Exploring Potential Sources of Differential Vulnerability and Susceptibility in Risk From Environmental Hazards to Expand the Scope of Risk Assessment

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Genetic factors, other exposures, individual disease states and allostatic load, psychosocial stress, and socioeconomic position all have the potential to modify the response to environmental exposures. Moreover, many of these modifiers covary with the exposure, leading to much higher risks in some subgroups.

These are not theoretical concerns; rather, all these patterns have already been demonstrated in studies of the effects of lead and air pollution. However, recent regulatory impact assessments for these exposures have generally not incorporated these findings.

Therefore, differential risk and vulnerability is a critically important but neglected area within risk assessment, and should be incorporated in the future. (*Am J Public Health.* 2011;101:S94–S101. doi: 10.2105/AJPH.2011.300272)

THIS ARTICLE EXPANDS ON the conceptual issues raised in our previous article in this issue,[1] illustrates them with empirical examples, and suggests strategies for incorporating the concepts in risk assessments. The central issue is the importance of capturing variation in the distribution of risk within a population as well as differences between populations in overall risk. This variation exists because of differential susceptibility of people to a single agent, interactions among multiple exposures, transgenerational propagation of risk, and because of differential exposure to other agents that affect the distribution of cumulative risk in the population. Finally, the distribution of exposures to such other agents, or to agents that convey susceptibility to the agent under study, and even to individual level factors that are risk modifiers (e.g., genes, chronic disease states, stress), are usually not independent. Capturing this lack of independence is critical to risk assessment. Finally, incorporating dose–response curves, as opposed to reference doses, is critical to accomplishing these tasks, and to understanding the actual magnitude of risk.

GENETIC SOURCES OF SUSCEPTIBILITY IN RESPONSE TO EXPOSURE

Genetic susceptibility to environmental exposures is well established. As early as the 1970s, studies of people experimentally exposed to ozone in chambers demonstrated substantial variability in response. This variability was repeatable, and unexplained by phenotype.[2] Animal studies identified genes with human homologs that might explain this result.[3] Common polymorphisms affecting phase I and phase II detoxification pathways are likely sources of important variation in response to multiple toxicants. If genetic susceptibility affects response to an exposure, and several pathways contribute to that susceptibility, substantial differences could result in the distribution of risk, particularly if the prevalence of genetic variants varies by race/ethnicity.

Lead

The role of genetic factors in lead toxicity is unclear at this time. In some studies, carriers of the 2 allele of the amino levulinic acid dehydratase gene (ALAD-2 carriers) were at increased risk of lead-associated neurobehavioral deficits,[4,5] whereas others of this subgroup were at reduced risk.[6,7] Some of the inconsistency might be a result of age-dependence in this association. A study of lead and cognitive function using National Health and Nutrition Examination Survey (NHANES) data suggested modification by ALAD status in adults, but not in adolescents or adults older than 60 years.[6] This highlights the importance of age at exposure, and not exposure alone. A similar age-dependence was reported for apolipoprotein-E (Apo-E). In adults, carriers of the Apo-E4 allele were at increased risk of lead-associated neurobehavioral deficits,[7] but not children.[8] The impact of Apo-E4 depends on other factors, including stress.[9] In males, the adverse effects of lead on executive function were greatest among those lacking the dopamine receptor D4-7.[10] Adult workers with the Vitamin D-B variant showed greater lead-associated impairment of renal function.[11] Vitamin D polymorphisms modified the effect of lead on cognition in children.[12]

Lead may increase the risk of neurodegenerative processes by an epigenetic mechanism. In animals, early exposure caused developmental reprogramming, resulting in over expression in adulthood of the amyloid precursor protein (APP) gene, specifically APP mRNA, APP, and β-amyloid.[13] In humans, prenatal lead exposure was inversely related to DNA methylation in cord blood,[14] and bone lead levels were inversely related to DNA methylation in leukocytes in the elderly.[15]

Air pollution

Genetic polymorphisms modified the response to air pollution, particularly along the oxidative defense pathway. Such polymorphisms modified the effects of particles on heart rate variability,[16,17] the effects of traffic particles on homocysteine levels,[18] the effects of traffic pollutants on lengthening of the QT interval on

electrocardiograms,[19] the effects of air pollution on lung function,[20,21] the risk of ozone-induced asthma[22] and wheezing,[23] and the risk of endothelial inflammation caused by traffic particles, etc. [24] Glutathione S transferase mu 1 (GSTM1) null variant was the most commonly reported modifier along this path, but the other genes along this pathway that matter varied among these studies. This might reflect differences in the outcomes studied, stochastic variability, or interactions with other risk modifiers. Other polymorphisms that might modify the effects of air pollution include those in the divalent metal metabolism pathway,[25] the angiotensin pathway,[26] the methyl metabolism pathway,[27] and genes related to processing of micro RNAs, which are small noncoding RNAs that posttranscriptionally control gene expression.[28]

Epigenetic mechanisms might serve both as pathways for the effects of air pollution and modifiers of response. Metal-rich particles were associated with reduced methylation of the promoter region of the iNOS gene.[29] Traffic officers showed changes in methylation of cancer suppressor and promotion genes similar to those seen in leukemia.[30] Exposure to traffic particles[31] and polycyclic aromatic hydrocarbons[30] altered DNA methylation patterns.

PHENOTYPIC SOURCES OF VARIABLE RESPONSE

In the early 1800s, Scottish public health advocates argued that the (unknown) agents that caused infectious disease were ubiquitous, and what mattered was the person's susceptibility, principally driven by malnutrition. They recommended prescribing food.[32] Others also argued that host factors that altered susceptibility were of paramount importance.[33] The phenotype might be characterized by disturbances among one or more physiological pathways that were also important to the toxicity of the environmental agent. An environmental disturbance to those pathways might have greater effects if the reserve capacity for dealing with such disturbances was already impaired by the presence of disease or allostatic load (the notion that repeated successful short-term adaptation to stressors might have long-term consequences).[34] For example, diabetes and obesity are phenotypes that are characterized by elevated baseline levels of oxidative stress. Coexposure to multiple agents that produce further oxidative stress might result in nonlinear increases in risk. Both lead and air pollution were shown to work, in part, by increasing oxidative stress. Interactions between lead exposure and air pollution were also reported.[35] Dietary antioxidants, such as Vitamins C and E, or methyl-related substrates such as B-vitamins or methionine, or *N*-3 fatty acids[36] modified responses to environmental agents.[28,37,38] The potential for highly skewed risk distributions existed because these dietary intakes tended to be lower in more disadvantaged areas, where the prevalence of obesity and diabetes also tended to be higher, and where exposure to some environmental chemicals was higher.

Lead

Few data are available on disease states that modify the effects of lead. Lead-associated decrement in renal function might be more pronounced in patients with preexisting chronic kidney disease.[39] In an elderly cohort, higher lead level was associated with impaired renal function, but only in diabetic individuals.[37] In adult men, the association between higher patella lead and autonomic dysfunction was greater among those with metabolic syndrome.[38]

Air pollution

Although several conditions appear to modify the effects of air pollution on health, the strongest evidence is for obesity and diabetes. The increasing prevalence of both conditions make these susceptibility factors especially important for risk assessments, which need to take into account the changing proportion of the population that is susceptible. In a study of 4 US cities, patients with diabetes had double the risk of a particulate matter (PM) 10 associated cardiovascular admission compared with nondiabetics[40] In Montreal, air pollution was associated with a much higher risk of death from diabetes than for all causes.[41] A 2-fold higher mortality risk associated with PM10 exposure was found for patients with diabetes in a case-crossover study.[42] Similar results were reported in 9 Italian cities.[43] Diabetes also modified the effects of air pollution on endothelial function[44] and on systemic inflammation.[45,46]

Obese individuals were found to have twice the PM2.5-induced reduction in heart rate variability than nonobese individuals and had more PM2.5-mediated heart rate increases.[47] Obese individuals had twice the estimated decrease in forced expiratory volume in 1 second because of ozone compared with nonobese subjects.[48] This was supported by animal data showing increased lung inflammation in response to ozone in obese animals.[49,50] In addition, obesity worsened the PM2.5 effects on the high frequency component of heart rate variability,[51] and there was a greater effect of traffic-related PM on inflammatory markers in obese individuals.[24,45,52] In the NHANES III, metabolic syndrome modified the PM10 effect on inflammatory markers.[53]

Diet modifies the effects of air pollution. In a randomized trial, ω-3 fatty acid supplementation reduced the effect of particles on heart rate variability.[54] A chamber study of asthmatics found that Vitamin C and E supplementation reduced the increase in bronchial responsiveness after ozone exposure.[55]

PSYCHOSOCIAL HAZARDS AND STRESS

Psychological stress is a physiological response to environmental stimuli. It can be positive and adaptive, but under certain conditions, including prolonged exposure, can become dysregulated, impairing health.[56] Stress partly arises from exposure to a psychosocial hazard, defined as relatively stable, visible features of the social and built environment, that gives rise to a heightened state of vigilance, alarm, and fear.[57,58] Dysregulation of the stress response was linked to cardiovascular and other diseases.[59] Animal and epidemiological studies suggested that social context modified environmental neurotoxicants.[60] Poverty causes stress, and in poor communities, social and chemical hazard exposures in childhood jointly altered the development of the central nervous system.[61]

Lead

The study of how stress exacerbates the influence of lead dates

back to classic studies by Selye et al.,[62] who investigated how stressors (both systemic and local) act as "conditioners," whose individual effects are minor, but when combined with lead exposure, are powerful and complex. Although their work on these "pluricausal" syndromes focused on physiological stressors (skin clip), the concepts were applied to the study of psychological and social stresses.

Stress is consistently observed to exacerbate the deleterious effects of lead. Rodent pups who experienced both early lead exposure and maternal stress during pregnancy (novelty, restraint, cold) showed more impaired learning compared with controls on fixed-interval, schedule-controlled responding, and had increased basal and stress-induced corticosterone responses than did pups exposed to stress alone or to lead alone.[63,64] Rats raised in social isolation were more affected by lead than rats raised in an enriched environment.[65] Stress increased the hormonal mobilization of lead from bone to blood,[66] and lead altered the response to environmental stress.[65,67] Exposure to psychosocial hazards increased cortisol production, the primary hormonal mediator of the hypothalamic–pituitary–adrenal axis. Cortisol itself is associated with impaired memory and executive ability in older adults.[68–70] Further, both lead and cortisol are thought to alter common pathways in the mesocorticolimbic system, including calcium- and glutamate-mediated processes.[64,67,71] Both cortisol and lead are associated with similar domains of cognitive function (especially memory and executive functioning). Glucocorticoid receptors are present in brain structures underlying these domains.

In 2 human studies, the inverse associations between bone lead level and cognition and blood pressure were more pronounced among men who self-reported greater stress.[72,73]

The role of the social or physical environment in modifying lead neurotoxicity was demonstrated by a study in which impaired spatial learning caused by lead exposure in utero through lactation was mitigated by rearing in an enriched environment.[74] It also remediated deficits in gene expression in the hippocampus (i.e., *N*-methyl-D-asparate receptor subunit 1 mRNA and brain-derived neurotrophic factor mRNA).

Early life lead exposure also impairs the response to later brain insult, which may be more common in persons with lower socioeconomic position (SEP). For example, lead-exposed rats showed reduced behavioral recovery to an induced ischemic stroke in the hind limb parietal sensory-motor cortex in adulthood.[75] Early lead exposure also impaired the topographic organization of the columnar processing units in the barrel field somatosensory cortex in rats[76] and reorganization of the barrel field after whisker follicle ablation.[77]

This general finding was also shown in humans. In children, higher cord blood lead levels were associated with higher baseline systolic blood pressure, and higher early childhood lead levels were associated with greater total peripheral (vascular) resistance responses to acute stress.[78] Few studies examined the environmental backdrop that gave rise to the spatial distribution of stress dysregulation. Among older adults living in neighborhoods with the most psychosocial hazards, tibia bone lead concentration had a more deleterious effect on certain domains of cognitive function.[58] Despite these findings, most studies either did not systematically investigate how host characteristics (e.g., stress) altered the effect of lead, or were underpowered to do so.[79]

Air Pollution

Psychological stress might alter susceptibility to air pollution. Social stress and SEP modifed traffic-related air pollution effects on asthma etiology[80] and exacerbation, and on birth weight.[81–83] Given that both psychosocial stress and air pollutants influence oxidative stress and cellular aging processes, future risk assessments must address whether social–environmental interactions contribute to cardiovascular disease.

SOCIOECONOMIC POSITION

SEP has a robust and complex association with many health states. Although the mechanisms underlying SEP gradients in health are not precisely known, different SEP groups clearly have markedly different health statuses as well as vulnerability to the impact of common exposures. The relationship between SEP and poor health is not confined to poor people because the dose–response is continuous.[84] This potential risk modifier cannot be addressed simply by looking at the extremes.

SEP can be conceptualized and measured at both the individual and the area level (e.g., neighborhoods). Each level exerts an independent influence on an individual's chances of health. A wealthy person living in a poor area is exposed to the same excess of fast food, lack of nearby fresh produce, higher crime rate, greater distance to pharmacies, and lack of attractive green space as their neighbors, and this tends to impact their health and potentially their response to environmental pollutants.

Lead

Several studies demonstrated that the impact of lead on health was modified by SEP.[85] Children from families of low SEP either expressed an exposure-associated deficit at lower levels of lead or failed to recover and compensate as quickly or completely as children of higher SEP.[79] The effect of increased blood lead levels on children's performance on an end-of-grade reading test was more pronounced at the lower end rather than the upper end of the distribution of reading scores[86] (i.e., the effect was greater among children facing other risk factors for lower achievement). This phenomenon was not restricted to lead. The adverse impact of prenatal exposure to secondhand smoke was significantly greater among children whose families faced greater material hardship.[87] To understand such findings, it is necessary to deconstruct the complex construct of SEP into its component features, including nutrition, stress, other chemical exposures, and the social and physical environment. All might contribute to the apparent modification of lead toxicity by SEP.

Many studies treated SEP solely as a confounder of the lead–health association.[88] Given the usual association between increased lead exposure and other risk factors, potential confounding by SEP must be considered, but careful consideration must also be given to the possibility that treating SEP solely as a confounder could lead to bias if lead exposure is on the causal pathway between SEP and health. This arises from the social patterning of lead exposure

along socioeconomic lines.[89,90] Methodological tools such as directed acyclic graphs or structural equation modeling might be useful in dissecting these complex relationships.

Air Pollution

Some evidence suggested that SEP modified the effect of air pollution. In a city where upper SEP individuals had higher exposures, the effects of PM10 on daily death varied by SEP,[91] a result consistent with other findings.[92,93] There was similar evidence on other outcomes, such as preterm delivery[94] or birthweight.[83]

AGE

The elderly represent a particularly susceptible population, and by 2030, the proportion of the US population aged 65 and older will double. Cognitive decline in the elderly is a growing burden, and the number with dementia is expected to almost triple by 2040. Heterogeneity in cognition is especially pronounced in the elderly compared with younger adults,[69] raising the question of whether environmental factors might be contributory. Air pollution was linked to increased inflammation in the brain,[95] which was implicated in the development of Alzheimer's disease.[96]

The elderly are also at increased risk of cardiovascular disease, and air pollution has differential effects for a number of cardiovascular endpoints, including mortality.[42,97–99]

Children are also considered to be a susceptible subgroup. Their greater vulnerability is attributed to metabolism (e.g., greater absorption of toxicants, reduced excretion, immaturity of detoxification pathways), developmental stage (e.g., ongoing development and organization of organs such as the central nervous system), and behavior (e.g., greater hand-to-mouth activity, greater relative dietary and respiratory intake of toxicants).[100]

Infants are born with only one-tenth the number of alveoli of adults and an underdeveloped epithelium. Alveolar development begins late in the third trimester.[101] This postnatal development pattern is not merely a theoretical concern for air pollutants. Compared with controls, infant monkeys exposed to 5 months of episodic exposure to 0.5 parts per million of ozone had fewer airway generations, hyperplastic bronchiolar epithelium, and altered smooth muscle in terminal and respiratory bronchioles.[102]

OTHER ENVIRONMENTAL AGENTS

Evidence that coexposure to other neurotoxicants increases the likelihood of lead-associated impairments is limited and comes mostly from animal models.[103–106] In humans, 2 studies[107,108] reported that the slope of the inverse relationship between blood lead level and neurodevelopment in infants was steeper among those with higher blood manganese levels. In NHANES (1999–2006), adults whose blood levels of cadmium and lead were both in the highest quartiles had greater odds of albuminuria and a reduced glomerular filtration rate.[109]

SOURCES OF SUSCEPTIBILITY

In addition to interacting with risk factors such as stress, SEP, genetics, and preexisting disease, lead and air pollution often covary with them, resulting in a further skewing of the risk distribution.

Lead

Since the 1980s, NHANES surveys have documented substantial socioeconomic and ethnic disparities in blood lead levels.[110,111] Although blood lead levels have fallen, disparities remain. Among 1–5 year olds in NHANES 1999–2004, the frequencies of blood lead levels greater than 10 micrograms per deciliter, by race/ethnicity, were non-Hispanic Black 3.4%, Mexican-American 1.2%, and non-Hispanic White 1.2%. The frequencies were higher among poorer children and those on Medicaid. The strongest risk factors for higher blood lead levels were residence in older housing, poverty, age, and being non-Hispanic Black.[112]

Several genetic variants or polymorphisms that affect lead metabolism were examined in relation to their influence on internal dose or lead-related health effects. These included ALAD, the dopamine receptor D4, the HFE protein, Apo-E, and peptide transporter 2. Several studies compared lead biomarkers in individuals with the 2 codominant ALAD alleles (ALAD-1 and ALAD-2). There were substantial inconsistencies across studies, although some reported that ALAD-2 carriers had greater blood or cortical bone lead levels.[5,113–115] The plasma and whole blood lead ratio might be greater in ALAD-2 carriers.[116] In a sample of Hispanic children, those homozygous for the peptide transporter 2 polymorphism had higher blood lead levels than those who were heterozygous or without this polymorphism.[115] Children who were carriers of the variant HFE or transferrin gene had significantly higher blood lead levels than wild-type children, and children carrying both variants were more likely to have a blood lead level $>$ 10 microgram per deciliter.[117] Adult workers with the Vitamin D B allele had significantly higher patella lead levels.[118]

Systematic data are not available on the distribution of genetic variants of interest in relation to ethnicity and other demographic characteristics.[119] However, the prevalence of some variants did vary by geographic region. The prevalence of ALAD-2 carrier status is 3% in Indian workers,[113] 8% in Chinese children,[120] and 16% in US men.[4] In another study, the frequencies of ALAD-2 allele were comparable in Asian and Caucasian samples but absent in African samples.[121]

Dietary factors such as iron and calcium might modify lead absorption or toxicity.[122] In adult men, reduced dietary vitamin D was associated with increased bone lead levels, whereas decreased dietary Vitamin C and iron were associated with increased blood lead levels.[123] Among children in the Philippines, higher folate and iron levels mitigated the inverse association between blood lead level and cognition.[124]

Air pollution

SEP is associated with exposure to a variety of air pollutants. In one study, Blacks and respondents of lower educational achievement and, to a lesser degree, lower income levels, were significantly more likely to live within a mile of a polluting facility.[125] Exposure to air pollution from traffic was higher in persons of lower SEP.[83,126,127] In addition, exposure to pollution from concentrated animal feed lots varied by SEP and race.[128] Ambient air pollution concentrations were higher in

neighborhoods where pregnant women were at higher risk for adverse pregnancy outcomes because of lower social conditions.[129] People living in disadvantaged communities had higher exposure to both indoor and outdoor air pollution, and factors associated with poverty (e.g., cooking time, gas stove usage, occupant density, humidifiers) contributed to higher indoor concentrations of PM2.5 and nitrogen dioxide.[130] Using such covariation of exposures with susceptibility factors, a recent risk assessment showed considerable disparity in the impact of air pollution on mortality in Mexico,[131] and, relevant to cumulative risk assessment, showed the same disparity gradient for poor water quality and cooking fuel use.

CUMULATIVE EXPOSURE

The phrase cumulative exposure is used to describe 2 phenomena: (1) long-term sequelae of continuing exposure to a substance, and (2) the cumulative burden resulting from exposure to many stressors. Regarding the first, links were demonstrated between cumulative lead exposure (i.e., bone lead) and heart rate variability,[38] hypertension,[132,133] ischemic heart disease,[134,135] and death.[136] Examples of the second phenomenon were provided, namely, the enhancement of toxicity through interactions among different stressors. Several frameworks were established to conceptualize cumulative exposure to all stressors over the life course. These included Geronimus's concept of weathering[137,138] and the concept of allostatic load.[34,139] Both attempted to capture the cumulative wear and tear that occurs as a result of long-term exposure to multiple stressors and results in increased vulnerability and decreased reserve capacity. Zartarian and Schultz[140] summarized various efforts undertaken by the Environmental Protection Agency to assess cumulative exposure in communities, including the "Cumulative Communities Research Program" within the National Exposure Research Laboratory. As Menzie et al.[141] argued, a key requirement for thinking about cumulative exposures is the development of clear conceptual frameworks. Complications arise when there are interactions among multiple exposures, or when there are latencies in the onset of biological effect.

MARKERS OF CUMULATIVE EXPOSURE

Assessing cumulative burden from multiple stressors is difficult, and consideration of this issue could be advanced if a biomarker of cumulative burden were available. Telomeres are regions of noncoding DNA at the ends of chromosomes that protect against structural degradation, inappropriate recombination, and end-to-end fusion of chromosomes.[142,143] Telomere length declines with each successive cell division and thus serves as a measure of biological aging.[144] Shorter telomeres are also associated with chronic diseases, including diabetes,[145] hypertension,[145–148] atherosclerosis,[149] coronary artery disease,[150,151] heart failure,[152] and increased cardiovascular risk.[145,153] Evidence from in vitro[154–156] and human studies[145,155] suggested that oxidative stress and inflammation accelerate telomere shortening. Reduced blood DNA telomere length was also related to cumulative long-life exposure to tobacco smoking[157,158] and to traffic pollution.[159] Whether this is a useful biomarker either of susceptibility or cumulative burden is unclear, but the possibility deserves consideration.

CONCLUSIONS

Many risk assessments use uncertainty factors to address variability in susceptibility. However, that is usually taken as reflecting both a stochastic issue in extrapolating from observed data and an assumed random variability in toxicokinetics. Studies based on human epidemiology in the exposure range of interest, such as those done for criteria air pollutants, rarely incorporate uncertainty factors. The examples provided show that these approaches are not tenable because not only are there substantial variations in the effects of exposure, but the factors that produce such variation often covary with the exposure of interest. Hence, the distribution of risk is a key issue, which must be directly quantitated and provided to decision makers to use in conducting risk assessments. ■

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