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LETTERS TO THE EDITOR

Putting Meta-Analysis Findings in Proper Perspective: Comment on "The Effects of Nonpharmaceutical Interventions on COVID-19 Cases, Hospitalizations, and Mortality: A Systematic Literature Review and Meta-Analysis"

Peters and Farhadloo[1] concluded that their meta-analysis "found that the nonpharmaceutical interventions (NPIs) studied were associated with reduced rates of cases, hospitalizations, and deaths" during the first coronavirus disease 2019 (COVID-19) wave. We believe that this conclusion was not warranted for 3 reasons.

First, there were methodologic weaknesses. No information was provided on the exact numbers obtained from most of the included studies, on the method used for meta-analyses (including the software used), nor on forest plots and measures of heterogeneity. Most of the systematic review results of high-quality studies were based on only 1 study, that is, not based on meta-analysis (Table 3[1] in their study, as summarized in our Table 1). That many results were based on 1 study and not meta-analysis was a limitation not mentioned by the authors.

Table 1. Effect of Nonpharmaceutical Interventions in High-Quality Studies in the Peters and Farhadloo Meta-Analysis Compared With That in the Meta-Analysis by Herby et al.

Intervention (number of studies included in the meta-analysis)	Per-capita effect over time period in high-quality studies (i.e., that controlled for covariates and cointerventions): *n* (95% CI)[1]			Herby et al. effect in difference-in-difference studies[2]
	2 weeks	3 weeks	4 weeks	
Cases avoided per capita				
SI Δ20 (2 studies, 1 in each that was statistically significant)	−1/15.2M (−1/12.8M, −1/18.5M)	−1/27.8M (−1/22.7M, −1/35.7M)	−1/22.9K (−7.8K, +23.9K)	—
Mask wearing (1 study)	−1/43.1K (−1/26.0K, −1/125K)	−1/44.2K (−1/25.6K, −1/163.9K)	−1/36.9K (−26.6K, −1/60.2K)	—
SIPO (1 study)	−1/222.2K (−1/57.6K, +1/119.8K)	—	—	—
Mortality avoided per capita				
SI Δ20 (5 studies, 2−4 in each)	−1/40K (−1/13.5K, +1/42.0K)	−1/20.7K (−1/8.3K, +1/43.1K)	−1/21.7K (−1/8.7K, +43.9K)	Comparing average SI in EU and U.S. (76 and 74) with solely recommendations (SI=44), corresponds to approximately 6K and 4K avoided deaths in EU and the U.S., compared with approximately 72K and 38K flu deaths each year, respectively
Mask wearing (4 studies, 3 in each)	−1/862.1K (−1/367.6K, +1/2.6M)	−1/2.3M (−1/1,1M, +1/33.3M)	−1/531.9K (−1/225.7K, +1/1.5M)	—
SIPO (4 studies, 2−3 in each)	−1/4.0M (−1/387.6K, +1/480.8K)	−1/529.1K (−1/177.3K, +1/537.6K)	−1/4.2M (−1/117.0K, +1/123.9K)	Corresponds to approximately 4K and 3K avoided deaths in EU and U.S., compared with approximately 72K and 38K flu deaths each year, respectively

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Table 1. Effect of Nonpharmaceutical Interventions in High-Quality Studies in the Peters and Farhadloo Meta-Analysis Compared With That in the Meta-Analysis by Herby et al. (*continued*)

Intervention (number of studies included in the meta-analysis)	Per-capita effect over time period in high-quality studies (i.e., that controlled for covariates and cointerventions): *n* (95% CI)[1]			Herby et al. effect in difference-in-difference studies[2]
	2 weeks	3 weeks	4 weeks	
Limited gatherings (1 study)	+1/588.2K (−1/724.6K, +1/209.2K)	—	+1/256.4K (+1/4.3M, +1/132.1K)	—
Business closures (2 studies, 1−2 in each)	−1/2.3M (−1/250.0K, +1/320.5K)	−1/354.6K (−1/99.2K, +224.7K)	+1/3.1M (−1/178.6K, +160.3K)	—
Bar/restaurant closures (1 study)	−1/294.1K (−1/136.6K, +1.9M)	—	−1/92.6K (−1/66.2K, −1/154.1K)	—

Intervention (number of studies included in the meta-analysis)	Growth rate effects (%) (the percentage change in daily new deaths) in high-quality studies[1]			Herby et al. precision weighted percentage change in COVID-19 deaths (range in sensitivity analysis)[a] (number of studies)[2]
SI Δ20 (1 study)	—	—	−0.8% (−1.4, −0.2)	**−3.2% (−3.0 to −4.4) (8 studies) for average of ΔSI=30−32.**
Mask wearing (1 study)	—	−1.9% (−3.38, −0.42)	—	**−18.7% (−19.9 to −12.5) (3 studies)**
SIPO (4 studies, 2 in each)	−3.28 (−7.75, 1.19)	**−1.66 (−2.82, −0.5)**	**−1.95 (−3.81, −0.9)**	**−2.0% (−4.1 to −1.4) (10 studies)**
Limited gatherings (1 study)	−6.41% (−8.7%, 4.12%)	—	—	**+5.9% (+4.9 to +8.9) (4 studies)**
Business closures (2 studies, 1 in each)	−5.32% (−7.42, −3.22)	−0.57% (−2.42, 1.28)	—	**−7.5% (−9.3 to −6.6) (5 studies)**
Bar/restaurant closures (1 study)	—	−0.17% (−1.88, 1.54)	—	Included in business closures
School closures (2 studies, 1 in each)	−3.98% (−6.94, −1.02)	−8.29% (−9.57, −6.57)	—	**−5.9% (−6.2 to −2.5) (4 studies)**
Traveling restrictions (1 study)	−4.32% (−11.57, 2.93)	—	—	**−3.4% (−4.7 to −0.4) (4 studies)**

Note: Boldface indicates statistically significant effects in meta-analysis (which must include >1 study).
For high-quality studies, we restricted to studies in Table 3 because these were "used as the primary source of findings of this review," and we agree with the authors that we can be more "confident in the results obtained from high quality papers because they controlled for confounders and the effects of other NPIs."[1] Of note, for cumulative effects (the cumulative percentage change in deaths), only limited gatherings was effective at 2 weeks (−49%; 95% CI= −78.7, −19.4) on the basis of 1 study; school closures were not effective at −25.7% (95% CI= −55.6, 5.25) on the basis of 1 study. For cumulative effects on hospitalizations, mask wearing was effective at 2, 3, and 4 weeks on the basis of 1 study, and for growth rate effects on hospitalizations, SIPOs were effective at 3 and 4 weeks on the basis of 1 study.
[a]Sensitivity analysis in Herby et al. described as "four sensitivity analyses, where we replace the outlier (min/max) estimate/weight with the nearest estimate/weight and recalculate the PWA (precision weighted average)."
CI, confidence interval; EU, Europe; K, thousand; M, million; max, maximum; min, minimum; NPI, nonpharmaceutical intervention; SI, Stringency Index; SIPO, stay-in-place order.

Second are reasons of perspective. Examining per-capita effect, for Stringency Index increase of 20, there was no effect on cases or mortality at 4 weeks, and at earlier times, there was a very small absolute effect on cases (at 2 weeks, −1 case per 15.2 million population; at 3 weeks, −1 case per 27.8 million population) but not on mortality. For mask wearing, on the basis of 1 study, there was a small decrease in cases (up to −1 case per 36.9 thousand population at 4 weeks); however, on the basis of 4 studies, no effect on mortality was reported. Examining growth rate (the percentage change in daily new deaths), meta-analyses (which must include >1 study) found statistically significant effect only for stay-in-place orders, with −1.66% and −1.95% at 3 and 4 weeks, respectively. Most of these effects found in the study by Peters and Farhadloo[1] were smaller than the findings of Herby et al.[2] (detailed in our Table 1).

Third are reasons for study exclusion. As explained by Herby and colleagues,[2] they included only difference-in-difference study design because this design "is used in observational settings where exchangeability between the treatment and control groups cannot be assumed. . . The approach removes biases in post-intervention period comparisons between the treatment and control groups that could be the result of permanent differences between those groups (e.g., caused by coincidences early in the pandemic), as well as biases from comparisons over time in the treatment group that could be the result of trends due to other causes of the outcome (e.g., changes in behavior or seasonality).”[2] Among the many confounders to adjust for, seasonality may be particularly important.[3,4] Thirteen difference-in-difference studies included in Herby et al.[2] were excluded by Peters and Farhadloo[1] owing to being considered of fair quality (*n*=8), being missed (*n*=3), or for reasons not usually considered adequate to exclude a study (*n*=2) (Appendix Table, available online).

We agree with the Herby and colleagues[2] conclusion that the results of meta-analysis “support the conclusion that lockdowns in the spring of 2020 had a negligible effect on COVID-19 mortality.” Given the immense collateral damage from lockdowns and nonpharmaceutical interventions during the pandemic, we are confident that a cost−benefit analysis will not be favorable. Labeling Sweden’s approach as “a more *laissez-faire* herd immunity approach”[1] may be telling because in the end, Sweden had one of the lowest excess mortality rates of all countries.[5,6]

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SUPPLEMENTARY MATERIALS

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REFERENCES

1. Peters JA, Farhadloo M. The effects of non-pharmaceutical interventions on COVID-19 cases, hospitalizations, and mortality: a systematic literature review and meta-analysis. *AJMP Focus.* 2023;2(4):100125. https://doi.org/10.1016/j.focus.2023.100125.
2. Herby J, Jonung L, Hanke SH. *Did lockdowns work? The verdict on Covid restrictions*. London, United Kingdom: Institute of Economic Affairs Perspectives; 2023. https://iea.org.uk/wp-content/uploads/2023/06/Perspectives-_1_Did-lockdowns-work__June_web.pdf.
3. Quinn GA, Connolly M, Fenton NE, et al. Influence of seasonality and public-health interventions on the COVID-19 pandemic in northern Europe. *J Clin Med.* 2024;13(2):334. https://doi.org/10.3390/jcm13020334.
4. Wiemken TL, Khan F, Puzniak L, et al. Seasonal trends in COVID-19 cases, hospitalizations, and mortality in the United States and Europe. *Sci Rep.* 2023;13(1):3886. https://doi.org/10.1038/s41598-023-31057-1.
5. Excess mortality − statistics. Eurostat Statistics Explained. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Excess_mortality_-_statistics#:~:text=The%20excess%20mortality%20indicator%20takes,by%20the%20COVID%2D19%20pandemic. Accessed January 6, 2024.
6. Björkman A, Gisslén M, Gullberg M, Ludvigsson J. The Swedish COVID-19 approach: a scientific dialogue on mitigation policies. *Front Public Health.* 2023;11:1206732. https://doi.org/10.3389/fpubh.2023.1206732.