

Draft Overview: Addresses Question: Are the Adverse Human Effects of Air Pollution Underestimated in the Literature? Implications for science, medicine and public policy.

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Outline:

Introduction: Researchers have not addressed the question above and to date we lack an answer to it. This scan is a non-scientific review of diseases causally linked to AP and reported infrequently in the peer reviewed literature. I think a prospective study of the true estimate of M/M and harm of AP would confirm current statistics upon which policy decisions are based are underestimated.

Diseases of organ systems with annotated bibliography (Cardiovascular to Sensory organs)

Addendum (Aeroallergens; pneumonia)

Summary

L'Envoi: Reflections on Bumblebees

Introduction

1. **AP PROBLEM:** Air pollution (AP) has overtaken poor sanitation and a lack of drinking water to become the main environmental cause of premature death (OECD [2014](#)). WHO reported that in 2012, approximately 3.7 million people died from outdoor urban and rural sources (WHO [2014](#)) The Lancet (April 14, 2017) Cohen AJ, et al 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, shows Ambient PM 2.5 was the fifth ranking mortality risk factor in 2015; PM 2.5 caused 4.2 million deaths and 103.1 million disability adjusted life years (DALYS in 2015, representing 7.6% of total global deaths. Deaths from AP increased from 1990 to 2015, primarily Asia. It was the 6th rank risk factor in the US with 18.5 (14.2-23.7) deaths per 100,000 people. However, unlike much of the world, the exposure rates have decreased in the US (attributed to effects of the Clean Air Act (1970) and related AP policies and regulations) and the decreases in exposure have resulted in lower mortality rates than China, India, for example. (The Lancet and Air Pollution April 14, 2017 by Paul Homewood.
<https://notalotofpeopleknowthat.wordpress.com/2017/04/14/the-lancet-and-air-pollution/>.) Despite improvements in air quality in the U.S. it is estimated that one half of all counties in the U.S. expose approximately 166 million Americans to ambient AP (ozone and PM 2.5) that exceeds government standards. (CDC <https://www.cdc.gov/nceh/airpollution/publications.html>.)
2. **WHAT IS AP?** Ambient air pollutants contain thousands of chemicals, many of which may be toxic to the human body. The Environmental Protection Agency in 1990 identified 188 specific pollutants and chemical groups, known as hazardous air pollutants (HAPs). (EPA 1990 List of HAPs: <https://www3.epa.gov/ttn/atw/orig189.html>.) These pollutants also known as "air toxics" are known to cause cancer and other serious health impacts. This list has been modified. The Clean Air Act requires the EPA to set National Ambient Air Quality Standards (NAAQS) for six

common air pollutants (aka “Criteria air pollutants”—ground-level Ozone; Carbon Monoxide; Sulfur Dioxide; Particulate Matter; Lead and Nitrogen Dioxide) that are found widely across the U.S. and can harm health and the environment. (EPA Criteria Air Pollutants 2016: <https://www.epa.gov/criteria-air-pollutants>.)

3. **ORIGENS OF AP?** Whether from Natural or manmade sources and indoor or out- of –doors, when organic material is burned, or pyrolyzed, a complex chemical mixture of thousands of compounds, including radionuclides, that may cause disease and premature death, are produced. There are approximately 7,000 chemicals, including more than 70 carcinogens known to cause cancer (carcinogens) produced from burning tobacco. (USDHHS The Health Consequences of Smoking—50 Years of Progress: Report of the Surgeon General. 2014, <https://www.surgeongeneral.gov/library/reports/50-years-of-progress/exec-summary.pdf>.) Likewise, burning coal (vehicles, industry, etc) produces hazardous pollutants including: SO₂; NO_x; Particulate Matter; Mercury; Lead; Carbon Monoxide; Volatile organic compounds (VOC) that form Ozone (O₃) and other metals, including arsenic.
4. **IS CO₂ AN AP?** Yes. Carbon Dioxide, a cause of global warming and climate change, is a major pollutant of burning organic material, including fossil fuels. For example, in 2015, emissions of CO₂ by U.S. electric power plants totaled 1,925 million metric tons (about 37% of the total U.S. energy-related CO₂ emissions of 5,271 million metric tons. (EIA, <http://www.eia.gov/tools/faqs/faq.cfm?id=77&t=11> CO₂ and other greenhouse gases cause global warming and climate change which in turn cause extensive global M/M and impaired quality of life. The focus of this summary concerns primarily the non-greenhouse gas morbidity and mortality from AP.
5. **AP LITERATURE.** Most peer-reviewed literature on the adverse effects of air pollution on health focus on cardiovascular (CV) and respiratory diseases, allergies and cancers. Specifically, risks of heart attacks (myocardial infarction); asthma and other obstructive air flow diseases (COPD), allergies, many of which cause respiratory (upper and lower) symptoms and lung cancer. Statistical analyses of AP related morbidity and mortality typically do not incorporate “low-frequency” diseases related to AP. A primary reason is the evidence for causality is often lacking. Low-frequency diseases are not widely researched and reported; numbers of cases are small relative to CV, Resp and Cancers. Research funding is allocated to the high frequency AP related diseases.
6. **WHERE IS AP?** Given the ubiquity of ambient AP in Indiana, the U.S., and globally, the wide prevalence of human exposure to air pollutants (AP) and the known systemic effects of APs for most all living organisms, it is not surprising that evidence of adverse human effects of AP may be found in all organ systems, tissues and cells of the body. Research over the past 70 years has documented basic mechanisms of genetic, cellular, tissue, and organ toxicity from AP. This toxicity is caused by pyrolysis of organic matter, (eg tobacco or fossil fuels), that produce thousands of toxic chemicals, aerosols, vapors, radionuclides and particles—the result: premature morbidity and mortality and widespread population health and cost impacts.
7. **AP HARMS: AP BENEFITS?** There are no known salutary effects of AP in humans; there are few examples of the “threshold effect”, a concentration vs. time exposure of humans to pollutants that does not produce evidence of genetic, cellular, tissue or organ damage. (Kelly et al. Air pollution and public health. 2015 *environ Geochem Health* 2015;37(4):631-49, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4516868/>.) APs adversely affect most all living organisms, whose impacts may directly or indirectly impact human health. Air pollutants cause

impairments in the structure and function of the human body with disruption in the physical, chemical, and metabolic functions via most all basic mechanisms of disease, including: 1. Genetic 2. Pathogenic 3. Tumor and Cancer 4. Physical and Chemical Agents 5. Malnutrition 6. Autoimmunity 7. Inflammation 8. Degeneration. Three leading mechanisms that result in tobacco- caused diseases include: DNA damage, inflammation, and oxidative stress. (How tobacco smoke causes disease. Report of the Surgeon General, 2010:

<https://www.ncbi.nlm.nih.gov/books/NBK53019/#ch1.s7><https://www.ncbi.nlm.nih.gov/books/NBK53019/#ch1.s7>. Dysfunctional gene regulation mechanisms are beginning to complement these more general descriptions of mechanisms of human disease. (Yang J, Wu SJ et al. BMC Syst Biol 2016;10:36. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4875653/>. And Das J, Fragoza R, Hao RL et al Mol. BioSyst 2014,10,9-17.

<http://pubs.rsc.org/en/content/articlelanding/2014/mb/c3mb70225a#!divAbstract>.) The list of harms of AP is growing; given the biological plausibility of toxicity of APs for humans, it is likely that exposure to pollutants, whether in air, water, food, or soil, will have bearing on most all aspects of the structure and function of the human body, from the genome and proteome to cells, tissues, and organs. (Dockery D, Evans JS. Tallying the bills of mortality from air pollution. The Lancet . DOI: [http://dx.doi.org/10.1016/S0140-6736\(17\)30884-X](http://dx.doi.org/10.1016/S0140-6736(17)30884-X)) (Cohen AJ Brauer M, Burnett R et al. Lancet 2017; [http://dx.doi.org/1016/S0140-6736\(17\)30505-6](http://dx.doi.org/1016/S0140-6736(17)30505-6).) Burnett RT, Pope CA, Ezzati M, et al. Environ Health Perspect. 2014 ;122 :397-403.

(<https://www.ncbi.nlm.nih.gov/pubmed/24518036?dopt=Abstract>. Doi: 10.1289/ehp.1307049. Epub 2014 Feb 11; [http://thelancet.com/journals/lancet/article/PIIS0140-6736\(17\)30884-X/fulltext](http://thelancet.com/journals/lancet/article/PIIS0140-6736(17)30884-X/fulltext).)

8. **AP HIGH & LOW FREQUENCY DISEASES & PRECISION MEDICINE:** The so called “orphan” (low frequency) diseases resulting from exposure to AP may account for a relatively small fraction of the total number of CV, respiratory diseases and cancers caused by AP. But since a large fraction of the population is regularly exposed to air pollutants, “low frequency diseases” will have significant impacts on health outcomes for millions of persons. The adage “A small % of a big number is—a big number” comes to mind. Underestimates impact consideration of research, clinical and policy actions. The complex interactions between the human genome and cumulative environmental exposures to pollutants will predict risks of disease, allow establishment of causality, and predict the probability of outcomes. ‘Precision medicine’ is a term used to describe this process; it is years away from implementation on large scale in clinical medicine. In precision medicine, clinicians need available evidence of “low frequency” disease impacts of AP to personalize their assessment and care of patients. A patient doesn’t care if they have a high frequency or low frequency disease. They want their clinician to recognize and deal with both, not one to the exclusion of the other. John Hickam MD, a famous IUSM researcher and public health giant (primary author of 1964 U.S. Surgeon General Report on smoking and lung cancer), famously posited ‘Hickam’s Dictum’ in rebuttal to Ockham’s Razor: “A patient can have as many disease as they damn well please.” <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3628473/>.
9. **AP AND OTHER TOXIN INTERACTIONS:** Research into the complexity of AP and the host’s susceptibility to adverse effects is in its infancy. Humans are daily ‘bathed’ in pollutants. But we are also exposed to a myriad of other chemicals: prescription medicines, over- the- counter drugs, ‘alternative’ drugs, both legal and illegal, pesticides, herbicides, and medical radionuclides. The complex interactions between and among these agents, and their adverse impacts in humans

are largely unknown, but may be synergistic or antagonistic, and impact human hosts variably depending on host defense mechanisms and susceptibility.

10. **AP, CAUSALITY, CAUTION:** Given these facts, the use of the word “causality” in peer-reviewed publications is problematic, and should require precise definition and statement of possible limitations. A more precise use of the term might include the probability that a causal relationship exists between human exposure to one or a myriad of potential toxic agents. Bradford-Hill criteria provides a template for assessing causal links; research in AP must adhere to basic definitions of causality, complemented by molecular biological information. <http://www.epidemiologyresearch.net>.
11. **LOW FREQUENCY DISEASES:** This section below provides a non- scientific overview of the less commonly reported adverse human impacts of APs. Taken in their totality and added to the common CV, respiratory diseases and cancers caused by AP, the burden of AP in humans is large and likely understated in the literature. Since models are used to estimate rates of AP attributable M/M, there may be overestimates or underestimates of rates based upon assumptions in models. Such errors plague model based predictions. One example, the Intergovernmental Panel on Climate Change (IPCC) simulations predicted melting of arctic ice sheets by 2100 but recent estimates based on direct observation show melting at a much faster rate than predicted by early models. (Scherer. How the IPCC underestimated climate change. Scientific American Dec 6, 2012. <https://www.scientificamerican.com/article/how-the-ipcc-underestimated-climate-change/>. To date models do not exist that incorporate true estimates of the disease burden of AP and human health. Population and epidemiological research is needed to fill this gap in knowledge.
12. **SCOPE OF AP HARMS:** Humans are exposed daily to natural sources of air pollutants (volcanic eruptions, fires, wind-blown dust) and to human made pollutants which may gain entrance to the body by direct contact with skin, GI tract, through inhalation into the lungs where, within seconds, chemicals may reach the circulation and be widely distributed throughout the body. Hazardous chemicals may alter intracellular structure and function, with damage to the genome and proteome and alter gene expression through epigenetic changes. Oxidant stress induced damage to tissues and organ systems, where tissue injury is produced through an imbalance between reactive oxygen species and the body’s defense mechanisms. All organ systems of the human body may be adversely impacted.
 - a. Cardiovascular/Circulatory
 - b. Digestive/Excretory
 - c. Endocrine
 - d. Integumentary/Exocrine
 - e. Lymphatic /Immune
 - f. Muscular/Skeletal
 - g. Nervous
 - h. Renal/Urinary
 - i. Reproductive
 - j. Respiratory
 - k. Sensory
13. **AP AND LOW FREQUENCY DISEASE SCAN:** The following section summarizes selected literature, primarily from the peer-reviewed journals, primarily on the non- CV, lung, and cancer diseases.

Some papers are basic science, including animal and human research. Others are clinical science. (Yunesian et al. BMC Public Health 2006;6:218. The true incidence and prevalence of these conditions is unknown. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1569380/>.)

Cardiovascular/Circulatory

CV (Blood pressure) –and other chronic disease

Ibald-Milli A, Stieber J, Wichmann H-E, et al. Effects of air pollution on blood pressure: a population based approach. Am J Public Health 2001;91(4):571-77. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1446632/pdf/11291368.pdf>. (The observed increase in systolic blood pressure associated with ambient air pollution could be related to a change in cardiovascular autonomic control.)

Zhong J, Urch B, Speck M et al. Endotoxin and beta 1,3 Glucan in concentrated ambient particles induce rapid increase in blood pressure in controlled human exposures. Hypertension. 2015;66(3):509-16. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4537367/>. (In epi studies exposure to PM is assoc with increase BP. Experimental exposure to PM components caused increase BP.)

Zhang Z, Laden F, Forman JP et al. Long-term exposure to PM and self-reported hypertension: a prospective analysis in the nurses' health study. Environ Health Perspect 2016;124(9):1414-1420. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5010392/>. (Long-term exposure to particulate matter was associated with small increases in risk of incident hypertension, particularly among younger women and the obese.)

Chen H, Goldberg MS. The effects of outdoor air pollution on chronic illnesses. McGill J Med 2009;12(1):58-64, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2687917/>.

1. Over the past 25 years, considerable epidemiological research has been conducted to investigate acute and chronic effects on health as a result of exposure to ambient air pollution. The bulk of this work has been focused on health effects from short-term (i.e., day to day) fluctuations in ambient levels of pollution.
2. The conclusion is clear: short-term elevations of ambient air pollution cause a variety of acute health events, especially in certain subgroups of the population, such as the elderly, children, and those who are impaired physiologically (e.g., congestive heart failure, diabetes, and cardiovascular disease) (47;51). In contrast, the effects of air pollution on chronic diseases have not been studied as extensively. This is due to the difficulty of assembling large cohorts, following subjects through a long enough period of time, and the difficulty in measuring personal exposures to ambient air pollution.
3. We have recently completed a structured review of the association between long-term exposure to ambient air pollution and the risks in adults of non-accidental mortality and the incidence and mortality from cancer and cardiovascular and respiratory diseases (52). A total of 17 cohort studies and 20 case-control studies, published between 1950 and 2007, of the long-term effects of air pollution were identified.

4. Our analysis of the published studies showed a 6% increase in non-accidental mortality for every increase of 10 µg/m³ of fine particles, independent of age, gender, and geographic region. This was derived from a log-linear exposure-response pattern; that is, mortality increased exponentially with increasing concentrations of fine particles.
5. Chronic health effects from exposure to urban air pollution have thus been estimated to account for almost 60% of the total environmentally-related health effects, exceeding the effects from other environmental risk factors, such as environmental tobacco smoking and lead contamination in drinking water (68).
6. Air pollution does not recognize national boundaries and it may be transported over distances of thousands miles (20). Even at its current level, air pollution threatens the health of entire populations. Air pollution is a growing, global problem. Yet approaches to controlling air pollution have not been up to the task. The overall evidence from the past and present epidemiological studies strongly supports tighter standards for air pollution, especially particulate pollutants, in Canada and in other countries.

CV: (pulmonary embolus)

Pun VC, Hart JE, Kabrhel C, et al. Prospective study of ambient particulate matter exposure and risk of pulmonary embolism in the Nurses' health study cohort. *Environ Health Perspect*; <http://ehp.niehs.nih.gov/1408927/>. (

Milojevic A, Wilkinson P, Armstrong B, Bhaskaran K, Smeeth L, Shakoor H. Short-term effects of air pollution on a range of cardiovascular events in England and Wales: case-crossover analysis of the MINAP database, hospital admissions and mortality. *Heart*. 2014. <http://heart.bmj.com/content/early/2014/04/10/heartjnl-2013-304963>. (We provide evidence that PM in the prior 1 and 12 months is associated with PE risk. Our results also suggest that women with underlying health conditions may be more susceptible to PE after PM exposure.)

Digestive (Pancreas/liver/gall bladder)

Digestive (Pancreas)

Nemmar A, Al-Salam S, Beegam S, et al Pancreatic effects of diesel exhaust particles in mice with Type 1 Diabetes Mellitus. *Cell Physiol Biochem* 2014;33:413-22. <https://www.karger.com/Article/FullText/356680>. (We conclude that Diesel Exhaust Particles caused detrimental effects on the pancreas of diabetic mice, and that oxidative stress is responsible, at least partially, for the observed effects. It is well-established that the effects of particulate air pollution are not only limited to the lung but they can affect distant organs including heart, brain and kidney [2,3,22]. There are three primary hypotheses which are being investigated to explain the extrapulmonary effect of nanoparticles [3]. The first one relates to the effect of particles on their ability to impact the autonomic nervous system. Inhaled particles may affect the extrapulmonary sites through inflammatory mediators produced in the lungs and released into the circulation [2,3,22]. In conclusion, our data showed, probably for the first time, evidence for an aggravating pancreatic effect of DEP in diabetic mice. Our findings expand the list of extrapulmonary organs that can be adversely affected by particulate air pollution to include the pancreas in a mouse model of type 1 diabetes. Epidemiological and clinical studies are needed

to assess the effect of particulate air pollution on the pancreas in healthy individuals and those with pre-existing chronic diseases such as diabetes.

Digestive (Liver)

Altered metabolism of drugs because of hepatic enzyme induction.

Keeri-Szanto, Pomeroy JR. Atmospheric Pollution and Pentazocine Metabolism. *Lancet* 1971;297(7706): 947-49. Originally published as Vol 1, Issue 7706.

<http://www.sciencedirect.com/science/article/pii/S0140673671914486>. http://ac.els-cdn.com/S0140673671914486/1-s2.0-S0140673671914486-main.pdf?_tid=0db543f0-bc9b-11e6-9415-00000aab0f6b&acdnat=1481128661_6635a3bb9b10349fd2667c8d0ac5dee3.

1. Enzyme induction becoming important cause of morbidity and mortality during drug administration in patients. We investigated the cumulative pentazocine requirement vs time curves.
2. A statistically significant correlation between weight-and-time-adjusted drug requirements and patients' domicile and smoking habits.
3. Changes in the rate of pentazocine disposal have been tentatively linked with ambient or self-induced (smoking) atmospheric pollution,
4. It is suggested that similar differences are likely to occur with other drugs and in other therapeutic settings.
5. Our experimental design was not suited to prove causal relation between atmospheric pollution and the metabolism rate of pentazocine, but results are suggestive. Atmospheric pollution will likely lead to increased drug requirements with many, of these drugs whose priming dose is less than a third of the daily maintenance dose.

Kim JW, Park S, et al. Role of air pollutants in initiating liver disease. *Toxicol Res* 2014;30(2):65-70. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4112066/>.

1. Along with the other well-known harmful effects of air pollution, recently, several animal models have provided strong evidence that air pollutants can induce liver toxicity and act to accelerate liver inflammation and steatosis.
2. This review briefly describes examples where exposure to air pollutants was involved in liver toxicity, focusing on how particulate matter (PM) or carbon black (CB) may be translocated from lung to liver and what liver diseases are closely associated with these air pollutants.)

Digestive (Cholesterol Gallstones)

Di Ciaula A, Wang DQH, et al. Current Views on Genetics and epigenetics of cholesterol gallstone disease. *Cholesterol* 2013. doi: [10.1155/2013/298421](https://doi.org/10.1155/2013/298421). (Various steps of pathogenesis of cholesterol gallstones and interaction between environmental, epigenetic and genetic factors Diet [101, 102] or environmental exposition to a number of chemical agents like heavy metals (e.g., cadmium, arsenic, nickel, chromium, and methylmercury) [103–107], air pollutants (e.g., particulate matter, black carbon, and benzene), and endocrine-disrupting/reproductive toxicants (e.g., diethylstilbestrol, bisphenol A, persistent organic

pollutants, dioxin, and pesticides [108–112]) are able to induce epigenetic changes (mainly DNA methylation, histone acetylation/deacetylation [113], and noncoding microRNAs) [114, 115], which are involved in a wide range of metabolic diseases including obesity [90, 116], abnormal hepatic triglyceride accumulation [91], and the metabolic syndrome [92, 117], type 2 diabetes [87–89], all well-known risk factors for gallstone disease and mainly attributable to insulin resistance. Interestingly, it has been recently reported by a cluster of analyses a significant association of gallbladder diseases with environmental pollutants (heavy metals) in drinking water [118].) <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3649201/>.

Endocrine (Diabetes; thyroid; adrenal)

Endocrine (Diabetes Mellitus)

Diabetes and the Environment. Air Pollution.

<http://www.diabetesandenvironment.org/home/contam/air>. (Extensive literature review show in animals and humans that exposure to air pollutants may contribute to development of type 2 DM and possibly type 1 DM. Most systematic reviews and meta-analysis corroborate this statement. Certain genes predispose one to this risk of air pollution.)

Goettems-Florin PB et al Fine PM potentiates type 2 diabetes development. J Physiol Biochem 2016;72(4):643-56. <https://www.ncbi.nlm.nih.gov/pubmed/27356529>. (Exposure to fine particulate matter (PM2.5) air pollution is a risk factor for type 2 diabetes (T2DM)

Nemmar et al 2014 (see above reference under pancreas).

Endocrine (Thyroid disease)

Brent GA. Environmental exposures and autoimmune thyroid disease. Thyroid 2010;20(7):755-761. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2935336/>. (It is likely that environmental chemicals are increasing susceptibility to autoimmune thyroid disease, but it is difficult to confirm and study.)

Korevaar TIM. Fine particle air pollution may alter newborn thyroid function. Clin Thyroidol 2016;28:337-39.

Endocrine (Adrenal)

Thomson EM. Neurobehavioral and metabolic impacts of inhaled pollutants: A role for the hypothalamic-pituitary-adrenal axis? Endocrine Disruptors 2013; 1(1). In addition to established effects on cardiovascular and respiratory systems, recent epidemiological studies show associations between air pollutants and impacts on the central nervous system such as depression and impaired cognitive ability, and on disease states associated with dysfunctional metabolism such as metabolic syndrome and type II diabetes. Although the relative risk attributed to air pollutants is small compared with established risk factors, the widespread exposure of the population translates into a substantial societal health burden. Controlled experimental studies support the notion that these associations have a biological basis. Recently, we reported that short-term exposure of rats to two pollutants associated with adverse health effects, particulate matter and ozone, activated the hypothalamic-pituitary-adrenal (HPA) stress response

axis, resulting in increased circulating levels of the glucocorticoid corticosterone and systemic impacts on a variety of biological pathways. While effects were transient after a single exposure in this healthy animal model, chronic activation and dysfunction of the HPA axis is associated with adverse neurobehavioral, metabolic, cardiovascular, immune, reproductive, and developmental effects.
<http://dx.doi.org/10.4161/endo.27489><http://www.tandfonline.com/doi/abs/10.4161/endo.27489>.

Integumentary (Skin)

Kim KE, Cho D, Park HJ. Air pollution and skin diseases: Adverse effects of airborne particulate matter on various skin diseases. *Life Sciences* 2016;152: 126-34.

<http://dx.doi.org/10.1016/j.lfs.2016.03.039>.

<http://www.sciencedirect.com/science/article/pii/S0024320516301886>. (Overall, increased PM levels are highly associated with the development of various skin diseases via the regulation of oxidative stress and inflammatory cytokines. Therefore, anti-oxidant and anti-inflammatory drugs may be useful for treating PM-induced skin diseases.)

Drakaki E, Dessinioti C, Antoniou CV. Air pollution and the skin. *Front. Environ. Sci* 2014.

(Exposure of the skin to air pollutants has been associated with skin aging and inflammatory or allergic skin conditions such as atopic dermatitis, eczema, psoriasis or acne, while skin cancer is among the most serious effects. On the other hand, some air pollutants (i.e., O₃, nitrogen dioxide, and sulfur dioxide) and scattering particulates (clouds and soot) in the troposphere reduce the effects of shorter wavelength UVR and significant reductions in UV irradiance have been observed in polluted urban areas.)

<http://dx.doi.org/10.3389/fenvs.2014.00011>.

<http://journal.frontiersin.org/article/10.3389/fenvs.2014.00011/full>.

Lymphatic/immune

Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society. Rebecca Bascom (Chair) State of the Art. Health Effects of Outdoor Air Pollution. *Am J Respir Crit Care Med* 1996;153:3-50.

http://www.atsjournals.org/doi/abs/10.1164/ajrccm.153.1.8542133?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed#readcube-epdf.

1. Immunologic Effects of Ozone p21.

Arnette R. The impacts of air pollution on the immune system. *Environmental Factor* 2015.

National Institute of Environmental Health Sciences. ([Nadeau](#) is associate professor of Pediatrics – Allergy and Immunology at Stanford University School of Medicine. She talked about the study, collaborations, and scientific insights that have resulted, during a Dec. 16 NIEHS Distinguished Lecture, "How Pollution Exposure Leads to Immune Dysfunction: The Role of Epigenetics and Multiplex Immunophenotyping Studies."

<http://www.niehs.nih.gov/news/newsletter/2015/1/science-nadeau/>.

Sherr DH. Environmental pollutants and the immune system. Department of Environmental Health Boston University School of Public Health. (Brief overview of literature re impacts of air pollution on the immune system in humans. Air pollutants disrupt the immune system and the molecular basis for changes are under intense research.)

<http://www.psr.org/chapters/boston/resources/environmental-pollutants-and-the-immune-system.html>.

Bauer RN, Diaz-Sanchez D et al. Effects of air pollutants on innate immunity: The role of Toll-like receptors and nucleotide-binding oligomerization domain-like receptors. *J Allergy Clin Immunol* 2012;129(1):14-26. 10.1016/j.jaci.2011.11.004

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4341993/>

1. Review
2. Interactions between exposure to ambient air pollutants and respiratory pathogens have been shown to modify respiratory immune responses.
3. In conclusion, concurrent exposures to pollutants and pathogens are likely, thus making potential interactions between the 2 insults and mechanisms mediating these responses of great public health importance.

Sherr DH. Environmental Pollutants and the immune system. OR “its not nice to fool Mother Nature’ PSR. 2015. <http://www.psr.org/chapters/boston/resources/environmental-pollutants-and-the-immune-system.html>. (Not a research paper but review by researcher in this area at BU School of Medicine and head of Sherr Laboratory research facility.

1. Our laboratory has shown that two classes of common pollutants, aromatic hydrocarbons and phthalates, disrupt B cell education. Hydrocarbons are ubiquitous and are produced every time something organic is burned - from fossil fuels in our cars and coal in our power plants, to charcoal broiled steaks. Phthalates, which leach from hundreds of common products containing plasticizers (e.g. medical tubing, plastic bags, cosmetics), can also be found throughout our environment.
2. The effects of these chemicals on immature B lymphocytes are dramatic. Hydrocarbons, many of which are carcinogenic, prematurely induce bone marrow B cells to initiate the cell death program. Notably, the doses of hydrocarbons required to suppress B cell development are significantly lower than those required to induce cancers. Consequently, estimates of hydrocarbon exposure risks, which generally involve cancer as an endpoint, may underestimate the dangers of pollutant exposure.

Immune Epigenetic effects

Lepeule J, Catherine Bind MA, Baccarelli AA, et al. Epigenetic influences on associations between air pollutants and lung function in elderly men: the normative aging study. *Environ Health Perspect* 2014;122(6):566-72. <http://ehp.niehs.nih.gov/1206458/>.

1. Sub-chronic exposure to traffic-related pollutants was associated with significantly reduced lung function in the elderly; non-traffic pollutants (particles, ozone) had weaker associations.
2. Epigenetic mechanisms related to inflammation and immunity may influence these associations.

Brookes E, Shi Y. Diverse Epigenetic Mechanisms of Human Disease. *Annual Review of Genetics* 2014;48:237-268. DOI: 10.1146/annurev-genet-120213-092518.

http://www.annualreviews.org/doi/full/10.1146/annurev-genet-120213-092518?url_ver=Z39.88-2003&rft_id=ori%3Arid%3Acrossref.org&rft_dat=cr_pub%3Dpubmed&.

1. Abnormal epigenetic profiles can serve as biomarkers of disease states and predictors of disease outcomes. Therefore, epigenetics is a key area of clinical investigation in diagnosis, prognosis, and treatment.
2. Epigenetics is the study of heritable changes in gene activity that are not attributable to alterations in genomic sequence. Epigenetic mechanisms are heavily implicated in human disease.
3. Genetic mutations in genes that encode chromatin regulators can cause monogenic disease or are incriminated in polygenic, multifactorial diseases. Environmental stresses can also impact directly on chromatin regulation, and these changes can increase the risk of, or directly cause, disease.
4. Exposure to environmental stresses in older generations may predispose subsequent generations to disease in a manner that involves the transgenerational inheritance of epigenetic information.
5. Thus, epigenetics can be viewed as a potential point of cross talk between the genome and the environment.
6. It is known that disease susceptibility, progression, and outcome are influenced by a person's genetic predisposition and by external factors. More recently, it has become understood that the environment exerts some of its effects through epigenetics.
7. Some diseases in which epigenetic mechanisms are implicated include: heritable genetic diseases caused by mutations in epigenetic regulator genes; neurological and behavioral abnormalities; aberrant neural crest development with cognitive and related cranio-facial, cardiac, and growth abnormalities; multifactorial diseases associated with genetic mutations in epigenetic genes: cancers, autism, schizophrenia and congenital heart disease; Cancers; diseases of aging and neurodegenerative diseases; nutrition;

Baccarelli A, Bollati V. Epigenetics and environmental chemicals. *Curr Opin Pediatr* 2009;21(2):243-251. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3035853/>.

1. In-vitro, animal, and human investigations have identified several classes of environmental chemicals that modify epigenetic marks, including metals (cadmium, arsenic, nickel, chromium, methylmercury), peroxisome proliferators (trichloroethylene, dichloroacetic acid, trichloroacetic acid), air pollutants (particulate matter, black carbon, benzene), and endocrine-disrupting/reproductive toxicants (diethylstilbestrol, bisphenol A, persistent organic pollutants, dioxin).
2. Epigenetics holds substantial potential for developing biological markers to predict which exposures would put exposed subjects at risk and which individuals will be more susceptible to develop disease.
3. These results indicate that exposure of germ cells, possibly at a specific developmental stage, is necessary to produce heritable epigenetic changes. In addition, epigenetic mechanisms may underlie the effects of in utero and early life

exposures on adult health, as in-utero/early-life exposures to epigenetically-active chemicals may produce health effects later in life even independently of environmental risk factors in adults.[84]

Ho SM, Johnson A, Tarapore P, et al. Environmental Epigenetics and its implication on disease risk and health outcomes. *ILAR Journal*. 2012;53(3-4):289-305. doi: [10.1093/ilar.53.3-4.289](https://doi.org/10.1093/ilar.53.3-4.289).
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4021822/>.

1. epigenetic effects of several major classes of environmental factors are reviewed in the context of pathogenesis of disease. These include endocrine disruptors, tobacco smoke, polycyclic aromatic hydrocarbons, infectious pathogens, particulate matter, diesel exhaust particles, dust mites, fungi, heavy metals, and other indoor and outdoor pollutants.
2. During early development (e.g., embryonic and fetal), epigenetics serves as a key mechanism controlling cell and tissue differentiation by partitioning the genome into transcriptionally active and quiescent domains.
3. Sperms and eggs are highly differentiated cells. After fertilization, epigenetic marks (DNA methylation marks) on sperm DNA are erased within hours; those on the egg remain intact and only begin to be removed during early development ([Migicovsky and Kovalchuk 2011](#)).
4. Epigenetic changes are sensitive readouts of the effects of acute and chronic exposures to environmental factors. However, the responses are often nonlinear and dependent on life stages. An acute, low-dose exposure to an environmental factor, if it occurs during the susceptibility window of development of the fetus, could have far greater effects than high-dose exposure in the adult.
5. Environmental factors such as endocrine disruptors, PAHs, infectious pathogens, outdoor pollutants, indoor allergens, and heavy metals have been shown to trigger epigenetic changes in an exposure- and/or a disease-related manner. These relationships are observed in many complex diseases, including cancer, cardiovascular disease, pulmonary diseases, asthma, obesity, stroke, and neurodegenerative disorders ([Irigaray et al. 2007](#); [Lorenzen et al. 2012](#); [Mathers et al. 2010](#); [Nise et al. 2010](#)).
6. Because epigenetic mechanisms control embryonic development, stem-cell programming, and differentiation, maternal exposure to tobacco smoke can have significant implications for a developing fetus ([Logrieco 1990](#)). Prenatal exposure to cigarettes can lead to increased risk of asthma, pulmonary diseases, and cardiovascular disease later in life ([Breton et al. 2009](#); [Pattenden et al. 2006](#)). Prenatal exposure to tobacco smoke is associated with gene-specific differences in DNA methylation patterns, including demethylation of *AluYb8* and an increase in methylation of *AXL* and *PTPRO* genes, indicating that altered DNA methylation may result in lifelong effects ([Breton et al. 2009](#)).
7. First, most environmental exposures involve mixtures. This is true for indoor and outdoor pollutants, PAHs, diesel exhaust, PM, EDCs, tobacco smoke, and smoke from incomplete combustion. Thus, the classical toxicology approach that focuses on the

health effects of environmental agents, one compound at a time, and on the exposure period to a particular life stage needs to be re-evaluated.

8. The paradigm-shifting concept of defining environmental exposure as an “exposome” ([Wild 2005](#)) has recently emerged. The term refers to the summation of all exposures an individual experiences over his or her lifetime, from conception to advanced age. Furthermore, the nature of these interactions can be synergistic, antagonistic, combinatorial, attenuating, summation, subtractive, opposite, and more.
9. With this concept in mind, genetics, epigenetics, transcriptomics, proteomics, metabolomics, bioinformatics, demographic informatics, exposomics, and the entire life-course forms a multidimensional “interactome” that integrates the internal and external environment to determine the health or disease outcomes of an individual. No solitary constituent of this environmental interactome has the predictive value of the whole.
10. To advance the field of environmental epigenetics and deepen our understanding of the detrimental effects of various environmental factors, we need to conduct future studies using the “interactome” approach. This requires consideration of the multidimensional corroborations between genetics, epigenetics, exposomics, and demographics of the study subjects or the populations.

Combatting epigenetic effects from outdoor air pollution. March 21, 2017. NIH Research Matters, NIH. Reviews research from Columbia University re DNA methylation in CD4+ T-helper cells involved in the inflammatory responses. Online March 13, 2017 in Proceedings of the National Academy of Sciences. <https://www.nih.gov/news-events/nih-research-matters/combating-epigenetic-effects-outdoor-air-pollution>.

Musculoskeletal (Skeletal growth; arthritis)

Musculoskeletal (Skeletal growth)

Holz JD, Sheu TJ, Drissl H, et al. Environmental agents affect skeletal growth and development. *Birth Defects Res C Embryo Today* 2007;81(1):41-50. DOI: [10.1002/bdrc.20087](https://doi.org/10.1002/bdrc.20087). (A number of agents such as heavy metals (i.e. lead) and polycyclic aromatic hydrocarbons (i.e. pesticides and cigarette smoke) interact with cells of the skeletal system and adversely affect development. These agents have not been of major research interest, nevertheless, given changes in the environmental profile of the United States and other developed countries, it is important that we understand their effects in bone and cartilage. Research in this area will identify strategies that may be used to help prevent musculoskeletal diseases due to toxicant exposure. <https://www.ncbi.nlm.nih.gov/pubmed/17539012>.)

Musculoskeletal (Arthritis)

Hart JE, Kallberg H, Laden F et al. Ambient air pollution exposures and risk of rheumatoid arthritis. (Nurses Health Study) *Arthritis Care Res (Hoboken)* 2013;65(7):1190-6. doi: [10.1002/acr.21975](https://doi.org/10.1002/acr.21975). (In this group of socioeconomically advantaged middle-aged and elderly women, adult exposures to air pollution were not associated with an increased RA risk.)

Sun G, Hazlewood G, et al. Association between air pollution and the development of rheumatic disease: A systematic review. *Int J Rheumatol* 2016. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5099457/>. (There was no consistent evidence of an increased risk for the development of rheumatoid arthritis (RA) with exposure to NO₂, SO₂, PM_{2.5}, or PM₁₀. Case-control studies in systemic autoimmune rheumatic diseases (SARDs) indicated higher odds of diagnosis with increasing PM_{2.5} exposure, as well as an increased relative risk for juvenile idiopathic arthritis (JIA) in American children <5.5 years of age. There was no association with SARDs and NO₂ exposure. *Conclusion*. There is evidence for a possible association between air pollutant exposures and the development of SARDs and JIA, but relationships with other rheumatic diseases are less clear.)

Nervous: (mental health; CNS development in kids; Dementia)

Nervous (mental illness, children)

Oudin A et al. Association between neighbourhood air pollution concentrations and dispensed medication for psychiatric disorders in a large longitudinal cohort of Swedish children and adolescents. *BMJ Open* 2016; 6 doi:10.1136/bmjopen-2015-010004.

<http://bmjopen.bmj.com/content/6/6/e010004.full>.

1. Two early studies linked ambient photochemical oxidants to anxiety symptoms⁴ and depression⁵ in humans in California. Monthly or weekly levels of air pollution were observed to be associated with anxiety symptoms in the Nurses' Health Study,⁶ and with perceived stress in the Veterans Administration Normative Aging Study in the USA,⁷ and a number of studies have observed associations between daily fluctuations in air pollution and mental health outcomes such as depressive symptoms, suicide and emergency calls.^{8–16}
2. Swedish National Register data. Cohort size 552,221.
3. The mean annual level of NO₂ was 9.8 µg/m³. Children and adolescents living in areas with higher air pollution concentrations were more likely to have a dispensed medication for a psychiatric disorder during follow-up (HR=1.09, 95% CI 1.06 to 1.12, associated with a 10 µg/m³ increase in NO₂). The association with NO₂ was clearly present in 3 out of 4 counties in the study area; however, no statistically significant heterogeneity was detected.
4. **Conclusion** There may be a link between exposure to air pollution and dispensed medications for certain psychiatric disorders in children and adolescents even at the relatively low levels of air pollution in the study regions.

Lundberg A. Psychiatric aspects of air pollution. *Otolaryngol Head Neck Surg* 1996;114(2):227-31. <https://www.ncbi.nlm.nih.gov/pubmed/8637739>.

1. Psychological and toxic effects of air pollution can lead to psychiatric symptoms, including anxiety and changes in mood, cognition, and behavior. Increased levels of some air pollutants are accompanied by an increase in psychiatric admissions and emergency calls and, in some studies, by changes in behavior and a reduction in psychological well-being.
2. Expanded research is recommended in three main areas: (1) how people perceive and cope with environmental health risks, (2) the effects of air pollution on behavior and neuropsychological functioning, and (3) neurotoxicologic evaluation of air pollutants with both behavioral and in vitro studies.

3. (NOTE: this simple clear paper was published in 1996)

Weir K. Smog in our brains. American Psychological Association (Review of research re pollution and children's cognitive abilities, risks of adults' cognitive decline.

<http://www.apa.org/monitor/2012/07-08/smog.aspx>.

Nervous (CNS Development in children)

Winneke G. Neurodevelopmental and Behavioral Effects. In Effects of Air Pollution on Children's Health and Development. WHO. A Review of the Evidence.

http://www.euro.who.int/_data/assets/pdf_file/0010/74728/E86575.pdf.

1. Among the groups of environmental chemicals for which neurodevelopmental and neurobehavioural effects in children are to some extent documented are some heavy metals and polyhalogenated aromatic hydrocarbons (PHAHs). The former primarily include lead, mercury and (less frequently) manganese, whereas the most extensively studied PHAH species include the polychlorinated biphenyls (PCBs); although the dioxins are also of relevance, there is typical co-exposure with the PCBs such that it is almost impossible to distinguish between PCBs and dioxins in paediatric cohort studies.
2. A recent report of a cohort study run in the city of Rochester, New York, has received particular interest because it demonstrated lead-related IQ deficits extending below the presumed critical level of 100 µg/l blood (26). The study cohort comprised 240 children. After careful adjustment for a set of predetermined confounders, an overall significant negative correlation between lifetime average PbB concentration and IQ was observed, with an effect size of 0.46 point deficit for each 10 µg/l.

Brockmeyer S, D'Angiulli. How air pollution alters brain development; role of neuroinflammation. *Translational Neuroscience* 2016;7(1). <https://www.degruyter.com/view/j/tnsci.2016.7.issue-1/tnsci-2016-0005/tnsci-2016-0005.xml>.

1. The present review synthesizes lines of emerging evidence showing how several samples of children populations living in large cities around the world suffer to some degree neural, behavioral and cognitive changes associated with air pollution exposure. The breakdown of natural barriers warding against the entry of toxic particles, including the nasal, gut and lung epithelial barriers, as well as widespread breakdown of the blood-brain barrier facilitate the passage of airborne pollutants into the body of young urban residents.
2. Extensive neuroinflammation contributes to cell loss within the central nervous system, and likely is a crucial mechanism by which cognitive deficits may arise. Although subtle, neurocognitive effects of air pollution are substantial, apparent across all populations, and potentially clinically relevant as early evidence of evolving neurodegenerative changes. The diffuse nature of the neuroinflammation risk suggests an integrated neuroscientific approach incorporating current clinical, cognitive, neurophysiological, radiological and epidemiologic research. Neuropediatric air pollution research requires extensive multidisciplinary collaborations to accomplish the goal of protecting exposed children through

multidimensional interventions having both broad impact and reach. While intervening by improving environmental quality at a global scale is imperative, we also need to devise efficient strategies on how the neurocognitive effects on local pediatric populations should be monitored.

Nervous (Dementia)

Underwood E. The Polluted Brain: Evidence builds that dirty air causes Alzheimer's dementia. AAAS Science. January 26, 2017: <http://www.sciencemag.org/news/2017/01/brain-pollution-evidence-builds-dirty-air-causes-alzheimer-s-dementia>.

1. Growing number of epi studies world-wide with data from animal and human studies a major concern especially exposure to PM2.5.
2. 11- year epi study published in Translational Psychiatry, USC researchers: living where EPA stds of 12 micrograms/m³ nearly doubled dementia risk in older women.
3. If replicated, findings suggest roughly 21% of dementia cases worldwide may be causally related to PM2.5 (Jiu-Chiuan Chen, Keck School of Medicine at USC).

Jennifer Weuve, Robin C. Puett, Joel Schwartz, et al: "Exposure to Particulate Air Pollution and Cognitive Decline in Older Women." Archives of Internal Medicine, Vol. 172 (No. 3), pages 219-227, 2012. <http://jamanetwork.com/journals/jamainternalmedicine/fullarticle/1108716>

1. Chr expos to PM2.5-10 may accelerate cognitive decline in older adults—data limited.
2. Nurses Health Study Cognitive Cohort 19409 US women 70-81. One mo and long term exposure studied.
3. Higher levels of long-term exposure to both PM2.5-10 assoc with significantly faster cognitive decline.
4. Effect of a 10 microg/m³ increment in LT PM exposure is cognitively equivalent to aging by about 2 yrs.

Block ML, Elder A, Auten R, et al The outdoor air pollution and brain health workshop. NeuroToxicity 2012;33(5):972-984. (EXCELLENT OVERVIEW OF Voluminous SCIENCE in this area) <http://www.sciencedirect.com/science/article/pii/S0161813X12002100>.

1. NIEHS/NIH convened panel of scientists to identify research gaps re this emerging human health concern.
2. Recent epi and animal toxicology studies have raised concerns about the potential impact of AP (CNS) outcomes including chronic brain inflammation, microglia activation, and white matter abnormalities leading to increased risk for autism spectrum disorders, lower IQ in children, neurodegenerative diseases (Parkinson's disease, PD; Alzheimer's disease, AD), multiple sclerosis, and stroke, as discussed below.
3. Human reports of effects of AP on brain reviewed.

4. Human studies have also shown that living in conditions with elevated AP pollution is linked to decreased cognitive function (Calderon-Garciduenas et al., 2008a, Chen and Schwartz, 2009, Power et al., 2011, Ranft et al., 2009, Suglia et al., 2008 and Weuve et al., 2012), lower neurobehavioral testing scores in children (Wang et al., 2009), a decline in neuropsychological development in the first 4 years of life (Morales et al., 2009), AD- and PD-like neuropathology (Calderon-Garciduenas et al., 2004, Calderon-Garciduenas et al., 2010, Calderon-Garciduenas et al., 2012 and Morales et al., 2009), increased stroke incidence (Mateen and Brook, 2011, Donnan et al., 1989, Henrotin et al., 2007 and Villeneuve et al., 2006), and elevated autism risk (Volk et al., 2011).
5. Evidence is accumulating for air pollution related CNS effects at multiple levels, including modulation of molecular/neurochemical/pathobiological pathways, neuroinflammation, neurotoxicity, and neurobehavioral changes that implicate subclinical/clinical manifestation of disease. However, the extent of these effects contributing to ill health, the components of air pollution responsible and the molecular mechanisms underlying the phenomena are poorly understood.

My bias is that there is overwhelming experimental, animal, human, epi and other evidence of a causal relationship between exposure to AP and CNS disease---more than enough to use the published literature to make the point and add neuro disease to the growing list of diseases associated with AP and the urgency to decrease ambient air pollution in IN and the country (world)---soon.

Renal

Fan Fan Hou, MD, PhD and Xin Xu, MD, PhD et al. **Long-Term Exposure to Air Pollution and Increased Risk of Membranous Nephropathy in China.** *Journal of the American Society of Nephrology*, June 2016 DOI: 10.1681/ASN.2016010093, <https://www.sciencedaily.com/releases/2016/06/160630214505.htm>.

1. Our primary finding is that the frequency of membranous nephropathy has doubled over the last decade in China. We show that the increase corresponds closely with the regional distribution of particulate air pollution

Reproduction:

Infertility (sperm and eggs) cervix; uterus implantation; ovarian function; ?other

Reproduction: Infertility:

Frutos V, Comadran M, Sola I, Jacquemin B, et al. Impact of air pollution on fertility: a systematic review. *Gynecol Endocrinol* 2015;31(1):7-13. <https://www.ncbi.nlm.nih.gov/pubmed/25212280>.

1. Focus: live birth, miscarriage, clinical pregnancy, implantation, and embryo quality.
2. 10 studies animal and human. Include epi studies and IVF/embryo transfer.
3. Results: sign impact of AP on miscarriage and clinical pregnancy rates in general pop.

4. In subfertile patients certain air pollutants seem to exert a greater impact on fertility outcomes, including miscarriage and live birth rates.
5. Lack of prospective studies problematic.

Adult air pollution exposure and risk of infertility in the Nurses' Health Study II. Mahalingaiah, S., Hart, J. E., Laden, F., Farland, L. V., Hewlett, M. M., Chavarro, J., Aschengrau, A., Missmer, S. A.; Hum. Reprod.. 2016 Jan 03. <https://www.ncbi.nlm.nih.gov/pubmed/26724803>
<http://humrep.oxfordjournals.org/content/31/3/638.long>.

1. Nurses Health Study Cohort 1989-2003 116,430 female nurses.
2. 36,294 included in analysis. AP and traffic exhaust near their homes analyzed.
3. 2508 incident reports of infertility.
4. Women living within 199 meters (about tenth of mi) were 11% more likely to have infertility than women living farther away from highway.
5. HR = 1.11 (CI 1.02-1.20) Primary or secondary infertility.
6. Strongest assoc observed between cumulative average exposures over the course of follow-up and risk of infertility—suggests chronic exposures may be of greater importance than short-term.
7. Since so many women are exposed to AP the 11% risk is a major public health problem affecting large numbers of women.
8. We observed association between incidence of infertility with roadway proximity and exposures to PM. Effect estimates for chronic exposures slightly elevated compared to that of 2- and 4-yr estimates. Suggest that chronic exposures may be of greater importance than short-term exposures, or that cumulative exposures may be more closely related to the time of infertility onset, as opposed to diagnosis. Further studies needed to confirm these associations. Prospective studies evaluating time to pregnancy in vulnerable populations such as those living close to sources of air pollution is warranted.

Checa Vizcaino MA, Gonzalez-Comadran M, Jacquemin B. Outdoor air pollution and human infertility: a systematic review. Fertility and Sterility. 2016;106(4):897-904. (Barcelona Spain—52 ref) <http://www.sciencedirect.com/science/article/pii/S0015028216625487>.

1. Systematic review; significantly associated with increased AP and decreased **fertility rates** in exposed population. Possibly due to traffic air pollution.
2. PM 2.5 associated with reduced fertility rates; reduced live birth rates and increased risk of miscarriage in IVF.
3. NO₂ associated with increase in **miscarriage rates**. And IVF decrease in **live birth rates**.
4. SO₂ causes chromosomal aberrations in in vitro studies. SO₂ associated with a slightly increased rate of miscarriages in the general and the sub-fertile population.
5. CO increases miscarriage rates.
6. There is biological plausibility of the above observed fertility decline in humans since experimental mammals have decrease in offspring when exposed to AP.
7. Possible causes: endocrine disruption and hormonal imbalance; heavy metals in PM are associated with **ova toxicity with premature ovarian failure**. Adverse impacts of

AP on sperm morphology, concentration and motility; **immune-mediated** injury during embryo develop. Increased carboxyhemoglobin in nucleated RBC are markers of fetal hypoxia—seen with CO in AP. Changes in **vascular compartment** of uterus reported in women exposed to AP who have miscarried.

8. Literature flawed by definitions; populations; various AP measurements; and no prospective trials.

Reproduction: Erectile Dysfunction in Older Men. Environmental Health Perspectives. ISEE. 2015. [iatehttps://ehp.niehs.nih.gov/isee/2015-2408/](https://ehp.niehs.nih.gov/isee/2015-2408/). Abstract Number 2408;ID:2015-2408.

1. ED status obtained in 2993 men (age 57-85) participating in National Social Life, Health and Aging Project—community dwelling older Americans. PM 2.5, summer O3 and NO2 were measured within 60 km of each participants' homes.
2. Logistic regression models, conditional logistic regression controlling for potential confounders. Exposure to O3 was associated with increased odds of developing ED among older men.

Fetal Growth:

Dejmek J, Selevan SG, Benes I, et al Fetal growth and maternal exposure to particulate matter during pregnancy. Environ Health Perspect 1999;107(6):475-480.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1566587/>.

1. Prior studies reported an association between ambient air concentrations of total suspended particles and SO2 during pregnancy and adverse pregnancy outcomes. We examined the possible impact of particulate matter up to 10 microm (PM10) and up to 2.5 microm (PM2.5) in size on intrauterine growth retardation (IUGR) risk in a highly polluted area of Northern Bohemia (Teplice District).
2. Adjusted ORs for IUGR related to ambient PM10 levels in the first gestational month increased along the concentration intervals: medium 1.62 [95% confidence interval (CI), 1.07-2.46], high 2.64 (CI, 1.48-4.71). ORs for PM2.5 were 1.26 (CI, 0.81-1.95) and 2.11 (CI, 1.20-3.70), respectively. No other associations of IUGR risk with particulate matter were found. Influence of particles or other associated air pollutants on fetal growth in early gestation is one of several possible explanations of these results.

Birth Outcomes:

Birth Outcomes: General

NIHEHS (National Institute of Environmental Health Sciences. EHP Children's Health Collection, 2014. (Review of science regarding disease outcomes, exposures to Air Pollutants, etc.)

<http://ehp.niehs.nih.gov/wp-content/uploads/chc/2014/CH-2014-final.alt.pdf>.

1. Includes sections on lung, neuro, autism, cancer, birth defects, eyes and ears, pregnancy outcomes, Infections, perinatal or early life exposures contributing to adult disease and obesity. Exposures include: heavy metals, pesticides and other chemicals, air pollution, climate change, radiation and built environment.

2. Fleischer NL, Meriardi M, van Donkelaar A, et al. Outdoor air pollution, preterm birth and low birth weight: Analysis of the WHO Global survey on Maternal and Perinatal Health. April 2014;122:425-430. (Outdoor PM2.5 associated with low BW.)
3. Vizcaino E, Grimalt et al. Gestational weight gain and exposure of newborns to persistent organic pollutants. August 2014;122:873-79. (Findings: suggest association between neonatal exposure to persistent organic pollutants and gestational weight gain during pregnancy.)
4. Rappazzo KM et al Exposure to PM during pregnancy and risk of preterm birth among women in NJ, OH, PENN, 2000-05. Sept 2014;122:992-97. (Exposures beginning around time of implantation and near birth more strongly assoc with preterm birth than exposures during other time periods.)
5. Dadvand P, Figueras F, Basagana X, et al. Ambient air pollution and preeclampsia: A spatiotemporal analysis. Nov-Dec 2013; 121:1365-1371. (Increased risk of preeclampsia associated with exposure to PM pollution. Our findings in combination with previous evidence suggesting distinct pathogenic mechanism for early-and late-onset preeclampsia support additional research on this topic.)

WHO European Centre for Environment and Health 2005. Effects of Air Pollution on Children's Health and Development. A Review of Evidence.

http://www.euro.who.int/_data/assets/pdf_file/0010/74728/E86575.pdf.

1. Sram Rj, Binkova B, Dejmek J, et al. Intrauterine growth retardation, low birth weight, prematurity and infant mortality. (Chapt 2, p14-) Summary: Overall, there is evidence implicating air pollution in adverse effects on birth out- comes, but the strength of the evidence differs between outcomes. The evidence is solid for infant mortality: this effect is primarily due to respiratory deaths in the post-neonatal period and it appears to be mainly due to particulate air pollution. Studies on birth weight, preterm births and IUGR also suggest a link with air pollution, but there were important inconsistencies in the results that were probably due to differences in design and measurement of exposure(s). Molecular epidemiological studies suggest biological mechanisms for the effect on birth weight and IUGR, and thus suggest that the link between pollution and these birth out- comes is genuine.
2. There is now substantial evidence concerning adverse effects of air pollution on different pregnancy outcomes and infant health.
3. Molecular epidemiological studies suggest possible biological mechanisms for the effect on birth weight, premature birth and intrauterine growth retardation, and support the view that the relationship between pollution and these pregnancy outcomes is genuine.
4. A significant body of evidence supports the explanation that much of the morbidity and mortality related to air pollution in children occurs via interactions with respiratory infections, which are very frequent among children.

Kelly FJ, Fussell JC. Air pollution and public health: emerging hazards and improved understanding of risk. Environ Geochem Health 2015;37(4):631-49.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4516868/>.

Brown JM, Harris G, Pantea C. Linking air pollution data and adverse birth outcomes: environmental public health tracking in NY state. *J Public Health Management & Practice*. 2015; 21 Suppl 2:S68-74.

1. 2001-2006 Final sample size 480,430 births of which 9782 (2.04%) were TLBW.
2. Conclusion: Little evidence to support positive associations between exposure to ozone or PM2.5 and TLBW (term low BW)
3. Authors have a page of numerous potential confounding factors, exposure misclassification, missing data.

Evidence suggests a causal relationship between exposure to ambient air pollution and increased incidence of upper and lower respiratory symptoms (many of which are likely to be symptoms of infection)

Birth Outcomes: Sudden Infant Death

Glinianaia SV, Rankin J, Bell R et al. Does particulate air pollution contribute to infant death? A systematic review. *Environ Health Perspect* 2004;112(14):1365-70.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1247561/>.

1. There is now substantial evidence that both short- and long-term increases in ambient air pollution are associated with increased mortality and morbidity in adults and children. Children's health is particularly vulnerable to environmental pollution, and infant mortality is still a major contributor to childhood mortality.
2. There was some evidence that the strength of association with particulate matter differed by subgroups of infant mortality. It was more consistent for post-neonatal mortality due to respiratory causes and sudden infant death syndrome. Differential findings for various mortality subgroups within studies suggest a stronger association of particulate air pollution with some causes of infant death.

Dales R, Burnett RT et al. Air pollution and Sudden Infant Death Syndrome. *Pediatrics* 2004;113.
<http://higienis.com/beta/wp-content/uploads/2011/08/Air-Pollution-and-Sudden-Infant-Death-Syndrome.pdf>.

1. Increases in both SO₂ and NO₂ were associated with a 17.72% increase in SIDS incidence.
2. 12 Canadian cities, time series analyses.

Armstrong HS, Wilkinson P, Busby A, Dolk H. National SIDS/Infant Death Resource Center. SIDS and air pollution: a selected annotated bibliography. *J Epidemiol Comm Health* 2007;61(8):719-22.
<https://www.ncemch.org/suid-sids/documents/SIDRC/AirPollution.pdf>.

1. Few associations were observed between infant deaths and most pollutants studied. The exception was sulphur dioxide (SO₂), of which a 10 µg/m³ increase was associated with a RR of 1.02 (95% CI 1.01 to 1.04) in all infant deaths. The effect was present in both neonatal and postneonatal deaths.

2. CONCLUSIONS: Continuing reductions in SO₂ levels in the UK may yield additional health benefits for infants.

Litchfield I, et al. Role of air pollution as a determinant of SIDS: A systematic review and Meta analysis. *Epidemiology*. 2011;22(1):S165-S166. DOI: 10.1097/01.ede.0000392182.47995.3c.

1. Both short-term exposure to NO₂ and CO prior the onset as well as long-term exposure to these pollutants in early infancy or months prior to the onset increase the risk of SIDS. In addition, short-term exposure to SO₂ may play a role in the onset of SIDS, but the role of PM₁₀ and PM_{2.5} remains inconclusive.
2. Nine studies included. Risk of SIDS estimated to increase by 8% (CI 4-14%) per 10 ppb exposure to NO₂ and 9% per 1ppm exposure to CO. The results for SO₂ and O₃ were inconclusive. The risk of SIDS was related to levels of NO₂ and CO exposure during the 3 days preceding the onset, as well as to the previous day level of SO₂.

Birth Outcomes: Birth Weight

Li L, Laurent O, Wu J. Spatial variability of the effect of air pollution on term birth weight: evaluating influential factors using Bayesian hierarchical models. *Environ Health* 2016;15:14. <http://ehjournal.biomedcentral.com/articles/10.1186/s12940-016-0112-5>.

1. Epidemiological studies have frequently linked air pollution with adverse birth outcomes [3].
2. 900,000 birth records 2001-08 in LA County CA, USA. Air pollution exposure modeled at individual level for NO₂, NO_x using spatiotemporal models
3. Higher air pollution exposure was associated with lower term birth weight (average posterior effects: -14.7 (95 % CI: -19.8, -9.7) g per 10 ppb increment in NO₂ and -6.9 (95 % CI: -12.9, -0.9) g per 10 ppb increment in NO_x).
4. The variation of the association across Census tracts was significantly influenced by the tract-level socio-demographic, exposure-related and land-use factors.
5. Our models captured the complex non-linear relationship between these factors and the associations between air pollution and term birth weight: we observed the thresholds from which the influence of the tract-level factors was markedly exacerbated or attenuated. Exacerbating factors might reflect additional exposure to environmental insults or lower socio-economic status with higher vulnerability, whereas attenuating factors might indicate reduced exposure or higher socioeconomic status with lower vulnerability.
6. Exposure to toxic compounds in traffic-generated air pollutants may result in impaired placental hemodynamics with subsequent reduction of nutrients and oxygen supply, which reduces intrauterine growth and probably causes low birth weight [1]. The adverse health effect of air pollution is likely heterogeneous in space and possibly influenced by other environmental, socioeconomic, demographical and psychological factors [3, 5, 6, 7]. In particular, neighborhood socioeconomic status (SES) was found to be significantly associated with the heterogeneity of the effects of air pollution on birth weight [8, 9].

7. A few studies quantified between-region heterogeneity of air pollution effects. Dadvand et al. [10] reported stronger associations of reduction in term birth weight with higher median levels of particulate matter (PM) with diameter $<2.5 \mu\text{m}$ (PM_{2.5}) across 14 study centers from North America, Europe, South America and Asia.
8. To our knowledge, this is the first study employing the Bayesian non-linear approach to examine spatial variability of the effects of air pollution on term birth weight across Census tracts and the factors contributing to such variability.
9. This study developed a new two-stage hierarchical model based on a Bayesian framework to quantify the effects of air pollution exposure on term birth weight and examine the factors contributing to spatial variability of such effects across Census tracts. The posterior results confirmed the adverse effect of air pollution on term birth weight.
10. (This is an excellent paper.)

Hien QL, Batterman SA, Wirth JJ, et al. Air pollutant exposure and preterm and term small for gestational age births in Detroit, MI: long term trends and associations. *Environ Int* 2012;44:7-17.

1. We investigated the association between ambient air pollutant concentrations and term SGA and PTB outcomes among 164,905 singleton births in Detroit, Michigan occurring between 1990 and 2001. SO₂, CO, NO₂, O₃ and PM₁₀ exposures were used in single and multiple pollutant logistic regression models to estimate odds ratios (OR) for these outcomes, adjusted for the infant's sex and gestational age, the mother's race, age group, education level, smoking status and prenatal care, birth season, site of residence, and long-term exposure trends.
2. Term SGA was associated with CO levels exceeding 0.75 ppm (OR=1.14, 95% confidence interval=1.02–1.27) and NO₂ exceeding 6.8 ppb (1.11, 1.03–1.21) exposures in the first month, and with PM₁₀ exceeding 35 $\mu\text{g}/\text{m}^3$ (1.22, 1.03–1.46) and O₃ (1.11, 1.02–1.20) exposure in the third trimester. PTB was associated with SO₂ (1.07, 1.01–1.14) exposure in the last month, and with (hourly) O₃ exceeding 92 ppb (1.08, 1.02–1.14) exposure in the first month.
3. This study, which included a large Black population, suggests the importance of the early period of pregnancy for associations between term SGA with CO and NO₂, and between O₃ with PTB; and the late pregnancy period for associations between term SGA and O₃ and PM₁₀, and between SO₂ with PTB. It also highlights the importance of accounting for individual risk factors such as maternal smoking, maternal race, and long-term trends in air pollutant levels and adverse birth outcomes in evaluating relationships between pollutant exposures and adverse birth outcomes.
1. Other than the well-documented effects on respiratory and cardiovascular health, an increasing number of studies have investigated the potential of PM air pollution to negatively influence several new health outcomes. We now have evidence linking long-term exposure to PM_{2.5} with adverse birth outcomes, whilst emerging data suggest possible effects of long-term PM_{2.5} exposure on diabetes, neurodevelopment, cognitive function.
2. Harmful effects have been shown for low birth weight, small for gestational age and preterm birth (Ritz and Wilhelm [2008](#); Sapkota et al. [2012](#); Proietti et al. [2013](#)).

Huang C, Nichols C, Liu Y, et al. Ambient air pollution and adverse birth outcomes: a natural experiment study. *Popul Health Metr* 2015;12:17. 10.1186/s12963-015-0050-4.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4506631/>.

1. Beijing Olympics 2008-radical regs to improve air quality. NO₂ and PM₁₀ were reduced in short window of time. Natural experiment for PM₁₀ and NO₂ during pregnancy and adverse birth outcomes.
2. Results: FT births: maternal exposure to NO₂ in 3rd trimester predicted birth weight with each 10 unit increment (per 10 microg/m³) in Now assoc with 13.78 g (CI - 21.12, --6.43; p< 0.0001 reduction in BW.
3. Assoc maintained after adj for CO, SO₂, PM₁₀. No relationship was found between the concentration of PM₁₀ and LBW among full-term births. Neither PM₁₀ nor NO₂ concentrations predicted risk of premature birth.
4. Conclusion: Exposure to ambient air pollution during certain periods of pregnancy may decrease birth weight, but the effect size is small.
5. Study has serious limitations re exposures, confounders. Need for biomarkers of exposure and prospective design.

Trasande L, Malecha, P and Attina TM. Particulate matter exposure and preterm birth: estimates of US. Attributable burden and economic costs. *Environ Health Perspect*. 2015. DOI:

10.1289/ehp.1510810. <http://ehp.niehs.nih.gov/wp-content/uploads/advpub/2016/3/ehp.1510810.acco.pdf>.

1. PM_{2.5} may contribute to burden and costs of Pre term birth in U.S. Health and economic benefits could be achieved through environmental regulatory interventions that reduce PM_{2.5} in pregnancy.
2. Estimated 3.32% of PTBs nationally (15,808) in 2010 attributed to PM_{2.5} (PM_{2.5}>8.8 µg/m³) Attributable PTB cost: \$4.33 billion (SA: \$2.06-8.22B) of which \$760 million spent for medical care (SA 362M-1.44 B).
3. Highest PM_{2.5} attributable fraction highest in urban counties in Ohio valley and southern US.

Sapkota A, Chelikowsky AP, Nachman KE et al Exposure to particulate matter and adverse birth outcomes: a comprehensive review and meta-analysis. *Air Qual Atmos Health* 2012;5:369.

doi:10.1007/s11869-010-0106-3. <http://link.springer.com/article/10.1007/s11869-010-0106-3>.

1. Comprehensive review of peer-reviewed lit and meta-analysis re association between maternal exposure to particulate matter PM_{2.5-10} during pregnancy and risk of LBW and PTB.
2. 20 articles met criteria.
3. Results from random-effect meta-analysis suggested a 9% increase in risk of LBW associated with a 10-µg/m³ increase in PM_{2.5} (combined odds ratios (OR), 1.09; 95% confidence interval (CI), 0.90–1.32), but our 95% CI included the null value. We estimated a 15% increase in risk of PTB for each 10-µg/m³ increase in PM_{2.5}

(combined OR, 1.15; CI, 1.14–1.16). The magnitude of risk associated with PM10 exposure was smaller (2% per 10- $\mu\text{g}/\text{m}^3$ increase) and similar in size for both LBW and PTB, neither reaching formal statistical significance. We observed no significant publication bias, with $p > 0.05$ based on both Begg's and Egger's bias tests. Our results suggest that maternal exposure to PM, particularly PM2.5 may have adverse effect on birth outcomes.

Maisonet M, Bush TJ, Correa A, Jaakkola JJ: Relation between ambient air pollution and low birth weight in the Northeastern United States. *Environ Health Perspect.* 2001, 109: 351-356. 10.1289/ehp.01109s3351. <https://www.ncbi.nlm.nih.gov/pubmed/11427384>.

1. Our results suggest that exposures to ambient CO and SO(2) increase the risk for term LBW.
2. This risk increased by a unit increase in CO third trimester average concentration [adjusted odds ratio (AOR) 1.31; 95% confidence interval (CI) 1.06,1.62]. Infants with SO(2) second trimester exposures falling within the 25 and < 50th (AOR 1.21; CI 1.07,1.37), the 50 to < 75th (AOR 1.20; CI 1.08,1.35), and the 75 to < 95th (AOR 1.21; CI 1.03,1.43) percentiles were also at increased risk for term LBW when compared to those in the reference category (< 25th percentile). There was no indication of a positive association between prenatal exposures to PM(10) and term LBW. Increased ambient levels of air pollution may be associated with an increased risk for LBW.

Seo JH, Leem JH, Ha EH, et al Population-attributable risk of low birthweight related to PM 10 pollution in 7 Korean cities. *Paediatr Perinat Epidemiol* 2010;24(2):140-8. doi: 10.1111/j.1365-3016.2009.01085.x. <https://www.ncbi.nlm.nih.gov/pubmed/20415770>.

1. We investigated the association between maternal exposure to air pollution during pregnancy and LBW, and calculated the Population Attributable Risk for air pollution and LBW in seven Korean cities.
2. Birth records from the Korean National Birth Register for 2004. A geographic information system and kriging methods used to construct exposure models. Associations between air pollution and LBW were evaluated using univariable and multivariable logistic regression; PAR for LBW due to air pollution was calculated. Of 177 660 full-term singleton births, 1.4% were LBW. When only spatial variation of air pollution was considered in each city, the adjusted odds ratios unit of particulate matter <10 microm in diameter (PM(10)) for LBW were 1.08 [95% confidence interval [CI] 0.99, 1.18] in Seoul, 1.24 [95% CI 1.02, 1.52] in Pusan, 1.19 [95% CI 1.04, 1.37] in Daegu, 1.12 [95% CI 0.98, 1.28] in Incheon, 1.22 [95% CI 0.98, 1.52] in Kwangju, 1.05 [95% CI 1.00, 1.11] in Daejeon and 1.19 [95% CI 1.03, 1.38] in Ulsan. The PARs for LBW attributable to maternal PM(10) exposure during pregnancy were 7%, 19%, 16%, 11%, 18%, 5% and 16% respectively. Because a large proportion of pregnant women in Korea are exposed to PM(10)--which is associated with LBW--a substantial proportion of LBW could be prevented in Korea if air pollution was reduced.

Pedersen M, Giorgis-Allemand L, Bernard C, Aguilera I, Andersen AM, Ballester F, Beelen RM, Chatzi L, Cirach M, Danileviciute A, Dedede A, Eijdsen M, Estarlich M, Fernández-Somoano A, Fernández MF, Forastiere F, Gehring U, Grazuleviciene R, Gruzieva O, Heude B, Hoek G, de Hoogh K, van den Hooven EH, Håberg SE, Jaddoe VW, Klümper C, Korek M, Krämer U, Lerchundi A, Lepeule J, et al: Ambient air pollution and low birthweight: a European cohort study (ESCAPE).

Lancet Respir Med. 2013, 1 (9): 695-704. 10.1016/S2213-2600(13)70192-9.

Evenson et al 2006 <https://www.scsadiagnostics.com/uploads/news/Theriogenology.pdf>

1. Sperm DNA fragmentation (due to apoptotic events of reactive oxygen species (DFIndex) caused by reactive oxygen species. Oxidative stress ROS. DNA frag linked to (cryptorchidism, CA, varicocele, fever, age, infection and leukocytospermia. Environmental factors can affect DNA frag: chemo, radiation, prescribed meds, air pollution, smoking, pesticides, chemicals, heat.
2. Czech study: episodic air pollution assoc with poor semen quality and sperm DNA damage. Selevan et al. seasonal air pollution and semen quality. Environ Health Perspective 2000;108(9):887-. Harmful metabolites from polycyclic aromatic hydrocarbons in polluted air are detoxified by glutathione S transferase. ? men lacking gene for this enzyme are susceptible to AP resulting in sperm DNA damage. Pollutants. For IVF patients some experts do DNA frag testing to predict success in IVF cycles.

Auger J, et al Decline in Semen Quality...Paris over 20 yrs. New Engl J Med 1995;332:281-85. <http://www.nejm.org/doi/full/10.1056/NEJM199502023320501#t=article>.

Environmental pollution suggested (without data) to be one cause. Ref 29 Giwercman

Giwercman A, Carlsen E, Keiding N et al. Evidence for increasing incidence of Abnormalities of the Human Testis: A review. Environ Health Perspect (Suppl) 1993;101(Suppl. 2):65-71.

1. The higher sperm density in Hawaiian men compared with Continental US may be due to lower atmospheric concentration of chemical pollutants (14) Murature DA, et al Phthalate esters and semen quality parameters. Biomed. Environ Mass. Spectr 14:473-77, 1987.

Trasande L, Wong K, Roy A, et al. Exploring prenatal outdoor air pollution, birth outcomes and neonatal health care utilization in a nationally representative sample. J Expo Sci Environ Epidemiol. 2013;23(3):315-21. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4391972/>.

1. No study has examined air pollution impacts on neonatal health care utilization.
2. descriptive, univariate and multivariable analyses on adm hospital record data from 222,359 births in the 2000, 2003 and 2006 Kids Inpatient Database linked to air pollution data drawn from the US Environmental Protection Agency's Aerometric Information Retrieval System.
3. PM2.5; NO₂, O₃, CO – 3 or 4 pollutant models.
4. increased low birth weight and neonatal health care utilization.
5. a three-pollutant model controlling for hospital characteristics, demographics, and birth month identified 9.3% and 7.2% increases in odds of low birth weight and very low birth weight for each µg/m³ increase in PM2.5 (both P<0.0001).
6. A \$1166 increase in per child costs was estimated for the birth hospitalization per p.p.m. CO (P=0.0002) and \$964 per unit increase in O₃ (P=0.0448).

Reproduction: Placental abruption; placenta previa

Ananth CV. Air pollution and risk of placental abruption in NY city. (proposed research protocol 2015—17) NIEHS.

http://tools.niehs.nih.gov/portfolio/index.cfm/portfolio/grantDetail/grant_number/R21ES025845

1. Placental abruption places a tremendous health burden on both the mother and the newborn, and efforts to understand the underpinnings of this devastating obstetrical complication have been disappointing.
2. Given that a fourth of all abruption cases have an acute etiology, the role of environmental triggers is a critically important, yet unexplored, opportunity to understand the pathophysiology of abruption. The project will capitalize on hospital discharge data linked to both stillbirths and live birth-infant deaths to resident mothers in New York City. These data, with geocoded residence information, include an estimated 840,000 births (about 7,000 abruption cases of which 4,810 will be "severe" cases to New York City residents during the period 2008-14. For each pregnancy, we will assign ambient exposure to fine particulate matter with an aerodynamic diameter $<2.5 \mu\text{M}$ (PM_{2.5}), its constituents (nickel, zinc, and iron), black carbon (BC) and gaseous pollutants including nitrogen dioxide (NO₂), ozone (O₃), and sulfur dioxide (SO₂) based on residential address and gestational age at the time of the exposure.
3. Given the ubiquitous nature of the air pollutants and their potential impact of adverse perinatal outcomes, and virtually no data on placental abruption, the proposed project represents a unique opportunity to make discoveries that will improve maternal and infant health and guide public health policy.

Erickson AC, Arbour L. The shared pathoetiological effects of particulate air pollution and the social environment on fetal-placental development. *J Environ and Public Health*. 2014.

<https://www.hindawi.com/journals/jep/2014/901017/>.

1. Exposure to particulate air pollution and socioeconomic risk factors are shown to be independently associated with adverse pregnancy outcomes; however, their confounding relationship is an epidemiological challenge that requires understanding of their shared etiologic pathways affecting fetal-placental development.
2. We review the experimental and epidemiological literature showing that diet/nutrition, smoking, and psychosocial stress share similar pathways with that of particulate air pollution exposure to potentially exasperate the negative effects of either insult alone.
3. The first trimester is a critical period in pregnancy involving implantation and initial placentation, two events highly susceptible to disturbance. The "Great Obstetrical Syndromes" [60] such as early/recurrent miscarriage, pregnancy induced hypertension and preeclampsia (PIH/PE), fetal growth restriction (FGR), placental abruption, prelabour rupture of the fetal membranes (PROM), and spontaneous preterm labour may share common etiological mechanisms arising from defective

deep placentation (DDP) [61, 62]. Together, these conditions may complicate between 17 and 29% of all pregnancies. [63]

4. Air pollution is a general term used to describe the presence of agents (particulates, biologicals, and chemicals) in outdoor or indoor air that negatively impact human health. Several common air pollutants have been associated with APOs, including carbon monoxide (CO), nitrogen dioxide (NO₂), sulfur dioxide (SO₂), ozone, particulate matter (PM), and polycyclic aromatic hydrocarbons (PAHs) [1]; however, attention has focused on the latter two compounds showing strong molecular evidence of cytotoxicity, mutagenicity, DNA damage, oxidative stress, and inflammation [55, 74–79]. While the observed risks of APOs in relation to air pollution tend to be modest, the population attributable risk can be quite large due to the pervasiveness of exposure to the general population [9]. Significant risks have been observed even in settings with relatively low ambient air pollution exposure [80, 81]. Therefore, a small increase in risk can have a large public health impact. Preterm birth (PTB) and FGR are major risk factors of perinatal mortality and serious infant morbidities contributing to increased health care and societal costs [82–87].
5. There is accumulating evidence that suggests UFPs may be the fraction of PM responsible for many of the adverse health effects reported in air pollution studies [78, 79, 97, 98]. UFPs are a small proportion by mass but make up a large proportion in particle number and have gone either unmeasured or misclassified as PM_{2.5} [88, 98]. Their small size facilitates better tissue penetration deep into lung alveoli and into epithelial cells restricting their clearance via macrophage phagocytosis [98]. Animal studies have shown that UFPs can translocate across the lung epithelium into blood circulation and accumulate in other organs, including the liver, spleen, kidneys, heart, brain, and reproductive organs [98].
6. This is an excellent exhaustive review. Research funded by Canadian Institute of Health Research Grant. sjj

Reproduction: Spontaneous AB (see Erickson paper above)

Di Ciaula A, Bilancia M. Relationships between mild PM₁₀ and ozone urban air levels and spontaneous abortion: clues for primate prevention. Intern J Environ Health Research 2015; <http://dx.doi.org/10.1080/09603123.2014.1003041>. <http://www.isde.it/wp-content/uploads/2015/06/2015-Intern.-J.-Environ.-Health-Research-Relationships-between-mild-PM10-and-zone-urban-air-levels-and-spontaneous-abortion-Di-CiaulaBilancia.pdf>.

1. 5 cities (514,996) residents with SAB and PM₁₀, NO₂ and O₃ levels. Median pollutant concentrations were below legal limits.
2. Monthly SABs positively correlated with PM₁₀ and O₃ but not with NO₂.
3. Mean monthly SAB rate increase was 19.7 and 33.6% per 10 microg/m³ increase in PM₁₀ or O₃ respectively. Cities with higher PM₁₀ had up to 2 fold increase in SABs than lower PM₁₀ communities.
4. SAB might be considered at least in part to be a preventable condition.

Moridi M, Ziaei S, Kazemnejad A. Exposure to ambient air pollutants and spontaneous abortion. J Obstet Gynaecol Res 2014;40(3):743-8. <https://www.ncbi.nlm.nih.gov/pubmed/24738119>.

1. Retrospective case control: 296 women 2010-11 in Tehran, Iran.
2. Average ambient air pollutants in cases sign higher than controls. ($P < 0.05$.)

Enkhmaa D, Warburton N, et al. Seasonal ambient air pollution correlates strongly with spontaneous abortion in Mongolia. *BMC Pregnancy Childbirth* 2014;14:146 . doi: [10.1186/1471-2393-14-146](https://doi.org/10.1186/1471-2393-14-146). <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4024019/>.

1. Monthly average O₃, SO₂, NO₂, CO, PM₁₀ and PM_{2.5} levels were measured at Mongolian Government Air Quality Monitoring stations. The medical records of 1219 women admitted to the hospital due to spontaneous abortion between 2009–2011 were examined retrospectively. Fetal deaths per calendar month from January–December, 2011 were counted and correlated with mean monthly levels of various air pollutants by means of regression analysis.
2. Regression of ambient pollutants against fetal death as a dose–response toxicity curve revealed very strong dose–response correlations for SO₂ $r > 0.9$ ($p < 0.001$) while similarly strongly significant correlation coefficients were found for NO₂ ($r > 0.8$), CO ($r > 0.9$), PM₁₀ ($r > 0.9$) and PM_{2.5} ($r > 0.8$), ($p < 0.001$), indicating a strong correlation between air pollution and decreased fetal wellbeing.
3. Air pollution has previously been strongly associated with adverse reproductive health. Several studies have examined the effects of air pollution on pregnancy, providing evidence that exposure to ambient air pollutants is associated with poor birth outcome, such as low birth weight [5-7], small for gestational age [8-10], preterm birth [11-14], congenital malformations [15-17] and pregnancy complications such as preeclampsia [18].
4. The present study has identified alarmingly strong statistical correlations between seasonal ambient air pollutants and pregnancy loss. Previous studies in China have examined the association between spontaneous abortion before 26 weeks of gestation, and found an increased rate in areas with an elevated mean annual level of hydrogen sulfide ($>4 \mu\text{g}/\text{m}^3$) [31]. A time-series study in Brazil [32] likewise found a strong association between stillbirth and both NO₂ as an individual pollutant and an index that combined NO₂, CO, and SO₂. Spontaneous abortion has also been associated with environmental tobacco smoke, which contains many of the same chemical pollutants as traffic exhaust [19,20].

Demjmek J, et al Impact of polycyclic aromatic hydrocarbons and fine particles on pregnancy outcome. *Environ Health Perspect* 2000;108(12):1159-64
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1240197/>.

1. The impact of c-PAHs and fine particles on IUGR was analyzed in Teplice and in Prachatice, a region with similarly high c-PAH but low particle levels. All European, single live births occurring in a 4-year period in Teplice ($n = 3,378$) and Prachatice ($n = 1,505$) were included.
2. The AOR of IUGR for fetuses from Teplice exposed to medium levels of c-PAHs in the first GM was 1.60 [confidence interval (CI), 1.06-2.15], and to high levels 2.15 (CI, 2.7-3.63). An exposure-response relationship was established by analyzing the continuous data. For each 10 ng increase of c-PAHs in the first GM, the AOR was 1.22

(CI, 1.07-1.39). About the same relationship was observed in Prachatice in spite of the low particle levels. The results prove that exposure to c-PAHs in early gestation may influence fetal growth. The particulate matter-IUGR association observed earlier may be at least partly explained by the presence of c-PAHs on particle surfaces.

Rubes J, Selevan SG et al. Episodic air pollution is associated with increased DNA fragmentation in human sperm without other changes in semen quality. *Human Reproduction* 2005;20(10):2776-83. <http://humrep.oxfordjournals.org/content/20/10/2776.short>.

1. This study examined potential associations between exposure to episodes of air pollution and alterations in semen quality. The air pollution, resulting from combustion of coal for industry and home heating in the Teplice district of the Czech Republic, was much higher during the winter than at other times of year with peaks exceeding US air quality standards.
2. CONCLUSION: Exposure to intermittent air pollution may result in sperm DNA damage and thereby increase the rates of male-mediated infertility, miscarriage, and other adverse reproductive outcomes.

Reproduction: Birth defects

Stingone JA, Luben TJ, Daniels JL. Maternal exposure to criteria air pollutants and congenital heart defects in offspring: results from the National Birth Defects Prevention Study. 2014. <http://dx.doi.org/10.1289/ehp.1307289>. <http://ehp.niehs.nih.gov/wp-content/uploads/chc/2014/CH-2014-final.alt.pdf>.

1. Nine state, case control study: CO, NO₂, O₃, SO₂ and PM.
2. 4632 live-birth controls and 3,328 live-birth fetal-death or electively terminated cases had exposure data.
3. Positive association observed between exposure to NO₂ and coarctation of aorta and pulmonary valve stenosis. PM exposure positively assoc with hypoplastic left heart syndrome.
4. Using daily maximum pollutant levels and exploring individual exposure-weeks revealed some positive associations between certain pollutants and defects and suggested potential windows of susceptibility during pregnancy.

Padula AM, Tager IB, Carmichael SL, et al. The association of ambient air pollution and traffic exposures with selected congenital anomalies in the San Joaquin Valley of California. *Am J Epidemiol* 2013; <http://aje.oxfordjournals.org/content/early/2013/03/27/aje.kws367.abstract>. <http://aje.oxfordjournals.org/content/early/2013/03/27/aje.kws367.full.pdf>.

1. We aimed to investigate whether ambient air pollutant and traffic exposures in early gestation contribute to the risk of selected congenital anomalies in the San Joaquin Valley of California, 1997–2006. Seven exposures and 5 outcomes were included for a total of 35 investigated associations.
2. For the present analysis, we used data from the California Center of the National Birth Defects Prevention Study (25) and the Children’s Health and Air Pollution Study

(<http://chaps-sjv.berkeley.edu/>) to investigate whether ambient air pollution and traffic metrics were associated with the risks of neural tube defects (spina bifida and anencephaly only), orofacial clefts, and gastroschisis in the San Joaquin Valley of California.

3. Increased odds of neural tube defects when comparing the highest with the lowest quartile of exposure for several pollutants after adjusting for maternal race/ethnicity, education, and multivitamin use.
4. The adjusted odds ratio for neural tube defects among those with the highest carbon monoxide exposure was 1.9 (95% confidence interval: 1.1, 3.2) compared with those with the lowest exposure, and there was a monotonic exposure-response across quartiles. The highest quartile of nitrogen oxide exposure was associated with neural tube defects (adjusted odds ratio = 1.8, 95% confidence interval: 1.1, 2.8).
5. The adjusted odds ratio for the highest quartile of nitrogen dioxide exposure was 1.7 (95% confidence interval: 1.1, 2.7). Ozone was associated with decreased odds of neural tube defects and increased odds of gastroschisis among mothers aged ≥ 20 years.
6. Epidemiologic studies in the past decade have identified associations between air pollution and adverse birth outcomes, including low birth weight, preterm birth, and infant mortality (7–9).
7. Studies focusing on congenital anomalies (3, 10–23) and their relationship with air pollutants have not produced clear results (24). Many studies have been limited to residential information at birth rather than during the first trimester, which is a known critical period for congenital anomalies. Only 1 previous study has incorporated data on traffic exposure (10).
8. Strengths of the present study include a rigorous, population-based design and careful case ascertainment. The study also allowed for detailed information to be gathered as potential covariates specifically during the critical period of the first 8 weeks of pregnancy, including maternal residence, multivitamin use, and smoking. These study characteristics limited potential selection bias and confounding.

Jin Lan, Qiu J, Zhang Y, et al. Ambient air pollution and congenital heart defects in Lanzhou, China. *Environmental Research Letters*. 2015;10:1-14. <http://iopscience.iop.org/article/10.1088/1748-9326/10/7/074005;jsessionid=1695476189511E66263A3699A34104EA.c4.iopscience.cld.iop.org>.

1. Researchers from China and Yale University investigated cohort 8969 singleton live births in Lanzhou, China, 2010-12. Study conducted in China to address the problem of not having high prevalence of congenital heart defects and high air pollution levels in studies in the West.
2. Used logistic regression to estimate the associations, adjusting for maternal age, education, income, BMI, disease, folic acid intake and therapeutic drug use, and smoking; season of conception, fuel used for cooking and temperature.
3. Congenital malformations of great arteries and pooled cases showed consistent patterns.
4. Found positive assoc for CM of cardiac septa and PM10 exposures in 2nd Trimester and the entire pregnancy, and SO2 exposures in the entire pregnancy.

Excellent study that addresses weaknesses of earlier research in Western countries where results of link between AP and congenital defects were mixed. Careful definitions, statistical measures were used.

Zhang B, Zhao J, Yang R et al. Ozone and other air pollutants and the risk of congenital heart defects. *Scientific Reports* 2016;6 . doi:10.1038/srep34852.

http://www.nature.com/articles/srep34852?WT.feed_name=subjects_epidemiology.

1. Do high levels of maternal exposure to O₃, SO₂, NO₂, CO increase risk of congenital heart defects (CHD) in Wuhan, China. WUHAN ENVIRON MONITORING CENTER AT 9 NATIONAL AMBIENT AIR QUALITY AUTOMATIC MONITORING STATIONS USED.
2. Collaborative research: Wuhan Medical Center, China and College for Public Health and Social Justice Saint Louis University, Saint Louis, MO, USA.
3. In one pollutant model increased risk of CHDs, VSD and tetralogy of fallot with increasing O₃ exposure.
4. In two pollutant model associations with all CHDs, VSD and TF for O₃—with strongest aORs with exposures during 3rd month of pregnancy. Also positive assoc between CO exposures during 3rd mo and VSD in two pollution model.
5. An increasing number of epidemiologic studies have examined whether air pollution exposure is associated with risk of adverse birth outcomes^{1,2}. Some studies have found strong evidence for an association between exposure to air pollution and infant mortality, particularly postneonatal respiratory mortality and low birth weight^{3–5}. In addition, some studies have found that exposure to air pollutants during specific time periods during pregnancy are related to some cardiac anomalies^{6–10}
6. Our results suggest that exposure to increased levels of O₃ during the first trimester of pregnancy may contribute to the risk of CHDs in Wuhan, China, which is a highly polluted region of the country. Our results contribute to the body of evidence regarding air pollution exposure and CHDs, but confirmation of these associations will be needed in future studies.

Vrijheid M, Martinez D, Manzanares S, et al. Ambient air pollution and risk of congenital anomalies: A systematic Review and Meta-analysis. *Environ Health Perspect* 2011;119(5):598-606. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3094408/>.

1. From bibliographic searches we extracted 10 original epidemiologic studies that examined the association between congenital anomaly risk and concentrations of air pollutants.
2. Each individual study reported statistically significantly increased risks for some combinations of air pollutants and congenital anomalies, among many combinations tested.
3. In meta-analyses, nitrogen dioxide (NO₂) and sulfur dioxide (SO₂) exposures were related to increases in risk of coarctation of the aorta [odds ratio (OR) per 10 ppb NO₂ = 1.17; 95% confidence interval (CI), 1.00–1.36; OR per 1 ppb SO₂ = 1.07; 95% CI, 1.01–1.13] and tetralogy of Fallot (OR per 10 ppb NO₂ = 1.20; 95% CI, 1.02–1.42; OR per 1 ppb SO₂ = 1.03; 95% CI, 1.01–1.05), and PM₁₀ (particulate matter ≤ 10 μm)

exposure was related to an increased risk of atrial septal defects (OR per 10 $\mu\text{g}/\text{m}^3$ = 1.14; 95% CI, 1.01–1.28).

4. Conclusion: We found some evidence for an effect of ambient air pollutants on congenital cardiac anomaly risk. Improvements in the areas of exposure assessment, outcome harmonization, assessment of other congenital anomalies, and mechanistic knowledge are needed to advance this field.

Gilboa SM, Mendola P, Olshan AF, et al. Relation between ambient air quality and selected birth defects, seven county study, Texas 1997-2000. *Am J Epidemiol* 2005;162(3):238-52.

<http://aje.oxfordjournals.org/content/162/3/238.full>.

1. Population-based case-control study investigated the association between maternal exposure to air pollutants, carbon monoxide, nitrogen dioxide, ozone, sulfur dioxide, and particulate matter <10 μm in aerodynamic diameter during weeks 3–8 of pregnancy and the risk of selected cardiac birth defects and oral clefts in livebirths and fetal deaths between 1997 and 2000 in seven Texas counties.
2. Positive associations between carbon monoxide and tetralogy of Fallot (odds ratio = 2.04, 95% confidence interval: 1.26, 3.29), particulate matter <10 μm in aerodynamic diameter and isolated atrial septal defects (odds ratio = 2.27, 95% confidence interval: 1.43, 3.60), and sulfur dioxide and isolated ventricular septal defects (odds ratio = 2.16, 95% confidence interval: 1.51, 3.09).
3. Suggestive results support a previously reported finding of an association between ozone exposure and pulmonary artery and valve defects.

Gulf War and Health: Volume 3. Fuels, Combustion Products and Propellants. Institute of Medicine, National Academies Press . 2005, Chapter 7: Reproductive and Developmental Outcomes. goo.gl/a6EQX7.

1. P 288. recent studies have reported excess cardiac birth defects and other adverse reproductive outcomes in offspring of men and women who served in the Gulf War.
2. P289. A large population VA study of 15,000 US Gulf War vets vs 15000 non-deployed vets found that men and women vets self-reported higher rates of BD among liveborn infants including moderate to severe defects (OR 1.8-2,8).
3. > million records of vets: three defects: tricuspid valve insufficiency (RR 2.7 (CI 1.1-6.6); aortic valve stenosis (RR 6.0 (CI 1.2-31.0) and renal agenesis (RR 2.4 (CI 0.7-8.3)
4. The study was not designed to determine whether the excess risk was caused by environmental agents. (SJJ: This is a remarkable though not surprising comment. Clearly independent studies have found that troops overseas are exposed to a myriad of complex mixtures of highly toxic chemicals known to be causally related to major human harms, including reproductive harms. Whether human exposure in vets was through skin, GI tract, lungs, water---a plausible hypothesis would be that these harms were related directly or indirectly to environmental exposures to toxic agents and expressed variably in the population, based on the host genetic and immune susceptibility and co-risk factors, including infections, etc)
5. Other large studies found higher miscarriage rates in Male Gulf War vets in their partners.

6. 5 reproductive outcomes (livebirth, stillbirth, spontaneous AB, ectopic preg and induced abortion) were analyzed among female vets from GW. Increase risk for Spontaneous AB and ectopic pregnancy (ORs 2.92 and 7.7 compared with nondeployed female vets) was found.

Ritz B, Fei Y, Fruin S, et al. Ambient air pollution and risk of birth defects in Southern California. *Am J Epidemiol* 2002;155:17-25.

<http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.556.4676&rep=rep1&type=pdf>.

1. California Birth Defects Monitoring Program in neonates and fetuses delivered in south CA 1987-93.
2. Using measurements from ambient monitoring stations of carbon monoxide (CO), nitrogen dioxide, ozone, and particulate matter <10 µm in aerodynamic diameter, they calculated average monthly exposure estimates for each pregnancy. Conventional, polytomous, and hierarchical logistic regression was used to estimate odds ratios for subgroups of cardiac and orofacial defects.
3. This is the first known study to link ambient air pollution during a vulnerable window of development to human malformations.
4. OR for cardiac VSDs increased in a dose response fashion with increasing second-month CO exposure; similarly risks for aortic artery and valve defects, pulmonary artery and valve anomalies and conotruncal defects increased with second-month ozone exposure.

SJJ reflections: Despite the long known biological plausibility linking AP to harms in the reproductive process and given this well done study in 2002, and given the almost universal exposure prevalence of AP in women and men in child bearing ages, and despite the human tragedies of losing the pregnancy or experiencing a congenital malformations at birth, there seems to be surprisingly little funded research in the U.S. to address the public health impacts.

Sensory: (eye; ear)

Sensory (Eye)

Murthy S. Pollution and Eye Disease: Irritation, Burning Sensation, Dryness and Allergy. (LV Prasad Eye Institute, <http://www.lvpei.org/EyeTopics/>. Hyderabad.

http://www.lvpei.org/EyeTopics/EyeHealth/EyeCare/Pollution_eyediseases.php.

1. Clinical summary on effects of AP on eye diseases.
2. AP causes eye symptoms.
3. A clinical assessment not research.

Goodman A. Air Pollution Increases Dry Eye Syndrome. American Academy of Ophthalmology 2013 Annual meeting. In *Medscape* Dec 9, 2016.

<http://www.medscape.com/viewarticle/815040>.

1. Living in cities with high levels of pollution increases risk for dry eye syndrome up to 3-4 fold for those living in greater Chicago and NY areas compared with living in areas with pollution levels.
2. Lead Investigator: Anat Galor MD from Bascom Palmer Eye Institute in Florida: "Our study links air pollution with dry eye syndrome, which is an epidemic that causes human suffering. These data are yet another reason to lobby for tighter controls on air pollution."
3. One in 6 Americans suffers from dry eye syndrome.
4. National db on environmental pollution exposure was matched with 606,708 pts attending a Veterans eye clinic (about 3 million total).
5. The researchers plotted these data on maps of the continental United States, and found that cases of dry eye syndrome clustered in urban areas of the country with high levels of pollution.
6. Air pollution, measured by aerosol optical depth, and atmospheric pressure emerged as the strongest risk predictors of dry eye syndrome. The risk for dry eye syndrome was highest in those exposed to high levels of aerosol optical depth (incident risk ratio [IRR], 1.12) and high atmospheric pressure (IRR, 1.13). Higher humidity decreased the risk for dry eye syndrome (IRR, 0.927).
7. Dry eye syndrome is typically treated with artificial tears, and it is estimated that these products account for \$800 million annually, Dr. Galor told *Medscape Medical News*.

Torricelli AA, Matsuda M, Novaes P, et al Effects of ambient levels of traffic-derived air pollution on the ocular surface: analysis of symptoms, conjunctival goblet cell count and mucin 5AC gene expression. *Environ Res* 2014;131:59-63.

<http://www.sciencedirect.com/science/article/pii/S0013935114000413>.

1. Quantify ocular symptoms and changes in gene expression on conjunctiva of 21 male healthy subjects exposed to traffic derived air pollution and estimate effects of NO₂ and PM_{2.5}.
2. Exposure to ambient levels of air pollution impacts conjunctival GC density. An increase in MUC5AC mRNA levels may be part of an adaptive ocular surface response to long-term exposure to air pollution.
3. An increase in MUC5AC mRNA levels on the ocular surface was found in our sample of taxi drivers and traffic controllers exposed to ambient levels of PM_{2.5} and NO₂, probably as a consequence of increased GC density in response to air-borne pollutants. Although much attention has been given to the study of the adverse affects of air pollution, to our knowledge this is the first study evaluating the relation between air pollution levels and ocular mucin gene expression.

Klossek JM, Annesi-Maesano I, Pribil C, et al. The burden associated with ocular symptoms in allergic rhinitis. *Intl Arch All and Immunol* 2012;158(4):411-7.

<http://search.proquest.com/docview/1023944458?accountid=7398>.

1. Cross-sectional observ survey Nov 2006 (n=4,019)

2. Troublesome ocular symptoms with trigger factors included pollens (51.3%; household dust/mites (34%), pets (12.2%) and air pollution (3.8%.)
3. Ocular Sx had negative impact on daily activities. Treatment often required.

Klopfer J. Effects of environmental air pollution on the eye. J AM Optom Assoc 1989;60(10):773-8. <https://www.ncbi.nlm.nih.gov/pubmed/2685084>.

1. Eye is vulnerable to air pollution—from minimal symptoms to chronic eye irritation and discomfort.
2. Contact lens wearers may be susceptible to harm.
3. The ocular effects are often overlooked by optometrists.

Bourcier T, Viboud C, Cohen JC, et al. Effects of air pollution and climatic conditions on the frequency of ophthalmological emergency examinations. Br. J Ophthalmol 2003;87(7):8098-11. <https://www.ncbi.nlm.nih.gov/pubmed/12812873>.

1. Paris, FR: relation between high levels of AP and number of eye emergencies.
2. 1999. Pollutants provided by Paris air pollution network, AIRPARIF: NO, NO₂, O₃, SO₂ and PM₁₀.
3. A total of 30 883 patients were examined in the emergency department of the Quinze-Vingts National Centre of Ophthalmology during year 1999 and 3042 diagnoses were recorded in the randomisation process. Among these, 41.8% were categorised as conjunctivitis and related ocular surface problems, 25.0% as trauma or surgical emergencies, and 33.3% as medical emergencies. Summary statistics for the study are presented in Table 1.
4. Of the 361 days of the study period, excluding the eclipse period, 276 days (76.4%) were considered as normal days for the total number of visits to the emergency department (less than 92 patients were seen), and 85 (23.5%) were considered as peak days. The selection procedure of the logistic model retained several environmental variables: NO, NO₂, atmospheric pressure, minimum humidity, and average wind speed. The sensitivity was 48.2% and the specificity was 93.4%, corresponding to a positive predictive value of 69.5% and a negative predictive value of 85.4%. As regards specific diagnoses—namely, conjunctivitis and related ocular surface problems, medical emergencies, trauma, and surgical emergencies, the selected models were not appropriate to predict the occurrence of peaks, and the resulting sensitivity was less than 2%.
7. In conclusion, our study suggests that the levels of air pollution experienced in Paris are linked to short- term increases in the number of people visiting an ophthalmological emergency department. Prospective research is needed on the association between weather and air pollutants and allergens in order to improve air pollution models and their linkage with climate change scenarios, and closing gaps in the understanding of exposure patterns and ophthalmological effects. Such studies will help to determine the long term effects of air pollutants on the eye, which are currently unknown. Br J Ophthalmol 2003;87:809–811

Sensory (Ear)

Jones LL, Hassanien A, Cook DG. Parental smoking and risk of middle ear disease in children. JAMA: Arch

Pediatr Adolesc Med 2012;166(1):18-27. doi:10.1001/archpediatrics.2011.158.
<http://jamanetwork.com/journals/jamapediatrics/fullarticle/1107682>.

1. Exposure to SHS (mother) increases risk of middle ear disease in childhood.
2. Risk of surgery for MED, post natal smoking increased the risk by OR of 1.86 (CI 1.31-2.63 and paternal smoking by 1.83.
3. Middle ear disease (MED) is a common illness among children that accounts for a large number of physician visits and that, if untreated, can cause considerable disability through hearing impairment.¹ It is estimated that around 10% of children have 3 episodes of acute otitis media (AOM) before their first birthday,² whereas middle ear effusion is the most common reason for admission of young children to hospitals for surgery, putting a heavy financial burden on health care services.³
4. The authors did not control for exposure to ambient air pollution.

Zemek R, Szyszkowicz, Rowe BH. Air pollution and emergency Department visits for otitis media; A case-crossover study in Edmonton, Canada. *Environ Health Perspect* 2010;118(11) DOI:10.1289/ehp.0901675
<http://ehp.niehs.nih.gov/0901675/>.

1. 10 years ED data linked to air pollution: CO, NO₂, SO₂, O₃, PM. Conditional logistic regression analysis.
2. 14,527 ED visits, children 1-3 yr. Significant positive associations between ED visits for Otitis Media and interquartile increases in CO and NO₂ levels after adj for temp and rel humidity.
3. Results support hypothesis that ED visits for OM are associated with air pollution.
4. Animal studies have demonstrated impairment of ciliary function and increased middle ear mucus secretion after sulfur dioxide (SO₂) exposure (Ohashi et al. 1989b). Consequently, the possible link between air pollution and OM is important to understand.
5. Rev of lit: studies (several with thousands of patients) show with improvement in air quality otitis media rates decrease.
6. OM exerts an enormous economic burden on the health care system, with estimated per episode costs ranging from \$108 to \$1,300 in the United States (Schwartz and Gates 2003). The costs and utility of observation and routine antibiotic treatment options for children with acute OM are in the range from \$132 to \$157 in the United States (Coco 2007). It is a common childhood illness that is one of the most frequent reasons for medical visits and antibiotic prescriptions (Rovers 2008).
7. Authors didn't focus on hearing impairment but other studies have clearly shown the link between hearing impairing and hearing loss.

Kousha T, Castner J. Air Quality Health Index and ED visits for Otitis Media. *J of Nursing Scholarship*. 2016. DOI: 10.1111/jnu.12195. <http://onlinelibrary.wiley.com/doi/10.1111/jnu.12195/full>.

1. Retrospective ED visits, air pollution and weather dbs. 4815 ED visits for Otitis Media over 6 yr in Windsor Ontario Canada.
2. OM is characterized by inflammation of the middle ear linked to anatomic, genetic, infectious, and environmental factors (Coticchia, Chen, Sachdeva, & Mutchnick, 2013; Lack, Caulfield, & Penagos, 2011). Environmental and behavioral factors that increase the risk for OM include exposure to tobacco smoke, bottle-feeding (as opposed to breast-feeding), daycare attendance, and specific outdoor pollutants (Ladomenou, Kafatos, Tselentis, & Galanakis, 2010; Zemek, Szyszkowicz, & Rowe, 2010). There is mixed evidence that allergies

are linked to OM (Lack et al., 2011). There is a paucity of both evidence and statistical modeling methods on the relationship of ambient multipollutant exposure and childhood OM.

3. Cross over analysis: increase in ED visits with OM diagnosis 6-7 days post exposure to increased ozone and 304 days after exposure to increased PM. For every 1 unit increase in the Air Quality Health Index, discharge DX of OM increased 5-6% three days post exposure.
4. Overall risk for OM in first 15 days after increase in AQIndex was 1.22 times the risk of OM on days following no increase in exposures.
5. Poor indoor and outdoor air quality is associated with an increased risk for OM. Exposure to second-hand smoke increases the amount of pathogens present in the nasopharynx (Brook, 2010; Fuentes-Leonarte et al., 2015). Exposing human middle ear epithelial cells to diesel exhaust particles and acrolein induces an inflammatory response and decreases the cell's viability, indicating a direct cellular link between air pollution and OM (Song, Lee, Lee, Chae, & Park, 2012, 2013).
6. This present study contributes important evidence to both research and healthcare practice with the use of the multipollutant index, the AQHI. While the AQHI was developed based on mortality, the results obtained for the AQHI indicate that such an index is also useful in morbidity. The study has important policy implications that the reduction of ambient air pollutant levels, particularly in this highly polluted international border setting, has the potential to reduce OM among children younger than 3 years.

Klein JO, Pelton S et al. Ear Infections (otitis media) in children. UpToDate 2016.

<https://www.uptodate.com/contents/ear-infections-otitis-media-in-children-beyond-the-basics>.

1. Ear infections, also called otitis media, are a common problem in children. About 50 percent of infants have at least one ear infection by their first birthday. Ear infections can cause pain in the ear, fever, and temporary hearing loss and general signs such as loss of appetite and irritability.
2. **Hearing loss** — The fluid that collects behind the eardrum (called an effusion) can persist for weeks to months after the pain of an ear infection resolves. An effusion causes trouble hearing, which is usually temporary. If the fluid persists, however, it may interfere with the process of learning to speak. (See "[Otitis media with effusion \(serous otitis media\) in children: Clinical features and diagnosis](#)" and "[Otitis media with effusion \(serous otitis media\) in children: Management](#)".)
3. Effusions usually resolve without any treatment. However, if the effusion persists for more than three months, the child may need treatment with a surgical procedure. The decision to treat is based upon how much the effusion affects the child's hearing and the child's risk of speech problems.

Ototoxicity (p167) In Effects of Air Pollution on Children's Health and Development. A Review of the Evidence. WHO 2005. http://www.euro.who.int/_data/assets/pdf_file/0010/74728/E86575.pdf.

1. Based on audiometric data from a subsample of 4519 children/adolescents 4-19 yrs from NHANES II Schwartz and Otto found a highly significant linear increase in pure tone hearing thresholds between 0.5 and 4 kHz, and confirmed this in 3262 subjects from the Hispanic Health and Nutrition Survey. An increase of PbB from 70-180 microg/l associated with about 2 dB loss of pure tone hearing.
- 2.

Smith RJS, Gooi A et al. Hearing Impairment in children: Etiology.

<https://www.uptodate.com/contents/hearing-impairment-in-children-etiology>.

1. Significant hearing loss occurs in 1 to 2 per 1000 newborns and in 2 per 1000 young children. However, nearly all children develop transient hearing loss related to middle ear infections during the period from birth to 11 years of age [4].
2. Otitis media (OM) is the most common childhood disorder associated with conductive hearing loss. By the age of three years, 83 percent of children will experience at least one episode of OM, and 46 percent will have experienced at least three episodes [11]. About 3 to 20 percent of children have six episodes of OM in a year [12].
3. Cadmium, mercury, and arsenic may have toxic effects on cochlear cells and mercury exposure may cause delayed auditory brainstem evoked potentials [87]. In addition, lead can have neurotoxic effects. In a series of 2535 adolescents aged 12 to 19 years, those with a blood lead level of ≥ 2 mcg/dL had a twofold increased odds of high-frequency hearing loss compared with those with a lead level < 1 mcg/dL [88].

Brauer M, Gehring U, et al. Traffic related air pollution and otitis media. *Environ Health Perspect*. 2006;114(9):1414-1418.

1. Although exposure to environmental tobacco smoke is a known risk factor associated with otitis media, little information is available regarding the potential association with air pollution.
2. Odds ratios (adjusted for known major risk factors) for otitis media indicated positive associations with traffic-related air pollutants. An increase in $3 \mu\text{g}/\text{m}^3$ PM_{2.5}, $0.5 \mu\text{g}/\text{m}^3$ elemental carbon, and $10 \mu\text{g}/\text{m}^3$ NO₂ was associated with odds ratios of 1.13 (95% confidence interval, 1.00–1.27), 1.10 (1.00–1.22), and 1.14 (1.03–1.27) in the Netherlands and 1.24 (0.84–1.83), 1.10 (0.86–1.41), and 1.14 (0.87–1.49) in Germany, respectively.
3. **Given the ubiquitous nature of air pollution exposure and the importance of otitis media to children's health, these findings have significant public health implications.**
4. Otitis media with effusion (OME), in which fluid and mucus stay trapped in the ear after infection, may lead to conductive hearing loss that, if persistent, may lead to delays in the development of speech, language, and cognitive abilities (Klein 2000; Teele et al. 1990). R

Dimes MM (Ed) EHP. Children's Health Collection 2014. Oct 2013-Sept 2014.

<http://ehp.niehs.nih.gov/wp-content/uploads/chc/2014/CH-2014-final.alt.pdf>.

Physicians for Social Responsibility (PSR) How Air Pollution Damages the Brain. (Much of this information is reproduced from the PSR report, Coal's Assault on Human Health (copyright PSR 2009).

<http://www.psr.org/assets/pdfs/air-pollution-effects-nervous.pdf>.

1. Mercury, a potent neurotoxin, from air pollution, converted to methylmercury in the environment, may expose humans via, fish consumption. Pregnant women who eat foods contaminated with MM expose their developing babies growing brain and nervous system and this may result in impacts on cognitive thinking, memory, attention, language, visual spatial skills, impairments in speech, hearing and walking, peripheral vision etc.

Choi Y-H, Hu H, Mukherjee B, Miller J, et al. Cadmium and lead linked to hearing loss in U.S. adults.

Environmental Health Sciences (News Feb 18, 2013.)

<http://www.environmentalhealthnews.org/ehs/newscience/2012/08/2013-0121-cadmium-lead-hearing-loss-adults>.

1. Low levels of lead and cadmium may contribute to hearing loss, according to a large study of U.S. adults. Hearing loss was seen at metal concentrations common in the general population and below current workplace standards. Hearing ability dropped about 14 to 19 percent. - See more at: <http://www.environmentalhealthnews.org/ehs/newscience/2012/08/2013-0121-cadmium-lead-hearing-loss-adults#sthash.6itMPUvk.dpuf>.
2. Human studies are limited, but exposure to high levels of lead has been linked to hearing loss in children and males exposed at work. Studies in teens have also linked cadmium exposure to hearing loss.
3. In this study, researchers looked at the association between hearing loss and exposure to lead and cadmium alone or together in 3,698 U.S. adults aged 20 - 69 years old who were part of the National Health and Nutrition Examination Survey (NHANES) from 1999 - 2004. Participants reported noise exposures through work, firearms or recreation. A hearing exam assessed the severity of hearing loss measured as a pure tone average (PTA).
4. Adults with the highest lead and cadmium exposures had more hearing loss. Lead levels above 2.8 micrograms per deciliter of blood related to an 18.6 percent rise in PTA and cadmium levels above 0.8 micrograms per liter had a 13.8 percent increase in PTA.

Mayo Clinic: Ear Infection (middle ear). <http://www.mayoclinic.org/diseases-conditions/ear-infections/symptoms-causes/dxc-20199484>.

1. **Risk Factors for ear infections: Poor air quality.** Exposure to tobacco smoke or high levels of air pollution can increase the risk of ear infection.
2. **Ear infections (chronic) may cause hearing loss.**

Hendrick B. Air quality up, ear infections down. Study shows reduction in air pollution is linked to fewer ear infections in kids. <http://www.webmd.com/cold-and-flu/ear-infection/news/20091007/air-quality-up-ear-infections-down>.

1. Bhattacharyya N, (Harvard Medical School) 2009 Amer Acad Otolaryngology, US data on 126,060 (aver age 9 yrs) from 1997-2007, used EPA air quality data focusing on CO, nitrous dioxide sulfur dioxide and PM.
2. Conclusion: toughening air standards through the Clean Air Act is reaping health benefits for kids with decreased frequency of frequent otitis media which is known to impair hearing.
3. The direct and indirect costs from treatment of otitis media is \$3-5 billion annually. Improvement in air pollution decreases hearing impairment.

Eustachian Tube Dysfunction. Baylor College of Medicine. 2016. <https://www.bcm.edu/healthcare/care-centers/center-hearing-balance/conditions/eustachian-tube-dysfunction>.

1. Chronic blockage of the Eustachian tube is called Eustachian tube dysfunction. This can occur when the lining of the nose becomes irritated and inflamed, narrowing the Eustachian tube opening or its passageway. Illnesses like the common cold or influenza are often to blame. Pollution and cigarette smoke can also cause Eustachian tube dysfunction.

Stanford University Medicine: Otolaryngology.

https://med.stanford.edu/ohns/healthcare/earinstitute/health-info/eustachian_tube_dysfunction.html.

1. Chronic blockage of the Eustachian tube is called Eustachian tube dysfunction. This can occur when the lining of the nose becomes irritated and inflamed, narrowing the Eustachian tube

opening or its passageway. Illnesses like the common cold or influenza are often to blame. Pollution and cigarette smoke can also cause Eustachian tube dysfunction.

National Sinus Institute: Eustachian Tube Dysfunction.

<http://nationalsinusinstitute.com/symptoms/eustachian-tube-ear-tube-dysfunction/>.

1. Eustachian tube dysfunction can be caused by the common cold, pollution or smoking, sinusitis and/or allergies which cause inflammation including swelling within the ear tube.

Addendum.

Aeroallergens

American Physiological Society (APS). "Global warming may cause spike in asthma, allergy symptoms." ScienceDaily. ScienceDaily, 6 June 2017.
<www.sciencedaily.com/releases/2017/06/170606123423.htm>.

Nathan A. Zaidman, Kelly E. O'Grady, Nandadevi Patil, Francesca Milavetz, Peter J Maniak, Hirohito Kita, Scott M. O'Grady. **Airway epithelial anion secretion and barrier function following exposure to fungal aeroallergens: Role of oxidative stress.** *American Journal of Physiology - Cell Physiology*, 2017; ajpcell.00043.2017 DOI: [10.1152/ajpcell.00043.2017](https://doi.org/10.1152/ajpcell.00043.2017)

1. Basic mechanism by which exposure to outdoor fungus, *Alternaria alternate*, may increase oxidative stress in the airways and thus weaken the lung defense system was researched at the University of MN. Normally, the mucociliary escalator mechanism in human lungs, in part, removes allergy causing organisms that are then swallowed or expectorated. But with increasing atmospheric CO₂ concentrations aeroallergens including *Alternaria* sp. fungal spores may induce allergy symptoms and asthma. And risks of infection in the lung from reduced epithelial cell barrier protection from alteration in ion transport mechanisms (calcium dependent anion secretion) in airways may allow bacteria to multiply and cause lung infections, including pneumonia.
2. It has been known for > 15 years (*Annals of Allergy Asthma and Immunology*, 8 2002) that increasing CO₂ raises the risks of hay fever, asthma and other allergic symptoms. These findings were independent of ambient concentrations of fossil fuel pollutants which are major causes of respiratory symptoms and diseases, such as asthma. This research and implications for human health are summarized in Epstein PR and Ferber D (Foreword, Jeffrey Sachs) *Changing Planet, Changing Health: How Climate Crisis Threatens Our Health and What We Can Do about it*. Berkley: Univ California Press 2011, Chapter 4: Every Breath You Take.

Pneumonia

Oehme FW, Coppock RW, Mostrom MS, Khan AA. A review of the toxicology of air pollutants: toxicology of chemical mixtures. *Vet Hum Toxicol* 1996;38(5):371-7.
<https://www.ncbi.nlm.nih.gov/pubmed/8888547>.

1. Superimposing spikes of 0.8 ppm nitrogen dioxide on a baseline of 0.2 ppm, as occurs on a calm winter day, increased the susceptibility of mice to bacteria-induced pneumonia. Exposure for 1 h to > 200 micrograms sulfuric acid/m³ depressed bronchomucociliary clearance.
2. To understand the effects of multiple chemical interactions of air pollutants, there is a need for a blend of epidemiological, laboratory and field studies. Studies are expensive. In the rural agricultural settings, the economic and environmental health risks are high. Should field observations and chemical problems be used as "red flags" for action?

Fullerton DG, Bruce N, Gordon SB. Indoor air pollution from biomass fuel smoke is a major health concern in the developing world. *Trans R Soc Trop Med Hyg.* 2008;102(9):843-51.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2568866/>.

1. One-third of the world's population burn organic material such as wood, dung or charcoal (biomass fuel) for cooking, heating and lighting. This form of energy usage is associated with high levels of indoor air pollution and an increase in the incidence of respiratory infections, including pneumonia, tuberculosis and chronic obstructive pulmonary disease, low birthweight, cataracts, cardiovascular events and all-cause mortality both in adults and children.
2. The first report of indoor cooking smoke associated with childhood pneumonia and bronchiolitis was in Nigeria ([Sofoluwe, 1968](#)), however not until the 1980s was this followed by reports from other areas ([Collings et al., 1990](#); [Mtango et al., 1992](#); [O'Dempsey et al., 1996](#); [Pandey et al., 1985](#); [Shah et al., 1994](#)).

Zanobetti A, Woodhead M. Air pollution and pneumonia: *Am J Respir and Crit Care Med.*

2010;181(1). DOI: <http://dx.doi.org/10.1164/rccm.200909-1445ED>.

<http://www.atsjournals.org/doi/full/10.1164/rccm.200909-1445ED>.

1. Air pollution might also play a role as a predisposing factor to CAP. A previous study showed that elderly subjects hospitalized for chronic obstructive pulmonary disease (COPD) were at higher risk of dying on high-air pollution days ([5](#)). Similarly, such individuals with CAP could be more susceptible to the effects of air pollution, and prolonged exposure to air pollution might predispose them to pneumonia. Increased risk to CAP associated with direct inhalation of tobacco smoke is a finding common to virtually all studies ([3](#), [4](#), [6](#)), but despite much concern about possible effects of environmental pollution, this has been little studied.
2. Neupane and colleagues used a robust pneumonia definition that required emergency department presentation with the presence of at least two pneumonia signs or symptoms together with new radiographic findings compatible with pneumonia. Environmental pollutant levels were estimated from outdoor monitor readings over the course of 1 to 2 years before the year of the pneumonia presentation at residential addresses, with three different methods to take into account the spatial variability of the pollutants. Associations were corrected for the known association of CAP with age, sex, functional status, socioeconomic status, smoking, and history of regular exposure to air-polluting fumes. This robust approach identified an independent association between NO₂ and PM_{2.5} levels in the previous

1 to 2 years and pneumonia hospitalization. It is worth mentioning that the effects were seen with pollutants derived mainly from traffic.

3. There are certainly plausible biological mechanisms by which pollution could increase pneumonia risk. Epidemiologic studies indicate that hospitalizations for respiratory causes are strongly related to PM exposure.
4. These findings of an association between CAP and long-term pollutant exposure have important implications for public health. They suggest that pneumonia is yet another disease outcome for which air pollution may contribute to enhanced susceptibility, and that reductions in air pollution should reduce disease burden.
5. Sjj Note: the lack of research on the AP link to pneumonia is unfortunate. In tobacco users 50 % of bacterial pneumonias are related to tobacco smoke inhalation.

Shen M, Chapmann RS, Vermeulen R, et al. Coal use, stove improvement, and adult pneumonia mortality in Xuanwei, China: a retrospective cohort study. *Environ Health Perspect* 2009;117:261-6. doi: 10.1289/ehp.11521. Epub 2008 Sep 19.

<https://www.ncbi.nlm.nih.gov/pubmed/19270797>.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2649229/>.

1. We conducted a retrospective cohort study among all farmers born 1917 through 1951 and living in Xuanwei as of 1 January 1976. The analysis included a total of 42,422 cohort members. Follow-up identified all deaths in the cohort from 1976 through 1996.
2. Use of coal, especially smokeless coal, was positively associated with pneumonia mortality. Coal smoke contains many chemicals (e.g., nitrogen oxides, sulfur oxides, ozone, carbon monoxide) and particles that irritate respiratory tracts and lung, adversely affect the host's defense systems against pathogens, and elevate the risk of respiratory tract infections ([Smith et al. 2000](#)). Coal smoke may also increase the severity of respiratory infections by causing inflammation in pulmonary airways ([American Thoracic Society 1996](#)).
3. Stove improvement was associated with a 50% reduction in pneumonia deaths (smoky coal users: HR, 0.521; 95% CI, 0.340-0.798; smokeless coal users: HR, 0.449; 95% CI, 0.215-0.937).
4. Our analysis is the first to suggest that indoor air pollution from unvented coal burning is an important risk factor for pneumonia death in adults and that improving ventilation by installing a chimney is an effective measure to decrease it.

Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society. Rebecca Bascom (Chair) State of the Art. Health Effects of Outdoor Air Pollution. *Am J Respir Crit Care Med* 1996;153:3-50.

http://www.atsjournals.org/doi/abs/10.1164/ajrccm.153.1.8542133?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed#readcube-epdf.

1. Health effects and biologic markers of response associated with air pollution.: Cardiorespiratory mortality; Increased health care utilization; Asthma exacerbations;

Increased respiratory illness; Increased respiratory symptoms; decreased lung function; increased airways reactivity; lung inflammation; altered host defense.

2. Table 2 health effects of air pollutants and populations at greatest risk: O₃; NO₂; SO₂; Acid Aerosols; PM₁₀; CO; Lead.

Summary:

Question: Are the Adverse Human Effects of Air Pollution Underestimated in the Literature? Answer. Probably, but until population studies are carried out it will be difficult to quantify this.

The evidence summarized above suggests that:

1. Reporting of rates of M/M, QALYs, other related measures and health, environmental and business costs associated with exposure of populations to AP may fail to incorporate the impacts of AP on a myriad of 'low frequency' diseases.
2. The true adverse effects of AP in populations is thus underestimated but the extent of this underestimation has not been delineated.
3. Population estimates of overall AP attributable disease must include analyses of these 'low frequency' diseases.
4. It is likely that the prevalence and incidence of AP attributable disease rates for Indiana are similarly underestimated; a note of this likelihood should be incorporated in estimates of the overall impacts of air pollution and climate change relevant to Indiana. Since the Midwest, including Indiana, has increased AP M/M, especially particle pollution (PM_{2.5}), relative to other parts of the U.S., it is expected that both the high frequency CV, Respiratory, and Cancer attributable disease rates and the 'low- frequency' disease rates would be similarly increased relative to other regions of the country.
5. Statistical projections of the population burden of AP related diseases and costs and of the potential impacts of various interventions to reduce these burdens must incorporate accurate estimates of all adverse impacts of AP related human diseases and disorders where biological plausibility coupled with quality research shows the connection.
6. Climate change is projected to worsen air quality in the U.S., especially in eastern, Midwestern and southern states especially O₃ and PM 2.5. It is critical that planning and development of interventions (mitigation and adaption) be based on best evidence of AP in all Indiana counties and the best estimates of total AP attributable diseases.
7. Federal and state research funding (public and private) should be increased to support research into the common AP attributable diseases (CV, Respir, CA) as well as the less common, but not rare, diseases outlined in this review.
8. The annual health costs of AP in America are \$400 per person, more in PA, OH and IN, where AP is worse than other states because of reliance on coal fired power plants. The Clean Air Act rules will yield about \$82 billion in Medicare, Medicaid and other health savings through 2021. EDF:

<https://www.edf.org/news/clean-air-act-rules-save-country-82-billion-health-care-costs-over-next-decade-according-new-an.> U.S. EPA: <https://www.epa.gov/clean-air-act-overview>

L'Envoi

This narrow focus on relatively uncommon human health effects of air pollution and climate change is not meant to belittle the extent to which planet earth's biomes are under severe duress, affecting all living creatures and flora and the physical environment.

Yesterday, while walking along the Monon Trail in Broad Ripple, I came across two bee hives tended by a bee keeper who was quieting an agitated hive with smoke. I asked how Indiana's bees were fairing in light -of national and international evidence of major threats to bees, the 'engines' of pollination and basis for world food production. (Potts SG, et al Global pollinator declines: trends, impacts and drivers. Cell Press 2010 doi:[10.1016/j.tree.2010.01.007](https://doi.org/10.1016/j.tree.2010.01.007)) Her reply to me: bee hive populations of bee keepers in Indiana and the U.S. decreased by about 40% over the past 2 years, a state, national, and global trend. <https://beeinformed.org/2016/05/10/nations-beekeepers-lost-44-percent-of-bees-in-2015-16/>. Her reasons for decline in IN included: disease, pesticide pollution and climate change. Climate change disrupts the relationship between bees and the plant growing seasons, disrupts the nature and nutrition of food that bees eat. Plants and bees are getting 'out of sync.' In the journal, Science, it was recently reported by Kerr et al that "Climate change appears to contribute distinctively, and consistently, to accumulating range compression among bumblebee species across continents." Kerr JT, et al. Climate change impacts on bumblebees converge across continents. Science. 10 Jul 2015 vol 349, Issue (6244): 177-180. DOI: 10.1126/science.aaa7031. <https://earthobservatory.nasa.gov/Features/Bees/bees3.php>. <https://honeybeenet.gsfc.nasa.gov>. Cressey D, Climate change crushes bee populations. Nature July 9, 2015. <http://www.nature.com/news/climate-change-crushes-bee-populations-1.17950> doi:[10.1038/nature.2015.17950](https://doi.org/10.1038/nature.2015.17950).

The adverse effects of air pollution we witness in humans are being seen in global biomes; bumblebees seem to be the 21st c 'canary in a coal mine'.