the detrimental modifications observed with omega-6 consumption appeared to be more robust across outcomes than the beneficial effects of omega-3 consumption. This might have implications for the type of intervention that could be successful. In addition, although the authors discuss two modifiable risk factors, diet and indoor particulate matter, they did not present any information regarding the potential sources of particulate matter, which would be necessary to design an intervention in this community.

In short, the study by Brigham and colleagues potentially provides novel insight into the intersection of environmental and dietary factors affecting asthma exacerbation that may be relevant to the as-of-yet unmitigated disproportionate burden of asthma morbidity in low-income urban communities in the United States. The important next steps include validation in other populations and demonstrating the efficacy of dietary modifications and/or particulate matter reduction to reduce the burden of asthma in these communities. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Maria José Rosa, Dr.P.H.
Department of Environmental Medicine and Public Health
Mt. Sinai School of Medicine
New York, New York

Matthew S. Perzanowski, Ph.D.
Department of Environmental Health Sciences
Columbia University
New York, New York

References

1. Orellano P, Quaranta N, Reynoso J, Balbi B, Vasquez J. Effect of outdoor air pollution on asthma exacerbations in children and adults: systematic review and multilevel meta-analysis. *PLoS One* 2017;12:e0174050.
2. McCreanor J, Cullinan P, Nieuwenhuijsen MJ, Stewart-Evans J, Malliarou E, Jarup L, *et al*. Respiratory effects of exposure to diesel traffic in persons with asthma. *N Engl J Med* 2007;357:2348–2358.
3. Yan B, Bopp RF, Abrajano TA, Chaky D, Chillrud SN. Source apportionment of polycyclic aromatic hydrocarbons (PAHs) into Central Park Lake, New York City, over a century of deposition. *Environ Toxicol Chem* 2014;33:985–992.
4. Brigham EP, Woo H, McCormack M, Rice J, Koehler J, Vulcain T, *et al*. Omega-3 and omega-6 intake modifies asthma severity and response to indoor air pollution in children. *Am J Respir Crit Care Med* 2019; 199:1478–1486.
5. Blasbalg TL, Hibbeln JR, Ramsden CE, Majchrzak SF, Rawlings RR. Changes in consumption of omega-3 and omega-6 fatty acids in the United States during the 20th century. *Am J Clin Nutr* 2011;93: 950–962.
6. Wang DD, Leung CW, Li Y, Ding EL, Chiuve SE, Hu FB, *et al*. Trends in dietary quality among adults in the United States, 1999 through 2010. *JAMA Intern Med* 2014;174:1587–1595.
7. Olsen SF, Østerdal ML, Salvig JD, Mortensen LM, Rytter D, Secher NJ, *et al*. Fish oil intake compared with olive oil intake in late pregnancy and asthma in the offspring: 16 y of registry-based follow-up from a randomized controlled trial. *Am J Clin Nutr* 2008; 88:167–175.
8. Bisgaard H, Stokholm J, Chawes BL, Vissing NH, Bjarnadóttir E, Schoos AM, *et al*. Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring. *N Engl J Med* 2016;375: 2530–2539.
9. Best KP, Sullivan T, Palmer D, Gold M, Kennedy DJ, Martin J, *et al*. Prenatal fish oil supplementation and allergy: 6-year follow-up of a randomized controlled trial. *Pediatrics* 2016;137:e20154443.
10. Best KP, Gold M, Kennedy D, Martin J, Makrides M. Omega-3 long-chain PUFA intake during pregnancy and allergic disease outcomes in the offspring: a systematic review and meta-analysis of observational studies and randomized controlled trials. *Am J Clin Nutr* 2016;103:128–143.
11. Miyake Y, Sasaki S, Tanaka K, Ohfuji S, Hirota Y. Maternal fat consumption during pregnancy and risk of wheeze and eczema in Japanese infants aged 16-24 months: the Osaka Maternal and Child Health Study. *Thorax* 2009;64:815–821.
12. Nwaru BI, Erkkola M, Lumia M, Kronberg-Kippilä C, Ahonen S, Kaila M, *et al*. Maternal intake of fatty acids during pregnancy and allergies in the offspring. *Br J Nutr* 2012;108:720–732.
13. Notenboom ML, Mommers M, Jansen EHJM, Penders J, Thijs C. Maternal fatty acid status in pregnancy and childhood atopic manifestations: KOALA Birth Cohort Study. *Clin Exp Allergy* 2011;41:407–416.
14. Lee-Sarwar K, Kelly RS, Lasky-Su J, Kachroo P, Zeiger RS, O'Connor GT, *et al*. Dietary and plasma polyunsaturated fatty acids are inversely associated with asthma and atopy in early childhood. *J Allergy Clin Immunol Pract* 2018;7:529–538, e8.
15. Whyand T, Hurst JR, Beckles M, Caplin ME. Pollution and respiratory disease: can diet or supplements help? A review. *Respir Res* 2018; 19:79.

Copyright © 2019 by the American Thoracic Society

Small but Mighty: Prenatal Ultrafine Particle Exposure Linked to Childhood Asthma Incidence

Research demonstrating a role for air pollution in the prenatal programming of asthma has largely considered exposures to criteria pollutants (pollutants routinely monitored to assess air quality), especially particulate matter with an aerodynamic diameter of 2.5–10 μm or fine particles ≤2.5 μm ($PM_{2.5}$) and ambient nitrates (NO_3) (1). Although air quality regulations currently do not address ultrafine particles (UFPs) ≤0.1 μm, submicron-sized particles may exert greater toxic effects compared with larger molecules because of their larger surface area/mass ratio, chemical composition, deeper lung penetration, and enhanced oxidative capacity and ability to translocate to the systemic circulation (2–4). A recent workshop identified the lack of studies differentiating the effects associated with UFP exposures from effects related to other particle size fractions and gaseous

This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (http://creativecommons.org/licenses/by-nc-nd/4.0/). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

Originally Published in Press as DOI: 10.1164/rccm.201903-0506ED on March 13, 2019

copollutants as a significant gap in the evidence needed to move toward regulation of UFPs (5).

In this issue of the *Journal*, Lavigne and colleagues (pp. 1487–1495) address this gap directly, as well as contributing further innovations to this field (6). The retrospective cohort combined data from a province-wide birth registry in Toronto, Ontario, Canada, with health administrative data identifying incident asthma cases during a 9-year period. They assigned pollution exposure levels during each week of pregnancy and each month of childhood at the centroid of the postal code for individuals (approximating a city block). A particular strength of the analysis is that the researchers were able to adjust for other components of ambient pollutants from similar sources, including $PM_{2.5}$ and nitrogen dioxide (NO_2). This is the first large-scale epidemiologic study to demonstrate independent risk associated with *in utero* UFP exposure, as well as corroborating previous findings linking prenatal $PM_{2.5}$ and nitrate exposures to asthma incidence (7, 8).

Because fetal development occurs through sequential biologic events, toxins that disrupt these processes can have a variable effect, depending on the nature of the pollutant, as well as timing and/or exposure level. The authors use distributed lag functions, an effective way to model critical windows of exposure in a more objective fashion (8). The focus on critical windows makes the temporal aspects of the exposure modeling central to their findings. The authors base their exposure modeling of the spatiotemporal variability in UFP exposures in the study region from 2006 to 2015 on 3 weeks of exposure data collected as part of a mobile monitoring campaign conducted over the course of 2 weeks in summer and 1 week in winter. They build a land use regression model that includes characteristics of a given location (distances to major roads, bus routes, etc.) to capture variation over time. An immediate question is how well this model trained on data from a highly targeted monitoring campaign conducted on the order of weeks extrapolates to the scale of nearly a decade. They report that the land use regression model explained 67% of the variation in mean UFPs. To better address the extrapolation of these model predictions to longer-term timescales, they use a temporal adjustment that computes ratios of weekly averages of $PM_{2.5}$ and NO_2 concentrations at each ground monitor location to the long-term estimates derived from their exposure models, spatially smooth these scaling factors on a weekly basis, and then apply these predicted scaling surfaces to their long-term estimates to obtain exposure measures at each residential location. To our knowledge, this scaling approach has not been reported previously. It would be interesting to know the out-of-sample predictive performance of this overall procedure, calculated on the basis of data from monitors held out of the modeling exercise. Moreover, it would be interesting to calculate these prediction statistics at timescales of interest: weekly, monthly, and trimesters. This would allow one to assess how well the proposed exposure assessment captures variation in UFP monitoring data at the scales of greatest interest in the health effects study.

The group implemented an approach that incorporates the estimation of critical windows of exposure via a distributed lag function in a multilevel Cox proportional hazards framework that accounts for clustering among children by family and by postal code. Another advantage of the distributed lag model is

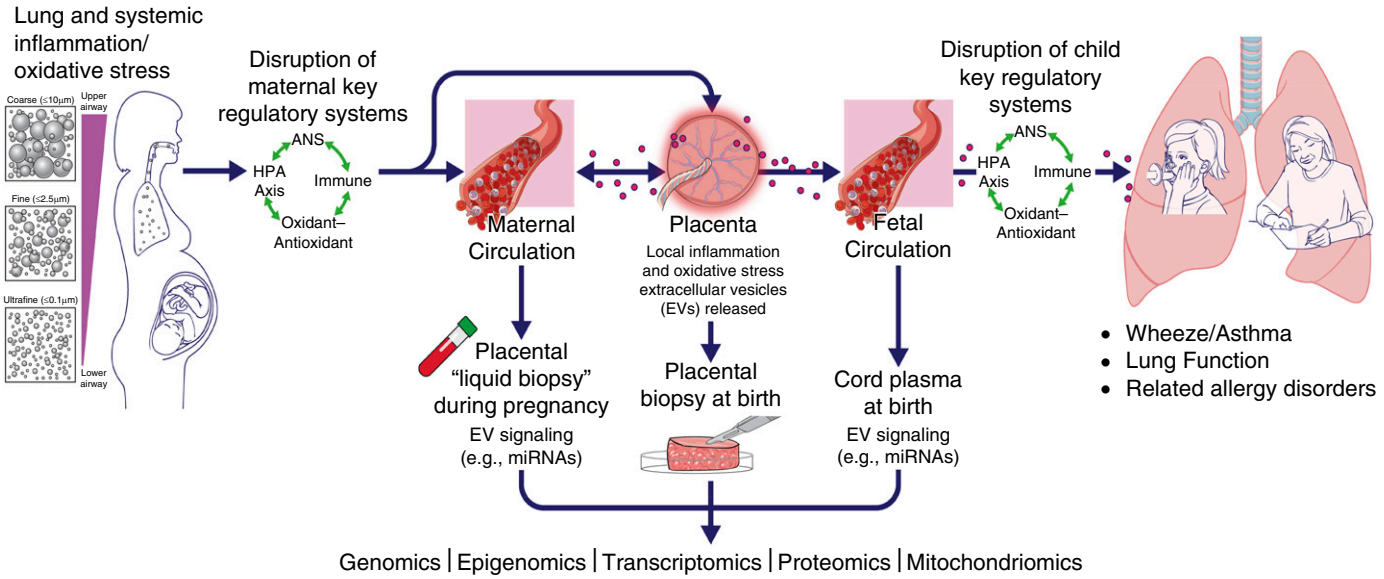


Figure 1. Placenta as a target of prooxidant pollutant effects: potential enhanced toxicity of ultrafine particles. Ultrafine particles penetrate deeper into the lungs, have greater ability to induce oxidative stress, and more readily enter the systemic circulation in mothers, all features that may enhance toxicity in this schema. Programming effects may result from pollutant-induced shifts in a number of molecular, cellular, and physiological states and their interacting systems in mothers and children. Specific key regulatory systems susceptible to programming may influence vulnerability to respiratory diseases including both central and peripheral components of neuroendocrine pathways and autonomic nervous system functioning, which, in turn, influence the immune system. ANS = autonomic nervous system; HPA = hypothalamic–pituitary–adrenal; miRNAs = microRNAs. Illustrated by J. Gregory (Mount Sinai Health System).

that in settings in which there is a strong seasonal trend in a pollutant, such as that observed for $PM_{2.5}$, the distributed lag function avoids the temporal confounding that arises in some simpler modeling approaches, such as separate models that use a single trimester-averaged exposure (9). Because trimesters are approximately the same length as a season, seasonal trends can result in unique correlation patterns among trimester-specific exposures. Notably, in Lavigne and colleagues (6), the trimester-specific UFP exposures do not exhibit such patterns, with all pairwise correlations around 0.6. It may be that for UFPs, the spatial variability is much higher than the temporal variability, so that seasonal variability is a smaller fraction of overall variability in UFP concentrations as compared with that for $PM_{2.5}$, highlighting that considerations for modeling critical windows of exposure can differ according to the specific pollutant under study.

When considering effect modification, it was unclear whether they included interactions in the distributed lag models or simply in the aggregated pregnancy averaged models. In distributed lag models, the lagged function can vary in magnitude, in the location of the critical window, or both. Thus, it can be useful to parameterize the distributed lag function as an overall effect times a weight function that characterizes the critical window of exposure, and to allow either or both of these features to vary by subject characteristic (10).

Notably, local and systemic induced oxidative stress is central to toxic effects of PM, with UFPs having even greater oxidative potential than other particle fractions. As optimal placental oxidant balance is critical for normal fetal development (11), signaling mechanisms operating at the level of the placenta are receiving increased attention with regard to the prenatal programming effects of air pollutants (12). Epigenetic mechanisms are already being examined in this context (13, 14). Recent studies focus on placental extracellular vesicles (EVs) as targets of environmental toxins. Placenta-derived EVs (i.e., 0.05- to 1-μm membrane-bound vesicles released into maternal and fetal circulations over gestation) prime maternal and fetal tissues via signaling molecules encapsulated in EVs (mRNA, microRNAs, DNA, lipids, and protein mediators), which interact with adjacent or distal cells to reprogram their phenotype and regulate their function. Although we cannot sample placenta during pregnancy to measure biological changes induced by particle exposures, we can readily assess the placental EVs and their content in a defined critical window via a maternal blood draw, conceptualized as a placental liquid biopsy (15). Figure 1 depicts a future strategy that would allow researchers to more comprehensively interrogate environmentally responsive mechanisms operating in the placenta, using a system biology approach that may provide markers of early risk and further elucidate underlying mechanisms. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Rosalind J. Wright, M.D., M.P.H.
Kravis Children's Hospital
New York, New York
and
Institute for Exposomic Research
Icahn School of Medicine at Mount Sinai
New York, New York

Brent A. Coull, Ph.D.
Department of Biostatistics
Harvard T. H. Chan School of Public Health
Boston, Massachusetts

ORCID ID: 0000-0002-4262-2807 (R.J.W.).

References

1. Wright RJ, Brunst KJ. Programming of respiratory health in childhood: influence of outdoor air pollution. *Curr Opin Pediatr* 2013;25: 232–239.
2. Ohlwein S, Kappeler R, Kutlar Joss M, Künzli N, Hoffmann B. Health effects of ultrafine particles: a systematic literature review update of epidemiological evidence. *Int J Public Health* [online ahead of print] 21 Feb 2019; DOI: 10.1007/s00038-019-01202-7.
3. Li N, Georas S, Alexis N, Fritz P, Xia T, Williams MA, *et al*. A work group report on ultrafine particles (American Academy of Allergy, Asthma & Immunology): why ambient ultrafine and engineered nanoparticles should receive special attention for possible adverse health outcomes in human subjects. *J Allergy Clin Immunol* 2016; 138:386–396.
4. Yang Y, Ruan Z, Wang X, Yang Y, Mason TG, Lin H, *et al*. Short-term and long-term exposures to fine particulate matter constituents and health: a systematic review and meta-analysis. *Environ Pollut* 2019; 247:874–882.
5. Baldauf RW, Devlin RB, Gehr P, Giannelli R, Hassett-Sipple B, Jung H, *et al*. Ultrafine particle metrics and research considerations: review of the 2015 UFP workshop. *Int J Environ Res Public Health* 2016;13: E1054.
6. Lavigne E, Donelle J, Hatzopoulou M, Van Ryswyk K, van Donkelaar A, Martin RV, *et al*. Spatiotemporal variations in ambient ultrafine particles and the incidence of childhood asthma. *Am J Respir Crit Care Med* 2019;199:1487–1495.
7. Hsu HH, Chiu YH, Coull BA, Kloog I, Schwartz J, Lee A, *et al*. Prenatal particulate air pollution and asthma onset in urban children: identifying sensitive windows and sex differences. *Am J Respir Crit Care Med* 2015;192:1052–1059.
8. Bose S, Chiu YM, Hsu HL, Di Q, Rosa MJ, Lee A, *et al*. Prenatal nitrate exposure and childhood asthma: influence of maternal prenatal stress and fetal sex. *Am J Respir Crit Care Med* 2017;196: 1396–1403.
9. Wilson A, Chiu YM, Hsu HL, Wright RO, Wright RJ, Coull BA. Potential for bias when estimating critical windows for air pollution in children's health. *Am J Epidemiol* 2017;186:1281–1289.
10. Wilson A, Chiu YM, Hsu HL, Wright RO, Wright RJ, Coull BA. Bayesian distributed lag interaction models to identify perinatal windows of vulnerability in children's health. *Biostatistics* 2017;18:537–552.
11. Herrera EA, Krause B, Ebensperger G, Reyes RV, Casanello P, Parra-Cordero M, *et al*. The placental pursuit for an adequate oxidant balance between the mother and the fetus. *Front Pharmacol* 2014;5:149.
12. Luyten LJ, Saenen ND, Janssen BG, Vrijens K, Plusquin M, Roels HA, *et al*. Air pollution and the fetal origin of disease: a systematic review of the molecular signatures of air pollution exposure in human placenta. *Environ Res* 2018;166:310–323.
13. Janssen BG, Byun HM, Gyselaers W, Lefebvre W, Baccarelli AA, Nawrot TS. Placental mitochondrial methylation and exposure to airborne particulate matter in the early life environment: an ENVIRONAGE birth cohort study. *Epigenetics* 2015;10: 536–544.
14. Abraham E, Rousseaux S, Agier L, Giorgis-Allemand L, Tost J, Galineau J, *et al*.; EDEN Mother-Child Cohort Study Group. Pregnancy exposure to atmospheric pollution and meteorological conditions and placental DNA methylation. *Environ Int* 2018;118: 334–347.
15. Salomon C, Nuzhat Z, Dixon CL, Menon R. Placental exosomes during gestation: liquid biopsies carrying signals for the regulation of human parturition. *Curr Pharm Des* 2018;24:974–982.

Copyright © 2019 by the American Thoracic Society