International Journal of Public Health (2020) 65:125–127
https://doi.org/10.1007/s00038-019-01329-7

EDITORIAL

Long-term effects of air pollution: an exposome meet-in-the-middle approach

Paolo Vineis[1,2] · Christiana A. Demetriou[3] · Nicole Probst-Hensch[4,5]

Received: 8 October 2019 / Revised: 23 December 2019 / Accepted: 30 December 2019 / Published online: 11 January 2020

Updated figures suggest that air pollution is the main environmental cause of death in the world (Cohen et al. 2017; Burnett et al. 2018). Most epidemiological research so far has been on air as a whole (e.g. TRAP, traffic-related air pollution), or on single ("criterion") pollutants such as oxides of nitrogen (NOx) or particulate matter (PM). However, concerns have been raised on causality and the effects of specific pollutants at low or very low doses, and therefore on the rationale for regulatory policies (Tollefson 2018; Goldman and Dominici 2019). Uncertainties also concern the differences between pollution due to gasoline versus diesel.

The identification of hazardous environmental pollutants—including air pollutants—is complex, particularly in relation to non-communicable diseases (Snyder et al. 2013; Prüss-Ustün et al. 2017; Vineis 2018). Obviously, chronic air pollution exposure cannot be randomized towards identifying adverse health effects. Air pollution exposure is also not associated itself with genetic traits, and subsequently its causal effects cannot be assessed by Mendelian Randomization, in contrast to other risk factors such as body mass index (Pierce et al. 2018). Prospective cohorts are therefore the gold standard in air pollution research and the source of risk-burden estimation.

However, observational studies are faced with confounding. Additional contributors to the complexity of identifying hazardous pollutants are the *diversity of hazards that may exist and their reciprocal correlations, the typically low levels of environmental contaminants combined with generally low effect sizes, long latency periods with unknown windows of susceptibility, and largely unknown modes of action*. The unravelling of environmental causes of disease is also limited by the technical difficulties in defining, and accurately measuring exposures, and by considerable spatial, temporal, and intra-individual variation. The complex and partially unknown interactions with underlying genetic and other factors that modulate susceptibility and response to environmental exposures, further complicate the process of understanding environmental hazards.

Approaches to causality: pathway perturbation

One response to concerns about the causality of air pollution effects has been based on statistical reasoning, i.e. refining tools for modelling and sound low dose extrapolation (Goldman and Dominici 2019). Another potential approach to causality is offered by the concept of the "exposome". It allows an empowerment of environmental research, by improving (a) measurements and modelling of external stressors taking advantage of novel opportunities arising from sensing technology, satellite data, or machine learning algorithms, and (b) measurement of internal biological changes, taking advantage of advancements in high-throughput technologies called "omics" (Siroux et al. 2016). Current possibilities of analysing (tens of) thousands of molecules in biological specimens allow the practical application of the "pathway perturbation" paradigm, as expressed in the National Academy of Science

✉ Paolo Vineis
p.vineis@imperial.ac.uk

Christiana A. Demetriou
demetriou.chri@unic.ac.cy

Nicole Probst-Hensch
nicole.probst@swisstph.ch

1 MRC Centre for Environment and Health, School of Public Health, Imperial College, London, UK

2 Italian Institute of Technology, Genoa, Italy

3 Department of Primary Care and Population Health, University of Nicosia Medical School, Nicosia, Cyprus

4 Swiss Tropical and Public Health Institute, Basel, Switzerland

5 University of Basel, Basel, Switzerland

(NAS) report on "21st Century Risk Assessment" (National Academies of Sciences 2017). According to this paradigm, causality can be strengthened by observations on meaningful biological pathways affected by environmental pollutants. Before the 2017 NAS report, the concept of pathways perturbation had been already introduced in another key NAS publication in 2007, "Toxicity Testing in the 21st Century: A Vision and a Strategy" (National Academies of Sciences 2007). The primary goals of this report were, among others: "(1) to provide broad coverage of chemicals, chemical mixtures, outcomes, and life stages, (2) to reduce the cost and time of testing, (3) to develop a more robust scientific basis for assessing health effects of environmental agents". These goals are becoming increasingly tangible thanks to exposome tools.

The exposome approach

High-throughput studies were first driven by genetics. In the context of genome-wide association studies (GWAS), thousands of genetic variants are agnostically tested for association with specific health phenotypes (Tam et al. 2019). Yet, the proportion of disease variance explained by genetic variation alone remains limited for most non-communicable diseases. As opposed to genetics, environmental exposures are modifiable and therefore more interesting from a primary prevention perspective.

The concept of the "exposome" was proposed initially by Wild (2005), with more recent detailed development in relation to its application to population-based observational studies (Wild 2012). The original concept was expanded particularly by Rappaport and Smith (2010) who functionalized the exposome in terms of chemicals detectable in bio-specimens. The exposome concept refers to the totality of exposures from a variety of external and internal sources including chemical agents, biological agents, radiation, and psychosocial components from conception onward, over a complete lifetime. Under this definition, the exposome comprises biologically active chemicals in response to both external environmental stimuli as well as the internal chemical environment, and offers a conceptual leap in studying the role of the environment in human disease.

Exposome findings on air pollution: impact on inflammation and the immune system

Studying the entirety of internal and external biologically active chemicals a human organism is exposed to from conception to death remains just a conceptual promise. But exposome studies focusing on specific compartments of the environment are also meaningful. For example, such studies have started to provide information on molecular pathways affected by air pollutants. Air pollution is itself a complex mixture of probably many thousands of chemicals. An exposome approach can reveal the molecular signatures of specific pollutants and their relevance for disease onset. Here we show some examples provided by a large European consortium, funded by the European Commission, Exposomics (Vineis et al. 2017).

Investigations on the effects of air pollution in the past either considered biomarkers as an outcome of exposure, or examined health outcomes in the long term. None has used the "meet-in-the-middle" approach we have proposed (Chadeau-Hyam et al. 2011). This approach (MITM) consists in measuring intermediate biomarkers (often with an agnostic omic investigation) and relating them (a) retrospectively to measurements of external exposure and (b) prospectively to a health outcome (disease, or ageing, or other outcomes). If the same set of markers is robustly associated with both ends of the exposure-to-disease continuum, this is a *validation of a causal hypothesis according to the pathway perturbation paradigm*. This approach also corresponds to a refinement of one of Bradford Hill's guidelines for causality assessment in epidemiology, i.e. biological plausibility, and is made possible both by the technological developments in omics and external measurements, and by the existence of long-term longitudinal population cohorts with biological samples stored for many years.

To exemplify how exposome data can be used to perform a meet-in-the-middle analysis, we have considered the mediation exerted by proteins, DNA methylation, and metabolome markers on the relationship of air pollution with coronary heart disease (CHD) and asthma. Exposure to ambient air pollution has been linked to a wide range of adverse health effects, including mortality and morbidity due to respiratory diseases and CHD (Uzoigwe et al. 2013; Newby et al. 2015; Wolf et al. 2015). Mechanistic hypotheses have been put forward to explain the effect of air pollution on the cardiovascular and respiratory system, particularly oxidative stress and inflammation, but no MITM study had previously been performed.

As an example of MITM approach, in a cerebro-cardiovascular disease (CCVD) study embedded in Exposomics, participants were part of a large cohort. From hospital discharge records, we identified all newly diagnosed cases of CCVD and revascularization, which arose during 12.2 years of follow-up on average. For biomarker analyses (inflammatory proteins, genome-wide DNA methylation, metabolites) in prospectively collected and archived blood, we designed a case–control study nested in the cohort (Fiorito et al. 2018). We detected enrichment of altered DNA methylation in "ROS/glutathione/cytotoxic granules" and "cytokine signalling" pathways-related genes, associated both with air pollution and with CCVD risk. More specifically, Interleukin-17 was associated with higher exposure to NO_2, NO_x, and CCVD risk (OR = 1.79; CI 1.04–3.11, comparing extreme tertiles) (Fiorito et al. 2018). In the subsequent metabolomics investigation (Jeong et al. 2018), we observed perturbation of the linoleate metabolism pathway to be associated with both air pollution exposure and two disease outcomes, namely CCVD and asthma. Linoleate is involved in the modulation of Interleukin-8 and thus also in the immune response. These results lend credibility to previously hypothesized mechanisms and suggest that immune proteins and DNA methylation alterations related to air pollution can be detected several years before CCVD diagnosis in blood samples. Thus, we identified both epigenetic and metabolomic signals that were intermediate between air pollution exposure and two different outcomes, an example of MITM.

Future perspectives

We believe we have provided proof-of-principle about the viability of an exposome approach to answer some open issues in air pollution toxicology and epidemiology. Larger studies are needed, and replication of findings is still problematic, but the biological plausibility of our findings in Exposomics is reassuring.

Acknowledgements This work was supported by the grant FP7 of the European Commission "Enhanced exposure assessment and omic profiling for high priority environmental exposures in Europe" (EXPOsOMICS Grant 308610 to PV).

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

References

Burnett R, Chen H, Szyszkowicz M et al (2018) Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. Proc Natl Acad Sci 115:9592–9597. https://doi.org/10.1073/pnas.1803222115

Chadeau-Hyam M, Athersuch TJ, Keun HC et al (2011) Meeting-in-the-middle using metabolic profiling—a strategy for the identification of intermediate biomarkers in cohort studies. Biomarkers 16:83–88. https://doi.org/10.3109/1354750X.2010.533285

Cohen AJ, Brauer M, Burnett R et al (2017) Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet 389:1907–1918. https://doi.org/10.1016/S0140-6736(17)30505-6

Fiorito G, Vlaanderen J, Polidoro S et al (2018) Oxidative stress and inflammation mediate the effect of air pollution on cardio- and cerebrovascular disease: a prospective study in nonsmokers. Environ Mol Mutagen 59:234–246. https://doi.org/10.1002/em.22153

Goldman GT, Dominici F (2019) Don't abandon evidence and process on air pollution policy. Science 363:1398–1400. https://doi.org/10.1126/science.aaw9460

Jeong A, Fiorito G, Keski-Rahkonen P et al (2018) Perturbation of metabolic pathways mediates the association of air pollutants with asthma and cardiovascular diseases. Environ Int 119:334–345. https://doi.org/10.1016/j.envint.2018.06.025

National Academies of Sciences: Toxicity Testing in the 21st Century. US NAS Press, Washington DC, 2007

National Academies of Sciences. Using 21st Century Science to Improve Risk-Related Evaluations. US NAS Press, Washington DC, 2017

Newby DE, Mannucci PM, Tell GS et al (2015) Expert position paper on air pollution and cardiovascular disease. Eur Heart J 36:83–93. https://doi.org/10.1093/eurheartj/ehu458

Pierce BL, Kraft P, Zhang C (2018) Mendelian randomization studies of cancer risk: a literature review. Curr Epidemiol Rep 5:184–196. https://doi.org/10.1007/s40471-018-0144-1

Prüss-Ustün A, Wolf J, Corvalán C et al (2017) Diseases due to unhealthy environments: an updated estimate of the global burden of disease attributable to environmental determinants of health. J Public Health Oxf Engl 39:464–475. https://doi.org/10.1093/pubmed/fdw085

Rappaport SM, Smith MT (2010) Environment and disease risks. Science 330:460. https://doi.org/10.1126/science.1192603

Siroux V, Agier L, Slama R (2016) The exposome concept: a challenge and a potential driver for environmental health research. Eur Respir Rev 25:124–129. https://doi.org/10.1183/16000617.0034-2016

Snyder EG, Watkins TH, Solomon PA et al (2013) The changing paradigm of air pollution monitoring. Environ Sci Technol 47:11369–11377. https://doi.org/10.1021/es4022602

Tam V, Patel N, Turcotte M et al (2019) Benefits and limitations of genome-wide association studies. Nat Rev Genet 20:467–484. https://doi.org/10.1038/s41576-019-0127-1

Tollefson J (2018) Science under siege: behind the scenes at Trump's troubled environment agency. Nature 559:316–319. https://doi.org/10.1038/d41586-018-05706-9

Uzoigwe JC, Prum T, Bresnahan E, Garelnabi M (2013) The emerging role of outdoor and indoor air pollution in cardiovascular disease. North Am J Med Sci 5:445. https://doi.org/10.4103/1947-2714.117290

Vineis P (2018) From John Snow to omics: the long journey of environmental epidemiology. Eur J Epidemiol 33:355–363. https://doi.org/10.1007/s10654-018-0398-4

Vineis P, Chadeau-Hyam M, Gmuender H et al (2017) The exposome in practice: design of the EXPOsOMICS project. Int J Hyg Environ Health 220:142–151. https://doi.org/10.1016/j.ijheh.2016.08.001

Wild CP (2005) Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol 14:1847–1850. https://doi.org/10.1158/1055-9965.EPI-05-0456

Wild CP (2012) The exposome: from concept to utility. Int J Epidemiol 41:24–32. https://doi.org/10.1093/ije/dyr236

Wolf K, Stafoggia M, Cesaroni G et al (2015) Long-term exposure to particulate matter constituents and the incidence of coronary events in 11 European cohorts. Epidemiology 26:565–574. https://doi.org/10.1097/EDE.0000000000000300