

12. McGarry ME, McColley SA. Cystic fibrosis patients of minority race and ethnicity less likely eligible for CFTR modulators based on CFTR genotype. *Pediatr Pulmonol* 2021;56:1496–1503.
13. McGarry ME, Gibb ER, Oates GR, Schechter MS. Left behind: the potential impact of CFTR modulators on racial and ethnic disparities in cystic fibrosis. *Paediatr Respir Rev* 2022;42:35–42.
14. McColley SA, Martiniano SL, Ren CL, Sontag MK, Rychlik K, Balmert L, et al. Disparities in first evaluation of infants with cystic fibrosis since implementation of newborn screening. *J Cyst Fibros* [online ahead of print] 21 Jul 2022; DOI: 10.1016/j.jcf.2022.07.010.
15. McGarry ME, McColley SA. Minorities are underrepresented in clinical trials of pharmaceutical agents for cystic fibrosis. *Ann Am Thorac Soc* 2016;13:1721–1725.

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⊗ Particle Constituents and Oxidative Potential: Insights into Differential Fine Particulate Matter Toxicity

The association between fine particulate matter (PM_{2.5}) and morbidity and mortality differ widely between and within regions (1–4). It is expected that differences in PM_{2.5} composition play a role in the observed differences by modifying the effects of PM_{2.5} on various biological processes (5). However, there is currently scarce evidence about which components have stronger impacts or health effects (6). It has been hypothesized that constituents that contribute to the oxidative potential (the ability of particles to generate reactive oxygen species by consumption of antioxidants and/or generation of oxidants) are likely to drive many of the observed health effects. Metals from various sources, including traffic and industrial emissions, are likely an important part of the oxidative potential (7). Furthermore, it's also important to consider the influence of sulfate in the toxicity of particles because sulfate found in PM_{2.5} facilitates the dissolution of metals, and solubility is an important determinant of particle oxidative potential (8).

The effects of air pollutants on children's respiratory health have been a focus of research for several decades (3, 4, 9). However, spatial and temporal misalignment in studies of environmental exposures (i.e., measuring a toxicant at a point in space as a weekly aggregate with daily changes in health) can bias the estimation of health risk (10, 11). The development of methods for processing large numbers of samples with low limits of detection, as well as methods to measure the oxidative potential of particles, allows the identification of PM constituents with a time resolution more suitable for the assessment of temporal changes in health effects. However, because of the cost of these analyses, data availability is still low compared with measurements for regulated pollutants (e.g., criteria air pollutants in the United States).

In this issue of the *Journal*, the paper by Korsiak and colleagues (pp. 1370–1378) provides evidence that associations between short-term PM_{2.5} mass concentration and respiratory hospitalizations in children are modified by metal and sulfur content in PM_{2.5}, as well as particle oxidative potential (12).

Two major strengths of this study are the large sample size of 10,500 children across 34 Canadian cities and the time-stratified case-crossover design that allowed time-invariant factors (e.g., sex) or factors that do not vary within subjects over short periods of time (e.g., age and body mass index) to be controlled for by design (13, 14). The time-stratified case-crossover design provides an alternative to conventional time series regression for analyzing associations between time series of environmental exposures (air pollution and weather) and counts of health outcomes (15). Another important strength of the Korsiak study is the 2-week per month periodicity of PM_{2.5} samples that were collected in each of the cities and analyzed for metals, sulfur, and oxidative potential (Figure 1), accounting for some of the temporal variability in PM_{2.5} composition over time.

A novel contribution to the field is the integrative analysis of the different PM constituents and oxidative potential using 2-week integrated filters each month. These analyses are likely too time-consuming and costly to be repeated in similarly large studies but can be useful tools to assess the toxicity of PM_{2.5} in more polluted regions of the world. It is likely that 2-week integrated samples were needed to capture enough mass for the Korsiak study, given the low ambient concentrations found in Canada, but it is unclear how rapidly metal concentrations or oxidative potential may change within this 2-week period or if the 2-week period is representative of the full month. More frequent filter samples can likely be collected in regions with higher PM_{2.5} concentrations, providing higher time resolution that reflects the daily variability in PM_{2.5} sources depending on air mass transport and can be better matched to acute health effect measurements.

Interestingly, there was a relatively low correlation between the three metrics of oxidative potential measured (particularly the DDT assay (dithiothreitol) with the other two assays). Although these different metrics can have a variable response to the different PM constituents, it is still not clear which metric should be prioritized for health research. It is possible that the low PM_{2.5} concentrations observed in Canada make it difficult to distinguish between these different metrics, and this remains an important area for future research.

Limitations of the study include that the study was conducted in Canada, where PM_{2.5} concentrations are low compared with much of the world. Ozone concentrations are also quite low year-round in Canada (75th percentile below 30 ppb in both seasons). Thus, there was a small range of exposures considered in the study, and metal

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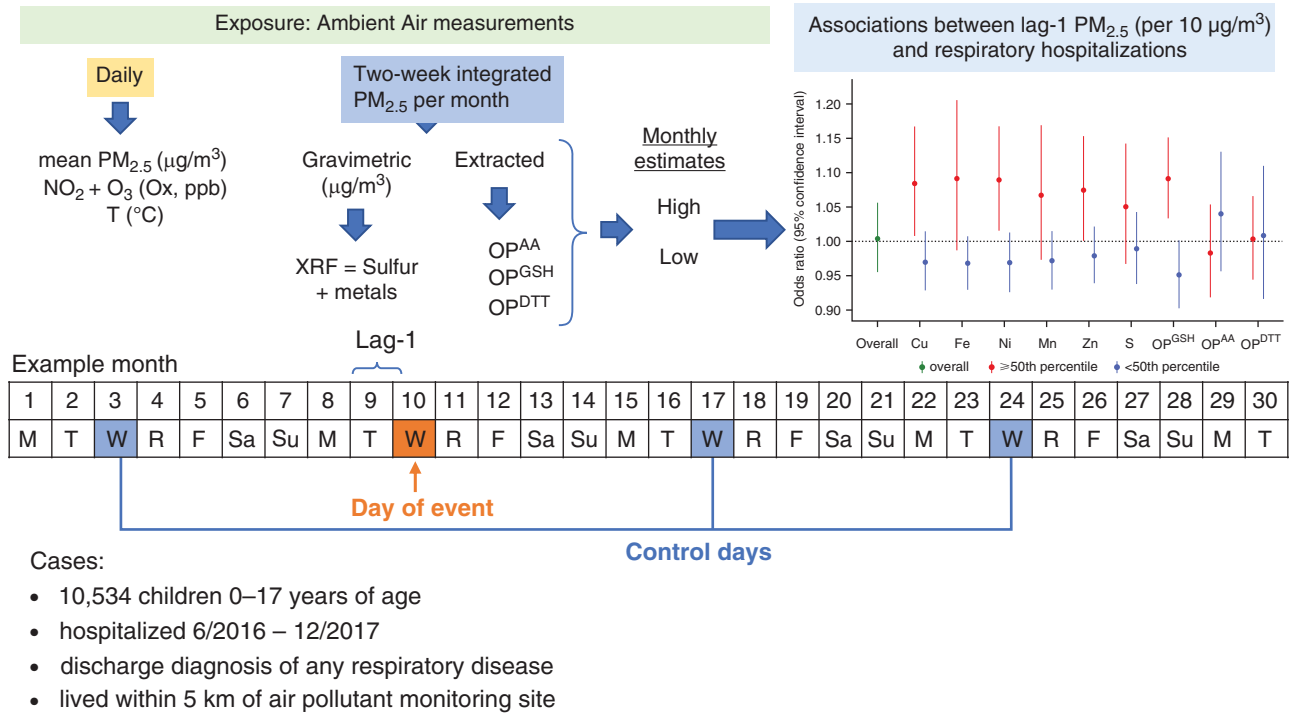


Figure 1. Summary of study design and main findings. Cu = copper; Fe = iron; Mn = manganese; Ni = nickel; OP^{AA} = oxidative potential of ascorbic acid; OP^{DTT} = oxidative potential of dithiothreitol; OP^{GSH} = oxidative potential of glutathione; PM_{2.5} = fine particulate matter; S = sulfur; XRF = X-ray fluorescence; Zn = zinc.

concentrations tended to be correlated, limiting the ability to assign exposures to specific sources. Second, the authors did not consider a cumulative metric accounting for the various metals measured in their study. This may be because they only had a chemical composition as a 2-week average per month when the analysis was a time-series study with exposures corresponding to the day before the outcome. Another important limitation is the time-intensive and costly sample collection and analyses performed, which still only allowed 2-week averages per month.

The findings from the study by Korsiak and colleagues provide important insight into certain PM components and oxidative characteristics that may contribute to the differential toxicity of PM_{2.5} found across space and time. However, more work is needed to prioritize the metrics provided and incorporate additional components to understand the health effects of PM_{2.5} constituents, especially given common sources and correlations among components. ■

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References

1. Schaumann F, Borm PJA, Herbrich A, Knoch J, Pitz M, Schins RPF, et al. Metal-rich ambient particles (particulate matter 2.5) cause airway inflammation in healthy subjects. *Am J Respir Crit Care Med* 2004;170: 898–903.
2. Huang BF, Chang YC, Han AL, Hsu HT. Metal composition of ambient PM_{2.5} influences the pulmonary function of schoolchildren: a case study of school located nearby of an electric arc furnace factory. *Toxicol Ind Health* 2018;34:253–261.
3. Wu KG, Chang CY, Yen CY, Lai CC. Associations between environmental heavy metal exposure and childhood asthma: a population-based study. *J Microbiol Immunol Infect* 2019;52:352–362.
4. Madrigal JM, Persky V, Pappalardo A, Argos M. Association of heavy metals with measures of pulmonary function in children and youth: results from the national health and nutrition examination survey (NHANES). *Environ Int* 2018;121:871–878.
5. Bell ML, Ebisu K, Peng RD, Samet JM, Dominici F. Hospital admissions and chemical composition of fine particle air pollution. *Am J Respir Crit Care Med* 2009;179:1115–1120.
6. Masselot P, Sera F, Schneider R, Kan H, Lavigne E, Stafoggia M, et al. Differential mortality risks associated with PM_{2.5} components: a multi-country, multi-city study. *Epidemiology* 2022;33:167–175.
7. Morgan J, Bell R, Jones AL. Endogenous doesn't always mean innocuous: a scoping review of iron toxicity by inhalation. *J Toxicol Environ Health B Crit Rev* 2020;23:107–136.
8. Fang T, Guo H, Zeng L, Verma V, Nenes A. Highly acidic ambient particles, soluble metals, and oxidative potential: a link between sulfate and aerosol toxicity. *Environ Sci Technol* 2017;51:2611–2620.
9. Goldizen FC, Sly PD, Knibbs LD. Respiratory effects of air pollution on children. *Pediatr Pulmonol* 2015;51:94–108.
10. Peng RD, Bell ML. Spatial misalignment in time series studies of air pollution and health data. *Biostatistics* 2010;11:720–740.
11. Chang HH, Peng RD, Dominici F. Estimating the acute health effects of coarse particulate matter accounting for exposure measurement error. *Biostatistics* 2011;12:637–652.

12. Korsiak J, Lavigne E, You H, Pollitt K, Kulka R, Hatzopoulou M, *et al*. Air pollution and pediatric respiratory hospitalizations: effect modification by particle constituents and oxidative potential. *Am J Respir Crit Care Med* 2022;206:1370–1378.
13. Wu Y, Li S, Guo Y. Space-time-stratified case-crossover design in environmental epidemiology study. *Health Data Science* 2021;2021:1–3.
14. Bozigar M, Lawson AB, Pearce JL, Svendsen ER, Vena JA. Using Bayesian time-stratified case-crossover models to examine associations between air pollution and “asthma seasons” in a low air pollution environment. *PLoS One* 2021;16:e0260264.
15. Lu Y, Symons JM, Geyh AS, Zeger SL. An approach to checking case-crossover analyses based on equivalence with time-series methods. *Epidemiology* 2008;19:169–175.

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Ⓐ An Experimental Human Colonization Model with Pneumococcal Serotype 3 has the Potential to be Used for Vaccine Studies

Pneumococcal infections are major contributors to morbidity and mortality worldwide, while being major causes of respiratory tract infections such as otitis, sinusitis, and community-acquired pneumonia with or without septicemia, and of meningitis (1, 2). *Streptococcus pneumoniae* (the pneumococcus) is a human specific pathogen, and a prerequisite for disease is pneumococcal colonization of the upper respiratory tract. Pneumococci can be divided into at least 100 different capsular serotypes (3). Pneumococcal conjugate vaccines (PCVs), targeting up to 13 of these capsules, have been introduced in the childhood vaccination program in many countries, leading to a dramatic decrease of invasive pneumococcal disease (IPD) in vaccinated children (4–6). Most serotypes covered by the PCVs have decreased postvaccine introduction, but concurrently non-PCV13 types have increased also in nonvaccinated age groups such as the elderly, and non-PCV13 serotypes now dominate in both invasive disease and carriage in several studies (5–8). However, no large reductions have been observed for the vaccine serotype 3, targeted by PCV13 (7, 9). Serotype 3 is an important prominent serotype that has been associated with high mortality (2, 10). Interestingly, pneumococcal capsules of serotypes 3 and 37 are anchored to the cell wall differently than other serotypes, and as a consequence, serotype 3 bacteria are fully covered by its capsular polysaccharide 3 (CPS3) that prevents phagocytosis (11). At the same time, the bacteria release large quantities of CPS3 antigen, potentially binding to available CPS3 antibodies (12). It is likely, but not proven, that this could be one explanation for the inability of PCV13 to give the required protection against IPD caused by serotype 3. In the current study, the authors have set up a pneumococcal human carriage model for studies of serotype 3 using a similar set up as they previously published for serotype 6B (13). This model will be important for increasing our knowledge on serotype 3 in humans, but also for future vaccine studies, especially considering that carriage may be used as a substitute for IPD.

In this issue of the *Journal* (pp. 1379–1392), 96 healthy volunteers with a median age of 21 years, without risk factors, were challenged with pneumococci of serotype 3 in escalating doses (14). Since most serotype 3 pneumococci belong to the clonal cluster CC180, the authors used three different serotype 3 strains, belonging to clades 1a, II, and no clade, of CC180. This seems appropriate, since prior to vaccine introduction clade Ia and 1b dominated, but following PCV introduction, whole genome sequencing has demonstrated that a clade II lineage expanded in carriage and IPD. Underlying mechanisms for the expansion of clade II is unknown. However, a sequence variant in the *galU* gene, encoding a key enzyme for CPS3 biosynthesis, was found among all clade II isolates (15). The participants were inoculated with four different doses with a maximum of 20,000 CFU/100 μ l per nostril for the no clade strain, and up to 160,000 CFU/100 μ l per nostril for the other two strains. Nasal washes were taken from the participants at Day 2, 7, and 14 postinfection and they identified carriage using culture and molecular methods. Carriage was successfully obtained in 33 (34.4%) participants that were culture positive at Day 2, of which 7 (21.2%) were administered antibiotics early and were terminated from the study. A total of 88.5% (23/26) of those that were colonized on Day 2 remained culture positive on Day 14. The recovered bacterial densities were comparable between the three strains. These data are promising and suggest that the challenge strains can be used to study colonization in the same way as in the serotype 6B model. The immune responses were also analyzed and compared with the serotype 6B strain used in the previously published human model (13). The cytokine expression was found to vary depending on the serotype of the challenge strain and the inoculum dose. No differences were seen in IgG fold changes between the three serotype 3 strains and the levels were comparable with those induced by serotype 6B. IgA and IgM were not measured and would be interesting to study in future studies.

Symptoms were reported daily, and 30.2% (29/96) of the participants experienced mild symptoms from the respiratory tract, with higher frequencies in colonized (52.6% [20/38]) versus noncolonized (15.5% [9/58]) individuals. A total of 24 out of 29 (82.8%) had a sore throat, which might be a bit unexpected and warrants further investigation in future studies. One participant got an otitis media already on Day 1 and was administered antibiotics. Most symptoms were reported within 7 days and were mild or

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