge	Europe	Confusion/Brain Fog
Venturelli	767	82	67.1	63	Hospitalised	81	Discharge	Europe	Anxiety

Note: Since all data related to the prevalence of people, when the calculated n value was not a whole number it was rounded up to the next highest whole number. <sup>a</sup>Converted from % to absolute values. <sup>b</sup>Not extracted in the original data extraction but added now. Converted from %.

Table 1: Data extraction for three exemplar studies.

limit the analysis to studies with follow-up longer than 111 days. As all studies covered a period of time, limiting the analysis to studies >4 months (or 111 days) would not provide a prevalence estimate for an average of 4 months. Rather it would provide an approximate prevalence estimate across studies with a follow-up of at least 4 months, resulting in an average follow-up that is necessarily longer than 4 months. It is reasonable to expect that symptom prevalence will reduce over time since acute infection, as some patients' symptoms will resolve (either spontaneously or with intervention from healthcare services). Thus, by only including studies with follow-up longer than 4 months, it is not surprising that Yao and colleagues produced a prevalence estimate that is lower than our own. However, we do agree that the variability in prevalence estimates is high and previously acknowledged this within the manuscript on Page 5 "Between studies heterogeneity was high for the majority of meta-analyses, ranging from 2 to 99.9%." We also provide confidence intervals for the pooled prevalence of any symptom across all groups 44.8% (95% CI 38.6%–51.2%).

In point three, Yao and colleagues discuss the accuracy of data extraction. We do appreciate it is difficult to identify the correct corresponding publication based on the names of the author alone. Therefore, we have now included full references in our corrigendum (and in Table 2 below) for all studies included in the analysis. With regards to the three papers that were crosschecked by the authors for accuracy,<sup>5</sup> as discussed above, the data included in Table S3 was not specific to at least one symptom at follow up, rather it was a range of varying

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Table 2. List of included study.	

symptom codes. We appreciate that this may cause confusion and as mentioned previously, we have removed the column for clarity.

Points four and five related to the impact of different strains of SARS-CoV-2 and vaccination on prevalence estimates. Whilst we agree different strains of SARS-CoV-2 may have had differing effects on prevalence rates very few (if any) included studies included information on strains and therefore this was beyond the scope of our review. We agree that vaccination status is an important issue and previously acknowledge this within the manuscript "As of July 2022, over 12 billion vaccine doses have been administered globally; however, assessing the impact of vaccination status on Long Covid prevalence was beyond the scope of the current review. Future reviews should seek to investigate the prevalence of Long Covid across vaccination status and different variants of SARS-CoV-2."

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### Contributors

LLO, AR, CG and KK conceptualised the manuscript. All authors critically revised the manuscript for intellectual content. All authors had final responsibility for the decision to submit for publication.

#### Declaration of interests

KK is Chair of the Ethnicity Subgroup of the UK Scientific Advisory Group for Emergencies (SAGE) and Member of SAGE and also Chair of the National Long Covid working group which reports to the Chief Medical Officer.

#### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101950.

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