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### **Sample size, timing, and other confounding factors: towards a fair assessment of stay-at-home orders.**

We read with interest the timely contribution from Bendavid et al. [1]. We would like to highlight specific concerns about the methodology and writing of the article that we detail below.

*The small sample size (n=10) and the sample's composition have not been justified and introduce a lack of representativeness.* Brauner et al. [2] (n=41), along with others, present contradictory results with bigger samples that are not discussed in the manuscript. The authors do not present adequate reasoning for such a small pool of data and exclude numerous countries that provide similarly appropriate data (e.g., Switzerland by canton). Given the small sample size, the study is also at a very high risk of uncontrolled confounding. For instance, Sweden and Iran are directly compared in terms of the outcomes of their interventions without considering the plethora of cultural, social, and political differences between them that might impact their case count. This is worrisome, because there are examples of other, more culturally similar, nations which could have been included in either group, such as Denmark for which case counts by administrative region are publicly available online. We therefore argue that the potential for unmeasured confounding could have been reduced with a larger and more careful composition of the sample and should be directly acknowledged.

*The arbitrary composition of the 'control group'.* The control group is composed of only two countries with "less-restrictive" measures: Sweden and South Korea. However, while they did not close businesses or use stay-at-home orders, both countries have implemented several other measures that could be considered as "more-restrictive." Sweden has implemented distant learning for high school and university students [3]. South Korea had one of the longest at-home learning periods in the world [4]. School closures are often described as the most restrictive/problematic interventions (the phrase "last to close and first to open" is commonly used), but both of these "less" restrictive "controls" closed (at least partially) schools for in-person teaching, one for much longer than many of the "more" restrictive "cases". South Korea also, as the references cited by the authors show, has

extraordinarily restrictive digital legislation. Whether or not this is a “more restrictive” intervention is subjective, but we posit that such detailed government oversight for contact tracing would not be welcome in many “more-restrictive countries”.

Using these countries as a strict “control” is therefore misleading. This dichotomization of responses into either “less” or “more” restrictive through an arbitrary and subjective designation from the authors is not substantiated in the paper.

*The analysis does not take into account the timing or implementations of the interventions.* Previous work has highlighted the importance of timing, order, periodicity and duration of interventions (see e.g., [2]). Brauner et al. [2] concluded that: “a stay-at-home order had a small effect when a country had already closed educational institutions, closed nonessential businesses, and banned gatherings.” There is also the question of implementation of interventions. In some cases, it is possible that behaviour changes occurred after interventions were announced, in others it may be the case that enforcement was needed after the initial implementation such that the effect was instead delayed. These are merely two examples of situations that could have occurred, demonstrating the numerous sources of time-related bias.

While we do not expect the model used by the authors to account for all possible confounding factors, the importance and impact of these factors on the authors’ results should be thoroughly discussed in particular in light of contradicting results in the literature.

*The analysis does not correct for the relationship between interventions and case counts.* While this is noted by the authors in the discussion, it is a fundamental problem that undermines the entire purpose of the study. It has previously been demonstrated that case counts and intervention adoption are closely interrelated: governments implement restrictions while cases are rising, not when they have plateaued or already started to fall. The current analysis is therefore geared towards finding a null effect, as in the vast majority of situations the case counts will continue to rise for some time after interventions are announced.

*The language used to describe the results is incorrectly causal.* As openly acknowledged in the discussion, case data from the studied countries is likely inadequate to generate causal conclusions. Nonetheless, the paper sometimes relies on statements implying a causal impact (or lack thereof) from interventions. For example, the phrase “effects of” is used in the paper to refer to the case numbers after interventions are implemented. It is merely the association between case counts after the intervention came into effect that is measured, not the effect. Testing capacity was limited during the first wave in all considered countries, and as the authors acknowledge this inherent flaw suggests that no causal conclusions can be drawn from this study. It is entirely possible that the lack of benefits highlighted when comparing countries to Sweden, for example, is due to the fact that Sweden had incredibly restricted testing during the assessed time.

Considering, on the one hand, how scientific papers shape opinions and public health measures and, on the other hand, all the limitations highlighted by the authors and in the present letter, we argue that the “results” and abstract of the paper should be changed to better reflect the study’s inherent limitations. We look forward to a response from the authors and hope that our letter fosters interesting scientific exchanges.

Conflict of interests:

The authors declare no conflict of interests.

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