RESPONSE TO GOLDEACRE ET AL. (OpenSAFELY Collaborative):

We write with respect to the recently prepublished work by The OpenSAFELY Collaborative (PI and corresponding author Goldacre), "OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients." [1] We have enormous respect for the technical efforts of the authors in creating and establishing this data resource, but serious concerns about both the way these results are presented and how they are likely to be interpreted. Our specific concerns revolve around whether the work is intended by the authors to estimate causal effects, or not – and how, regardless of their intent, it seems likely to us that their work will be interpreted as causal.

We write this in the spirit of open peer-review, and invite responses from the authors, as well as revision of their work if appropriate.

First, it is notable that the authors describe what they are investigating as *risk factors*; as others have pointed out [2], the phrase "risk factor" can mean a number of things, including "possible cause under investigation" and "predictor, without attention to cause," as well as possibly "covariate with a statistically significant association with the outcome." Here, it is unclear what the authors mean by this phrase.

On the causal side of the ledger, the word "confounding" occurs in this work ("Hazard ratios for other risk factors, adjusted for ethnicity, were also obtained from this model and are presented in the sensitivity analyses to allow assessment of the potential for confounding by ethnicity in the primary model.") Confounding is an intrinsically causal idea; as confounding does not exist in purely predictive or descriptive models, this usage indicates that the authors consider this work as an exercise in causal effect estimation, as least to some extent.

Causal language likewise emerges in the Discussion, where the authors state that "the effect of increased deprivation appeared to be smaller in the earlier period", "[i]n current smokers there was a slight protective effect," and "disentangling the effects of [hypertension and age] is difficult." Effects are, definitionally, not mere associations and thus implicitly causal in character and implication. Similarly though perhaps to a lesser degree, discussion of whether observed associations are "attributable" to other factors in the text and on Twitter [3] implies that the authors believe at least to some extent that those other factors are causally related to hospital death in COVID-19 patients.

As has been discussed elsewhere, the mutually adjusted hazard ratios from a single model (as in Table 2 of this paper) are not generally interpretable as causal effects [4]. Rather, to estimate the causal effect of some factor (exposure or treatment) on an outcome requires the researcher to *consider the confounding structure* (most accessibly, in the form of a DAG [5]) *for the exposure-outcome pair being explored* and *use an appropriate approach to account for a minimally sufficient set of confounders* (which in practice often involves fitting a regression model). To estimate a *series* of causal effects, one must establish the confounding structure for each exposure-outcome pair separately, and pursue a separate data analysis for each pair. To interpret the authors' Table 2 as if all the mutually adjusted HRs in it have causal interpretations [6] is to commit a classic Table 2 Fallacy [4].

Despite the use of the word confounding in this report, the authors do not appear to have considered the causal structure of confounders between any of their exposures and the outcome,

much less to all of their possible exposure-outcome pairs independently. As such interpretations such as “We found the higher risk among BME people is NOT attributable to other factors” or “Smoking is protective” (not by the authors, but found on Twitter [6]) are unsupported by these results. Indeed, it is entirely possible that such apparent protection or (lack of) attribution is in fact due to uncontrolled confounding, overadjustment, conditioning on a collider, measurement error, missing data, or other issues related to causal identification [7].

Again, though, the authors are not explicit in making causal interpretations of this work, discussing these numbers primarily again as “risk factors.” If by risk factors the authors meant this work to be solely or primarily predictive or descriptive in nature then the interpretation and utility of individual HRs (in Table 2) is problematic in a different way. It remains unclear how best to interpret an association adjusted for various factors, or what utility an individual HR from a large model has in predictive terms, when that HR is considered alone. The analyses also fall short of developing a usable clinical prediction model to determine the risk of hospital death in COVID-19 confirmed patients. While this possibility is underlined by the c-statistic calculated by the authors, such a model would require a more thorough evaluation of predictive performance as well as a clearly defined target population on which the model should be used [8].

We are thus very concerned that the public [3] and the press will interpret the findings from this study in causal terms. If the authors agree with these critiques, we urge them to improve this work before publication by (i) being more clear in articulating the goal of the work, whether predictive or causal, and (ii) making the methods more transparently in service of that specific goal. In particular, the authors’ Table 2 and Figure 3 both invite readers to commit “Table 2 Fallacies” and we therefore strongly advise them to improve - or remove – those presentations of their findings from any future iterations of this work.

Thank you.

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