ACKNOWLEDGMENTS

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OPEN | # The Authors Respond

To the Editor:

We thank Dr. Reyes Sanchez[1] for their thoughtful comments on our article.

We agree that causal inference assessment should not rely only on statistical methods but also on the evidence

of biologic plausibility resulting from the conduct of experimental studies and on the strength of evidence supporting a particular scientific conclusion.[2] Assessing the extent to which an air pollution study provides evidence of a cause-and-effect relationship, in particular, requires the use of an appropriate study design,[2] and we cannot emphasize more that accurate assessments of assumptions, methods, and study designs should serve as the foundation for any causal findings. We thank the commenter for giving us the opportunity to re-emphasize this key message of our article.

We also thank the commenter for pointing out the prominent challenges associated with the selection of confounders in epidemiologic studies. We are aware of the limitations of data-driven methods, such as the change-in-estimate criterion, for selecting confounders,[3] and we agree that expert knowledge along with the use of causal graphs represent valid alternatives to choose confounders in multivariable models. In our study, we selected potential confounders of the associations between air pollution and overall mortality based on results from preliminary studies,[4–6] and we used the change-in-estimate criterion, which to date represents one of the most popular data-driven method for selecting confounders in epidemiologic studies,[7] to supplement such a priori knowledge and to help identify the final set of confounders to include in the analysis. With respect to this point, and to strengthen the validity of our results, we have added some additional analyses on our GitHub page (https://github.com/andreabellavia/causalpm), including the full set of possible relevant confounders in the multivariate generalized propensity score model. Results did not show any deviation from those presented in our article.

Finally, we appreciate discussing the specific issues related to the use of propensity score in this context in terms of confounding balance. We agree that assessing balance between exposure(s) and confounders is key when performing causal analysis using propensity scores.[8] This potential issue has also been addressed and the reader can find additional analyses on our GitHub page where we tested the balancing property of the weights using the set of balance diagnostics proposed by Williams and Crespi for inverse probability weighting (IPW), and available in the mvGPS package.[9]

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Re. Assessing Uncontrolled Confounding in Associations of Being Overweight With All-Cause Mortality

To the Editor:

Mathur and VanderWeele[1] suggest that uncontrolled confounding might explain the differences between the hazard ratio estimates for overweight (BMI, 25–29.9) and all-cause mortality, relative to normal weight, from 2 meta-analyses, 1 by Flegal et al[2] and 1 by the Global BMI Mortality Collaboration (GBMC).[3]

The Flegal et al[4] article was a systematic review of published studies, all of which we identified through formal search procedures. The GBMC was a meta-analysis of individual participant data that does not appear to have been

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derived from a formal search procedure.[4] The GBMC chose exclusively data from studies already known to the GBMC senior authors whose results were largely already known, used sample size criteria not relevant to the topic, and applied those and other criteria inconsistently. This suggests likely reviewer selection bias.[5]

The GBMC describe one search procedure but did not use all the data from that search, and stated that most of their data came from other sources. The GBMC's peculiar sample size constraints alone excluded 40% of the data used in the Flegal et al[4] meta-analysis, as well as many other otherwise eligible data sets. Although the GBMC stated that they identified only 2 eligible studies that were unable to contribute data, they did not use other studies from the search that met their requirements; several are easily available.

The GBMC limited their final analyses to the subgroup of nonsmokers without preexisting illnesses and with the first 5 years of follow-up excluded, arguing that analyses without such restrictions lack validity. Their subgroup contained only 37% of participants from their original data set and only 25% of the deaths. The GBMC results changed direction after their restrictions were applied (Table), but the effect of such restrictions is not consistent across studies, weakening their argument. Numerous other studies have found that such exclusions made little or no difference to the results (e.g., see a study[6] of 12 million participants, larger than the original GBMC sample, and many of the studies cited in the Flegal et al[4] article).

These major differences in data selection procedures and analytic methods between the two meta-analyses are likely to be the most important contributors to the differences in results.

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The Authors Respond

To the Editor:

We thank Flegal[1] for her response to our recent article on potential uncontrolled confounding in estimated effects of being overweight (but not obese) on all-cause mortality.[2] Our article did not aim to "explain the differences between … [estimates from] Flegal and Ioannidis[3] and … the Global BMI Mortality Collaboration (GBMC),"[4] nor

Table. Hazard Ratios for All-Cause Mortality of Overweight BMI Relative to Normal Weight BMI from Two Meta-Analyses

Study	Hazard Ratios	Adjustment Methods
Flegal et al	0.94 (0.91–0.96)	Adjusted for age, sex and any other covariates within original studies
	0.94 (0.90–0.97)	Exclude studies that were not adjusted for smoking or that adjusted for variables possibly in the causal pathway
GBMC	0.96 (0.95–0.97)	Adjusted for age and sex
	0.96 (0.95–0.97)	Additionally exclude pre-existing chronic disease
	0.99 (0.98–1.01)	Additionally adjust for smoking
	1.03 (1.01–1.04)	Additionally exclude the first 5 years of follow-up
	1.08 (1.07–1.08)	Exclude preexisting disease, smokers
	1.11 (1.10–1.11)	Exclude pre-existing disease, smokers, and the first 5 years of follow-up

GBMC, Global BMI Mortality Collaboration.