CHEST

Editor's Note: Authors are invited to respond to Correspondence that cites their previously published work. Those responses appear after the related letter. In cases where there is no response, the author of the original article declined to respond or did not reply to our invitation.

Beyond Parametric Assumptions

Reevaluation of Environmental Interactions in Prenatal Exposure Studies

To the Editor:

In a recent issue of *CHEST*, Hu et al[1] offer important insights into the developmental origins of respiratory health through a prospective birth cohort study. Investigating joint effects, they reported relative excess risk caused by interaction point estimates that range from −6.22 to 5.65 for particulate matter ≤ 2.5 μm in aerodynamic diameter ($PM_{2.5}$) temperature pairs and from −5.72 to 1.21 for nitrogen dioxide (NO_2) temperature pairs and concluded that no significant additive interactions exist because all 95% CIs included zero (e-Tables 3-6). Although their identification of critical windows for individual exposures is compelling, this interpretation warrants closer methodologic consideration.

They use a distributed lag non-linear model (DLNM), which is well-suited for capturing delayed and non-linear effects of individual environmental exposures. However, interaction assessment was conducted separately with the use of dichotomized exposure categories and additive interaction metrics, rather than modeling continuous pollutant-temperature interactions within the DLNM framework.[2,3] This approach, although standard, may have limited sensitivity to localized or threshold-dependent synergistic effects, particularly under extreme thermal conditions or high pollutant levels for short gestational windows. Wide CIs further suggest potential power limitations, so that the absence of statistical significance should not be equated with biological absence. The sample size ($n = 429$) and the information loss because of dichotomizing exposures at the median may have contributed to these limited power issues.

Furthermore, DLNM's reliance on smooth basis functions for lag and exposure-response relationships inadvertently can obscure abrupt deviations from prespecified curves. Although this enhances stability and interpretability, it may mask acute, nonlinear phenomena relevant to combined exposures. In dynamic environmental systems, in which pollutants and temperature interact through complex physicochemical and physiologic pathways, additive structures and spline-based smoothing risk oversimplifying high-order dependencies and concealing meaningful synergistic regions.

To address these limitations in interaction assessment, future research should integrate nonparametric, data-driven approaches, such as unsupervised feature selection (eg, Feature Agglomeration) and rank-based correlation methods (eg, Spearman rho, Kendall's tau), which better reflect the inherent complexity of environmental systems.[4,5] Model-agnostic interpretability tools, which include partial dependence and accumulated local effects, can further illuminate synergistic regions while preserving transparency and reproducibility. The study of Hu et al[1] provides a vital foundation for the identification of prenatal windows of susceptibility. Framing the interaction results as "no statistically significant additive interaction under the current specification" and advancing toward more flexible modeling strategies will improve detection of complex joint effects. This evolution is critical for accurate health risk assessment under growing climate variability and for the protection of vulnerable populations worldwide.

Yoshiki Takahashi
Souichi Oka, PhD
Kanagawa, Japan
Yoshiyasu Takefuji, PhD
Tokyo, Japan

AFFILIATIONS: From the Science Park Corporation (Y. Takahashi and S. O.), and the Faculty of Data Science (Y. Takefuji), Musashino University.

CORRESPONDENCE TO: Yoshiki Takahashi; email: ytakahashi@sciencepark.co.jp

DOI: https://doi.org/10.1016/j.chest.2025.12.029

Financial/Nonfinancial Disclosures

None declared.

Acknowledgments

Other contributions: We extend our sincere gratitude to Koichiro Shoji of Science Park Corporation for invaluable support and helpful input throughout the preparation of this manuscript.

References

1. Hu CY, Alcala CS, Lamadrid-Figueroa H, et al. Identifying critical windows and joint effects of prenatal air pollution and temperature exposure and lung function in schoolchildren: findings from a prospective birth cohort study. *Chest*. 2026;169(1):179-193.
2. Mork D, Wilson A. Treed distributed lag nonlinear models. *Biostatistics*. 2022;23(3):754-771.
3. Parikh MN, Manning ER, Niu L, et al. Increasing temporal sensitivity of omics association studies with epigenome-wide distributed lag models. *Am J Epidemiol*. 2025;194(5):1418-1425.
4. Zhang J, Wu X, Hoi SCH, Zhu J. Feature agglomeration networks for single stage face detection. *Neurocomputing*. 2020;380:180-189.
5. Okoye K, Hosseini S. Correlation tests in R. Pearson Cor, Kendall's Tau, and Spearman's Rho. In: Okoye K, Hosseini S, eds. *R Programming: Statistical Data Analysis in Research*. Springer Nature; 2024:247-277.

Response

To the Editor:

We appreciate the thoughtful commentary on our study that examined critical windows of prenatal air pollution and temperature exposure and their joint effects on lung function in school children.[1] The author raises important methodologic considerations regarding the challenges of detecting interactions in environmental epidemiologic evidence, particularly with distributed lag nonlinear models (DLNMs).

We agree that dichotomizing exposures at the median, although facilitating interpretation of additive interactions via relative excess risk because of interaction, may reduce statistical power. This approach was chosen to align with common practices in the assessment of departures from additivity,[2] especially given our sample size (N = 429). However, the wide CIs indeed highlight potential limitations in the detection of subtle synergistic effects; we concur that absence of statistical significance does not preclude biological relevance. As suggested, future analyses could incorporate continuous exposures within DLNM frameworks to model air pollutant-temperature interactions more flexibly, potentially capturing threshold-dependent or localized synergies.[3]

Regarding parametric assumptions in DLNMs, our use of smooth basis functions (eg, natural splines) intended to balance model stability with the need to account for temporal autocorrelation in weekly exposures. Although this may smooth over abrupt non-linearities, it effectively identified critical windows for individual exposures, which is consistent with prior applications.[4] Nonparametric alternatives, such as feature agglomeration or rank-based correlations (eg, Spearman rho), could complement DLNMs by revealing complex dependencies without predefined structures.[5] We view these approaches as promising for larger cohorts or multi-omics data, by enhancing interpretability through tools like partial dependence plots.

Our findings underscore early prenatal vulnerabilities to air pollution, with no evidence of additive interactions under the current specification. We welcome this dialogue, because it advances methodologic rigor in assessment of joint environmental risks amid climate change.

Cheng-Yang Hu, PhD
Maria José Rosa, DrPH
New York, NY

AFFILIATIONS: From the Department of Environmental Medicine (C.-Y. H. and M. J. R.), Icahn School of Medicine at Mount Sinai; and the Department of Epidemiology and Biostatistics (C.-Y. H.), School of Public Health, Anhui Medical University, Hefei, China.
CORRESPONDENCE TO: Maria José Rosa, DrPH; email: maria.rosa@mssm.edu

DOI: https://doi.org/10.1016/j.chest.2025.12.030

Funding/Support

The parent studies included in the manuscript relating to this letter were funded by National Institute of Environmental Health Sciences grants R00ES027496 and R01ES033245 (Rosa MJ, PI). The PROGRESS project received funding through grants R01ES014930, R01ES013744, U24ES028522, P30ES023515 (Wright RO, PI), and R01ES021357 (Baccarelli A and Wright RO, MPI).

Financial/Nonfinancial Disclosures

See earlier cited article for author conflicts of interest.

Acknowledgments

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.