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Developmental Exposure to Air Pollution, Cigarettes, and Lead: Implications for Brain Aging

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Abstract

Brain development is impaired by maternal exposure to airborne toxins from ambient air pollution, cigarette smoke, and lead. Shared postnatal consequences include gray matter deficits and abnormal behaviors as well as elevated blood pressure. These unexpectedly broad convergences have implications for later life brain health because these same airborne toxins accelerate brain aging. Gene-environment interactions are shown for *ApoE* alleles that influence the risk of Alzheimer disease. The multigenerational trace of these toxins extends before fertilization because egg cells are formed in the grandmaternal uterus. The lineage and sex-specific effects of grandmaternal exposure to lead and cigarettes indicate epigenetic processes of relevance to future generations from our current and recent exposure to airborne toxins.

Contents

INTRODUCTION

Environmental factors are the main cause of the 15-year divergence of life spans across socioeconomic status (SES). We consider the role of airborne toxins from ambient air pollution (AirPoll), cigarette smoke (CigS), and lead (Pb) as part of the ambient exposome across the life span (see the sidebar titled Definitions). Developmental consequences of airborne toxins for later life health are

DEFINITIONS

Air pollution (AirPoll): The ambient air we breathe includes a complex mixture of particles and vapors that is constantly changing during daily and seasonal cycles of sunlight and wind-borne sources (Finch 2018). Its multifarious components include organic and elemental carbon, polycyclic aromatic hydrocarbons (PAHs), metals, ions, earth dust, and smoke from burning biomass. Airborne particulate matter (PM) is classified by size: coarse PM10 ($\geq$10 μm diameter), fine PM2.5 ($\leq$2.5 μm), and ultrafine PM0.1 (<0.1 μm). The US Environmental Protection Agency monitors PM10 and PM2.5, but not PM0.1. PM0.1 may be the most dangerous because it deeply penetrates into the lungs and because the greater surface area per mass ratio increases the chemical exposure. The larger PM10 are considered less dangerous; most are trapped by mucosa of the upper airways or swallowed. Rodent experimental studies typically use PM0.1 or PM0.2, which limits comparisons with epidemiological findings on PM2.5 and PM10.

    Exposome: The exposome framework was developed to comprehensively assess interactions of multiple exogenous and endogenous toxins across the human life course (Natl. Acad. Sci. Eng. Med. 2017). The exposome concept extends prior approaches that characterized each factor with limited accounting for their interactions and synergies. Wild (2012) identified three domains: the exogenous macrolevel (rural versus urban, social stratification), the exogenous individual (diet, infections), and the endogenous domain (biomes, fat depots, injuries). The exposome includes environmental exposure in all stages of life history, from prefertilization gametes to development and later life. We developed this framework for brain aging in the Alzheimer exposome (Finch & Kulminski 2019) and in human evolution (Trumble & Finch 2019).

    Gerogen: We introduce the term gerogen to represent environmental toxins and stressors that accelerate aging processes as discussed for AirPoll and CigS. Exogenous gerogens shorten life expectancy in association with increased risk of AD, cancer, and ischemic events. Endogenous gerogens include fat depots, hypercholesterolemia, and hyperglycemia; all are risk factors for accelerated brain aging, cardiovascular disease, and premature mortality.

    Polycyclic aromatic hydrocarbons (PAHs): These multiring organic compounds include carcinogens, e.g., benzo[a]pyrene, found in tobacco smoke and to varying extents in AirPoll. Besides carcinogenicity, some PAHs are endocrine disruptors through interactions with steroid receptors.

Table 1   Global mortality from air pollution, cigarette smoke, and lead

Pollutant	Mortality, million/year	Reference
Ambient air pollution	6.5–9	Burnett et al. 2018, Landrigan et al. 2018,
Household air pollution	4	WHO 2018
Cigarette smoke, direct	8	GBD 2015 Tob. Collab. 2017
Secondhand smoke	0.65	
Lead	1	Inst. Health Metrics Eval. 2018

not widely discussed. Gerogens that accelerate later brain aging may have had a first impact on a mother's ovaries before her birth, when all egg cells are formed within the environment of the grandmaternal uterus. Genetic influences on health and disease can be understood only in terms of gene-environment (G×E) interactions for the individual exposome. As described in the section titled Synthesis and Summary, this diverse literature shows unexpected convergences of AirPoll, CigS, and Pb on development and aging, implying shared mechanisms throughout the life span.

AirPoll is associated with accelerated cognitive aging and Alzheimer disease (AD) (Calderón-Garcidueñas et al. 2020b, Costa et al. 2020, Finch & Kulminski 2019). G×E interactions of *ApoE4* increased the association of AirPoll with AD risk in population-based studies (Cacciottolo et al. 2017, Kulick et al. 2020). The ambient exposome of AD also includes CigS and Pb (Finch & Kulminski 2019). Together, 20 million excess deaths are attributed to these three classes of airborne toxins (**Table 1**). However, their interactions are not resolved for mortality or AD during improvements in air quality. Since 1950, use of leaded gasoline has gradually decreased, but Pb continues to contaminate food and water (Frank et al. 2019). While smoking has decreased, more than 13% of US adults smoke, exposing 40% of children to secondhand smoke (SHS), with a lower SES excess.

The brain is vulnerable to AirPoll, CigS, and Pb during development and in adult life. The later-life impact on the brain is less described for AirPoll than for CigS, and that of Pb is almost uncharted. We hope to show how their impact on development is relevant to later-life brain health. A life history approach to environmental toxicity was utilized for Pb toxicity (Reuben et al. 2017, Sobolewski et al. 2020), but has not considered interactions of Pb with AirPoll and CigS. However, AirPoll and CigS interact with synergies exceeding twofold excess additivity (**Table 2**). Three-way interactions are undefined for AirPoll, CigS, and Pb and merit examination for the low SES exposome.

Inhaled and ingested AirPoll, CigS, and Pb may share toxic pathways and epigenetics. Because AirPoll and CigS accelerate many aging processes, we consider them to be gerogens. We anticipate cohort-specific G×E interactions for outcomes of brain development that impact cognitive aging.

Table 2   Synergies of air pollution and cigarette smoke

Entity affected	Study	Supra-additivity
Body mass index	Southern California Children's Health Study[a];	1.3-fold excess
	meta-analysis, 12 studies[b]	1.6-fold excess
Cardiovascular mortality	American Cancer Society Prevention Study II[c]	1.1-fold excess
Cancer of the lung	American Cancer Society Prevention Study II[b]	2.2-fold excess
Cognitive decline	Health and Retirement Survey 2004[d]	1.9-fold excess

Table adapted from Forman & Finch (2018).
[a]McConnell et al. (2015).
[b]Turner et al. (2014).
[c]Turner et al. (2017).
[d]Ailshire & Crimmins (2014).

Multigenerational effects are expected because ovarian oocytes are formed in the grandmaternal uterus (Finch & Loehlin 1998). Lineage- and sex-specific effects of grandmaternal exposure to Pb in mouse models indicate epigenetic processes of relevance to future generations from past exposure to Pb from the decades of tetraethyl Pb in gasoline.

AirPoll AND BRAIN DEVELOPMENT

AirPoll adversely influences brain development. While many consequences are recognized for childhood behavior and cognition, their implications for brain health in later life have not been widely appreciated. We discuss examples from the rapidly expanding body of human observations, followed by a detailed discussion of rodent experimental studies that identify cell and molecular mechanisms.

Early Phases of Brain Aging

In 1907 Alzheimer described neurofibrillary degeneration in a woman aged 56 (Stelzmann et al. 1995), which became known as neurofibrillary tangles and was further characterized by hyperphosphorylation of tau (P-tau). Recently, brain imaging by PET (positron emission tomography) showed the increasing prevalence of P-tau during middle age together with aggregates of the amyloid peptide Aβ, despite apparent cognitive health, and wide variations between individuals (Jack et al. 2018). Vascular micropathology and blood-brain barrier leakage also begin in early middle age (Sweeney et al. 2019). Criteria for AD and other dementias include selective atrophy of brain regions indicative of neuron death in the entorhinal cortex-hippocampal pathway as well as increased levels of P-tau and amyloid. The boundaries between normal aging and AD are unresolved, and no biological definition of AD is widely accepted (Jack et al. 2018, Musiek & Holtzman 2015). Even children may have P-tau, as shown in postmortem histological studies (Braak et al. 2011, Calderón-Garcidueñas et al. 2020a). Because P-tau also increases at later ages in chimpanzees and macaque monkeys that do not develop neurodegenerative AD (Finch & Austad 2012), we consider P-tau as a biomarker for brain aging rather than for AD.

Air pollution and brain development. Inhaled urban black carbon particles reach the placenta on the fetal and maternal sides and in proportion to their ambient residential levels, up to 30,000 particles/mm^3 [Environmental Influence on Early Ageing (ENVIRONAGE) study] (Saenen et al. 2015). Further studies showed oxidization of placental proteins and mitochondrial DNA, shorter telomeres, and altered methylation of genes for DNA repair and tumor suppression (Ladd-Acosta et al. 2019; Saenen et al. 2016, 2017, 2019). Placental telomere length was shortened in proportion to ambient maternal particulate matter $\leq$2.5 µm (PM2.5), suggesting accelerated aging.

Risks of premature birth are also increased by maternal exposure to AirPoll in the third trimester. A benchmark study of 183 countries estimated that 18% of prematurity (<37 weeks) was associated with PM2.5 exposure >10 µg/m^3 (Malley et al. 2017). During the Summer Olympic Games of 2008 when traffic was restricted, full term birthweights in Beijing were 23 g heavier than for these months in prior or following years (Rich et al. 2015). In both studies, the third trimester was most vulnerable to AirPoll. Premature birth may increase risks for accelerated cognitive decline of aging, as suggested by retrospective studies that associated prematurity with 2.7-fold risk of mild cognitive impairment at age 68 (Helsinki Birth Cohort) (Heinonen et al. 2015) and 1.66-fold risk of premature cardiac disease (Ontario, Canada) (Silverberg et al. 2018).

AirPoll impairs brain development (Guxens et al. 2018), as shown in three examples. In the Cincinnati Childhood Allergy and Air Pollution Study, gray matter volumes were 3% smaller by
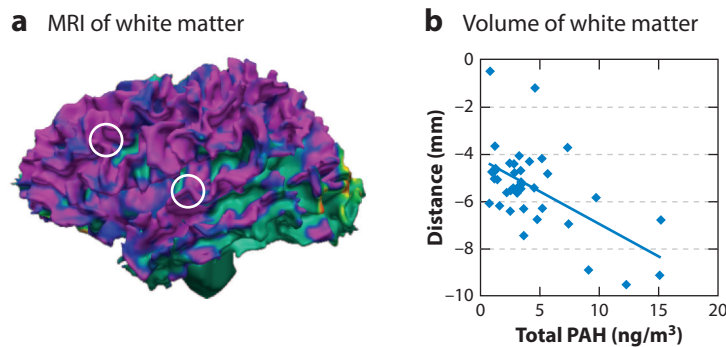
a MRI of white matter   **b** Volume of white matter

Figure 1

(*a*) Magnetic resonance imaging (MRI) of white matter surfaces. (*b*) Myelination growth (volume) was retarded in children with inverse correlation to third trimester levels of polycyclic aromatic hydrocarbon (PAH) (data from Mothers and Children Study, New York City). Figure adapted with permission from Peterson et al. (2015). Copyright 2015 American Medical Association; all rights reserved.

magnetic resonance imaging (MRI) volume for high versus low residential exposure up to age 12 years (Beckwith et al. 2020). The vulnerable regions included posterior frontal and anterior parietal lobes and the cerebellum. Because lower SES typically increases exposure to AirPoll (Hajat et al. 2015), it is not surprising that lower SES was also associated with impaired brain development. The Generation R Study further showed myelin deficits in preadolescents in association with developmental exposure; AirPoll factors were further resolved in multicomponent models for NOx, silicon, and zinc (Lubczyńska et al. 2020). Maternal polycyclic aromatic hydrocarbons (PAHs) are also implicated. In the Mothers and Children Study, myelin volume varied inversely with maternal levels of PAHs (see the sidebar titled Definitions), as shown for frontal cortex (**Figure 1**) (Peterson et al. 2015). These same prefrontal cortical regions are altered in autism spectrum disorder (ASD). The slower cognitive processing speed and impaired impulse control varied linearly with myelin volume and PAH exposure. Sources of maternal PAH included urban traffic together with maternal and household smoking.

Autism spectrum disorder. AirPoll has emerged as an environmental risk factor for ASD. A multiethnic sample showed 1.2-fold ASD risk for boys per 6.5 μg/m³ of PM2.5 in the third trimester (Jo et al. 2019). These 2,471 cases came from 246,420 births from Kaiser Permanente of Southern California, 1999–2009. This largest cohort study to date confirmed the male bias of AirPoll-associated ASD for Los Angeles (Volk et al. 2011), other US states (McGuinn et al. 2020), and Sweden (Oudin et al. 2019). Experimental studies also show gestational vulnerability of males to AirPoll for behavior dysfunctions, as discussed in the section titled Behavior.

Metabolism and obesity. Gestational AirPoll exposure is associated with postnatal adiposity and diabetes in population-based studies. Fetal leptin and adiponectin increased with higher maternal exposure to PM2.5 (MIREC Study, 1,257 maternal-infant pairs) (Lavigne et al. 2016). Elevated leptin anticipates postnatal adiposity because cord blood leptin is correlated with fat mass at birth (Avon Longitudinal Study of Parents and Children) (Simpson et al. 2017). Risk of pediatric diabetes (insulin deficient) was doubled for first trimester exposure to elevated ozone (Elten et al. 2020).
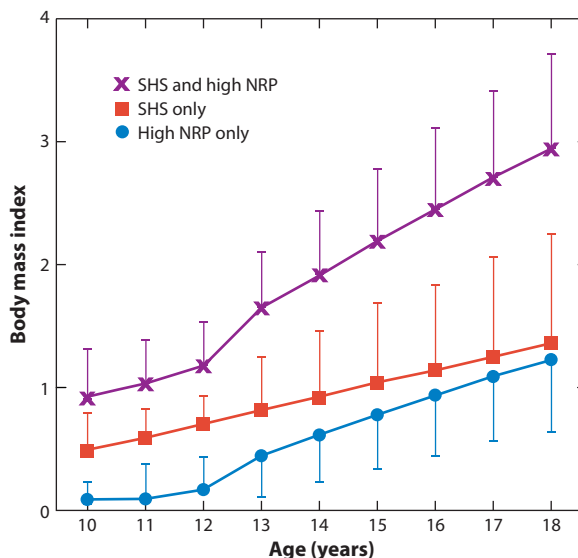
Figure 2

The body mass index of children aged 10–18 years exposed to secondhand smoke (SHS) and near roadway air pollution (NRP). From longitudinal annual measurements of 3,318 children and subadults aged 10–18 years in the Southern California Children's Health Study. These effects showed dose responses with the number of household smokers. Figure adapted from McConnell et al. (2015) (public domain).

Childhood obesity was associated with prenatal and postnatal PM2.5 exposure in the Boston Birth Cohort (1,446 mostly low SES children) up to age 7 years (Mao et al. 2017). Associations with PM2.5 were strongest for pregnancy and the first 2 years.

CigS interacts with AirPoll. Children living near a roadway had higher body mass index (BMI) at ages 10–18 in the Southern California Children's Health Study (McConnell et al. 2015) (**Figure 2**). SHS exposure also increased BMI. Moreover, the combination of living near a roadway and SHS exposure was synergistic, with 30% higher impact than simple additivity. Together, these epidemiological findings show the continuity of prenatal and postnatal AirPoll effects on childhood obesity into young adulthood and interactions of overlapping biological substrates. AirPoll-CigS interactions are discussed further in the section titled Tobacco.

Arterial aging and cardiovascular disease. Children's blood pressure was increased by gestational exposure to PM2.5 in two prospective studies, the Boston Birth Cohort (1,293 mothers; Zhang et al. 2018) and the Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) study from Mexico City (537 mothers; Rosa et al. 2020). The latter study defined a critical window during midgestation for association of ambient PM2.5 with systolic pressure at age 4 years. The carotid artery stiffness of young adults varied in proportion to prenatal PM2.5 exposure (Breton et al. 2016). The loss of 5% carotid elasticity per 15 μg/m^3 of PM2.5 was equivalent to premature arterial aging by two or more years. The acceleration of carotid aging by AirPoll for prenatal and postnatal exposure shows its scope as a gerogen.

Rodent exposure models. The main AirPoll source for experimental studies is ambient PM collected from traffic-related air pollution (TRAP). The diverse experimental paradigms used for developmental exposure differ in composition and exposure schedules (**Table 3**). Some studies

Table 3 Developmental exposure paradigms for rodents

Pollutant	Mass	Delivery/schedule	Age examined
Diesel exhaust			
Direct (Bolton et al. 2012)	2 mg/m^3	Inhalation/E9–E17: daily (9 days)	E18; 4–5 months; 6 months
Direct (Yokota et al. 2016)	90 μg/m^3	Inhalation/E2–E17, 8 h/day	3 months
DEPs (Bolton et al. 2013, 2014, 2017)	50 μg	Oropharyngeal aspiration/E2–E17, every 3 day (6 doses)	PND 60; 4–5 months; 7 months
DEPs (Ehsanifar et al. 2019)	350–400 μg/m^3	Inhalation/3-week gestation: 2, 4, and 6 h/day	8–9 weeks
TRAP			
CAPs (Klocke et al. 2017, 2018a,b)	90 μg/m^3	Inhalation/gestation 0.5–16.5, 6 h/day	PNDs 11–15 and 57–61
Filter nPM (Davis et al. 2013)	350 μg/m^3	Inhalation/premating 7 days + 3-week gestation 5 h/day*; 3 days/week (150 h)	5 months
Filter nPM (Haghani et al. 2020a)	300 μg/m^3	Inhalation/gestation: 5 h/day; 3 days/week (total 45 h)	8 months

Asterisk indicates 7 weeks before conception + 3-week gestation. Abbreviations: CAPs, concentrated ambient particles; DEPs, diesel exhaust particles; nPM, nanosized particulate matter; PND, postnatal day; TRAP, traffic-related air pollution.

use diesel exhaust (DE) directly or as DE particles (DEPs) collected on a filter, which are suspended in water for intubation directly into lungs (oropharyngeal aspiration) (Bolton et al. 2013) or reaerosolized for inhalation (Ehsanifar et al. 2019). However, both DE and DEPs lack roadway dust and chemical modifications by sunlight, ozone, etc. Ambient TRAP is collected as concentrated ambient particulate matter for direct inhalation (Klocke et al. 2017, 2018a,b). We collected PM0.2 on filters developed by Constantinos Sioutas (University of Southern California) (Misra et al. 2002). Filter-deposited PM0.2 is eluted by sonication and reaerosolized for inhalation studies at stable concentrations (Morgan et al. 2011). We designated these eluates as filter-collected PM0.2 from which we eluted nanosized PM (nPM). The nPM is a subfraction of total PM0.2, which is deficient in PAHs, iron, and other reactive metals; total PM0.2 was also collected directly in slurry (sPM0.2) (Haghani et al. 2020a). Ozone also adversely impacts rodent brains (Costa et al. 2019, Jiang et al. 2019, Mumaw et al. 2016) but is not discussed because of space constraints.

Our initial study exposed female mice for 7 weeks 5 h/day, 3 days/week before mating to expose the preconceptual oocyte during its maturation and continuing through gestation (Davis et al. 2013). Subsequently, we showed that gestation exposure alone had the same impact (Haghani et al. 2020a). Other groups exposed pregnant mice on specific gestational days: The Bilbo lab used oropharyngeal aspiration every 3 days during E2–E17 (Bolton et al. 2013), while the Cory-Slechta lab exposed mice for 6 h/day from E0.5–E16.5 (Klocke et al. 2017).

Developmental Exposure of Rodents Alters the Brain and Behavior of Neonates and Adults

Next, we discuss how the exposure of rodents to AirPoll during early development can induce neuroinflammation. Males are more vulnerable to long-lasting effects on behavior, neurogenesis, myelination, and neurotransmitters. The developmental impact of AirPoll may be seated in differentially expressed genes, which are more numerous in adult males than females. These effects in rodents parallel human responses.

Neuroinflammation. Gestational AirPoll exposure induces multiple inflammatory responses in brains of prenatal, neonatal, and adult rodents. Specifically, E18 brains from gestational DE/DEP
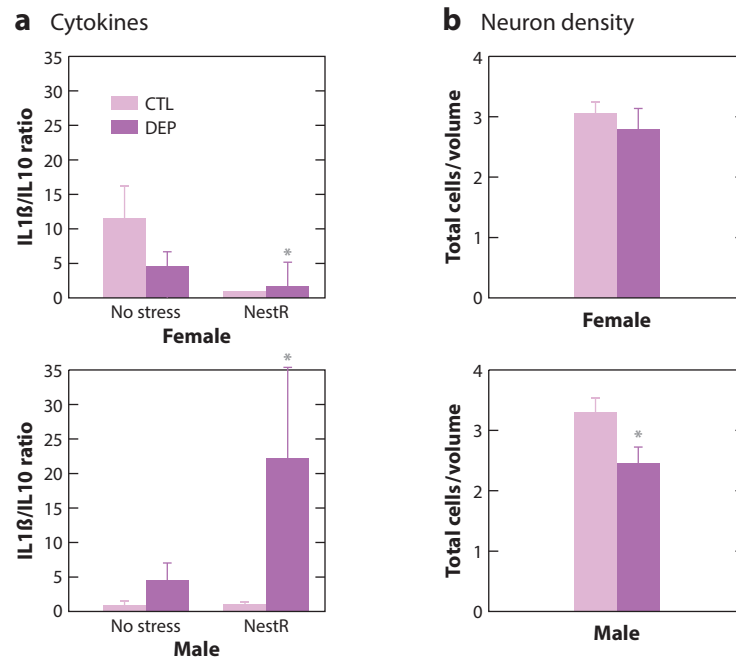
a Cytokines

b Neuron density

Figure 3

(*a*) Proinflammatory cytokines are increased in mice by gestational exposure to diesel exhaust particles (DEPs) alone (No stress) compared to control air (CTL) or with the added stress of nest restriction (NestR). Ratios of IL1β/IL10 in adult forebrains of mice. Sexes diverged in direction of response to DEPs and NR. Panel *a* adapted from Bolton et al. (2013) (public domain). (*b*) Male-specific neuron vulnerability of neonatal mice. Neuron density in the nucleus accumbens at postnatal day (PND) 14 after exposure to concentrated ambient particles (PM0.2 at 45 μg/m³) on PNDs 4–7 and 10–13. Panel *b* adapted with permission from Cory-Slechta et al. (2019). Asterisks in both panels indicate $p < 0.05$.

exposure had elevated proinflammatory cytokines, including IL1β, IL6, and MCP1 (Bolton et al. 2012), and microglial activation (Bolton et al. 2012, 2017). These effects persist into adult ages with major sex differences (Bolton et al. 2013, 2017). The ratio of IL1β:IL10 in the adult forebrain showed opposite responses by sex to gestational exposure to DEPs; sex differences were augmented by combining DEPs with nest restriction as a maternal stress (Bolton et al. 2013) (**Figure 3a**). Some responses are mediated by TLR4 (Bolton et al. 2017), an inflammatory pathway also activated by adult nPM exposure (Haghani et al. 2020a, Woodward et al. 2017a). Sex differences in cerebral cortex transcriptomes are described below.

Behavior. A sex-specific increase of depressive behaviors from gestational nPM was found for males in two studies: at age 4 months (forced swim test) (**Figure 4a**) (Haghani et al. 2020a) and persisting to 8 months (tail suspension test) (Davis et al. 2013). Similarly, Bilbo's lab showed increased anxiety (open field or elevated zero maze) in males but not females from gestational DEPs combined with a high-fat diet (Bolton et al. 2012, 2014). The sex specificity of impulsivity differed by age of exposure assessed by a fixed-interval schedule of reinforcement. Postnatal exposure increased the impulsivity of F1 males, whereas adult exposure induced female excess (Allen et al. 2014b).
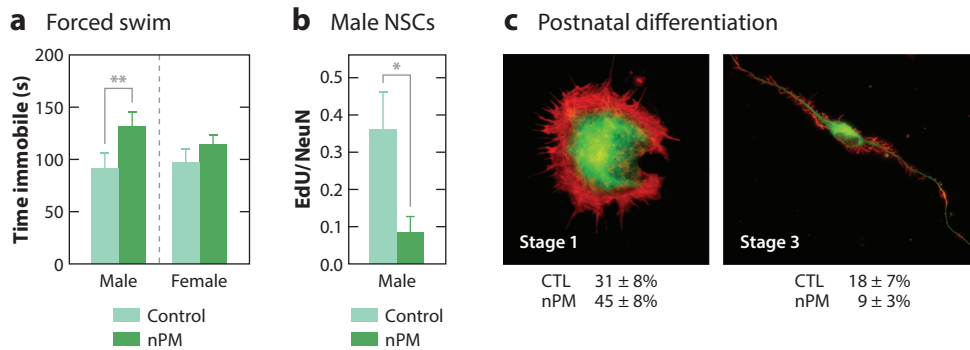
a Forced swim   **b** Male NSCs   **c** Postnatal differentiation

Figure 4

Gestational nPM exposure impairs behavior, neurogenesis, and neuronal differentiation. (*a*) Male mice exhibit depressive-like behaviors (forced swim test), but females do not. Panel *a* adapted from Haghani et al. (2020a) (CC BY-NC-ND 4.0). (*b*) Neurogenesis (EdU+NeuN+ cells) in the dentate gyrus was reduced 50% by gestational nPM. The *p*-values are indicated by asterisks: *, $p < 0.05$; **, $p < 0.01$. Panel *b* adapted from Haghani et al. (2020b) (CC BY). (*c*) In vitro postnatal neuronal differentiation was reduced by 50% for stage 3 nonpyramidal and pyramidalneurons, while stage 1 neurons were increased 50%. Panel *c* reproduced from Davis et al. (2013) (CC BY). Abbreviations: CTL, control air; EdU, ethynyl-2′-deoxyuridine; NeuN, neuronal nuclei; nPM, nanosized particulate matter; NSCs, neural stem cells.

Neurogenesis, myelination, and neurotransmitters. Processes underlying the behavioral effects of gestational exposure are emerging for related cell and biochemical changes. Three studies show impaired neuronal proliferation. Postnatal TRAP caused 35% lower neuron density in the nucleus accumbens of male rats (Cory-Slechta et al. 2019) (**Figure 3***b*). Proliferation of adult neuronal stem cells was decreased by 50% by gestational exposure alone (**Figure 4***b*) (Haghani et al. 2020b) and by exposure during gestation plus young adulthood exposure (Woodward et al. 2018). Neuronal differentiation assessed in cell culture was also impaired by gestational exposure (Davis et al. 2013): Neonatal cultures from the cerebral cortex had 50% fewer maturing stage 3 neurons with long neurites and more early-stage neurons (**Figure 4***c*). While this suggests impaired development, adult brain weight is normal.

Brain structures were grossly altered in some experimental paradigms. Postnatal exposure enlarged cerebral ventricles of males (Allen et al. 2014a, 2017), whereas gestational exposure enlarged ventricles of both sexes (Klocke et al. 2017). The corpus callosum was enlarged by gestational exposure in both sexes by age 2 months (Klocke et al. 2017). This hypermyelination corresponded to a maturational stage shift of oligodendrocytes (postnatal days 11–15: mature CC1$^+$ > immature Olig2$^+$) (Klocke et al. 2018a). Microbleeds, an accelerated aging pathology, were increased by gestational exposure brain-wide followed by postnatal exposure (Cory-Slechta et al. 2019, Klocke et al. 2018b) and in the hippocampus after gestational plus adult exposure (Woodward et al. 2018).

Behavioral changes were accompanied by changes in neurotransmitters and receptors. For example, DE-exposed male mice exhibiting greater social isolation-induced territorial aggressive behavior than controls also had more dopamine in the prefrontal cortex and nucleus accumbens, but lower serotonin (Yokota et al. 2016). DEP-exposed male mice had decreased hippocampal NR2A and NR3B [measured by polymerase chain reaction (PCR)] (Ehsanifar et al. 2019). The greater sensitivity of males to early postnatal exposures and of females to adult exposures in fixed-interval performance (discussed in the section titled Behavior) was associated with increased glutamate/dopamine ratios in postnatally exposed males and adult exposed females. Importantly, both sexes showed increased glutamate in the hippocampus and frontal cortex. In prenatally
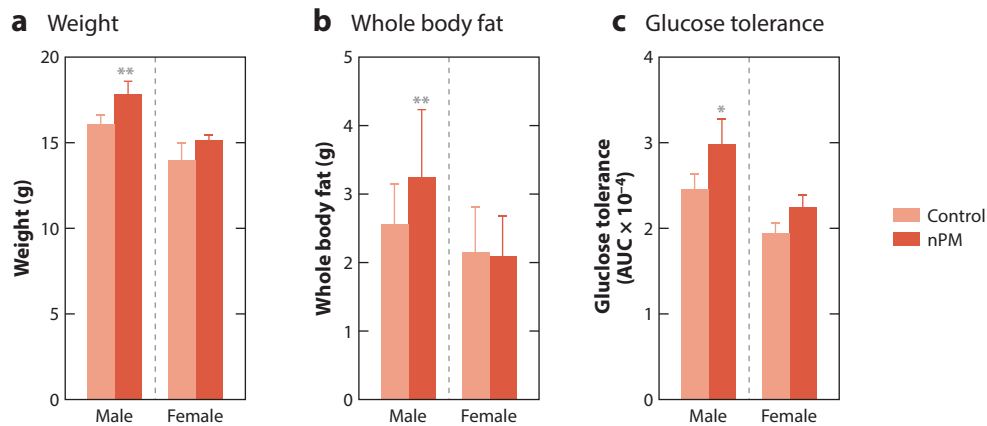
Figure 5

Male-specific metabolic effects of gestational filter-collected PM0.2 [nanosized particulate matter (nPM)] exposure. (*a*) Gestational nPM increased the body weight of male mice (prepubertal, 4 weeks) but did not alter female weight at this age. (*b*) Body fat was greater in males at 4 weeks. (*c*) Glucose tolerance at 16 weeks was impaired in males. The area under the curve (AUC) for blood glucose (mg/dL) during a 2-h glucose challenge was increased by gestational exposure, indicating glucose intolerance. Asterisks indicate *p*-values: *, $p < 0.05$; **, $p < 0.01$. Figure adapted from Haghani et al. (2020a) (CC BY-NC-ND 4.0).

exposed males, but not females, increased hippocampal glutamate levels caused an imbalance of excitatory:inhibitory neurotransmission (glutamate:gamma aminobutyric acid) (Allen et al. 2017). Changed gene expression for neurotransmitter functions is discussed in the section titled Transcriptome Responses to Developmental AirPoll Exposure.

Metabolic effects. While gestational exposure of rodents did not alter litter size or initial birthweight (Bolton et al. 2012, Davis et al. 2013, Klocke et al. 2017), metabolic effects emerged in later life. Prepubertal males were heavier (**Figure 5*a***) and fatter (**Figure 5*b***) at age 4 weeks (Haghani et al. 2020a), confirming effects of gestational DE exposure (Bolton et al. 2012). Glucose tolerance was impaired in males but not females (**Figure 5*c***) (Haghani et al. 2020a). Gestational-to-adulthood nPM exposure also caused male-specific increased food intake, adiposity, and glucose intolerance (Woodward et al. 2019). Corresponding regulators include decreased levels of neuropeptide Y (anorexigenic) in the hypothalamus and insulin receptor mRNA in adipocytes (Woodward et al. 2019). These findings confirm the male specificity for lower hypothalamic neuropeptide Y and increased obesity in a different TRAP model, beginning 7 weeks before mating and continuing through weaning (University of Maryland and Fudan University; Chen et al. 2017). Moreover, premating exposure to concentrated ambient PM2.5 alone enlarged adipocytes for grandsons (Xu et al. 2019). This key observation shows that AirPoll can impact maturing oocytes before fertilization.

Transcriptome responses to developmental AirPoll exposure. The transcriptome of the adult hippocampus and cerebral cortex responded to AirPoll during development with 29 differentially expressed genes, e.g., IL17 and other cytokines, as well as the AD-related Psen2 (**Figure 6**) (Haghani et al. 2020b). PCR also identified decreased expression of synapse-related genes including glutamatergic genes (GluA1, GluA2, Glt1, Glul, Glast, Grin1, and Nmda3a) (Haghani et al. 2020a). The increased expression of serotonin receptors HTR1b (1.5×) and HTR1D (2.5×) was male specific (Haghani et al. 2020b). Another subset with Mir9 (noncoding microRNA) and IL12
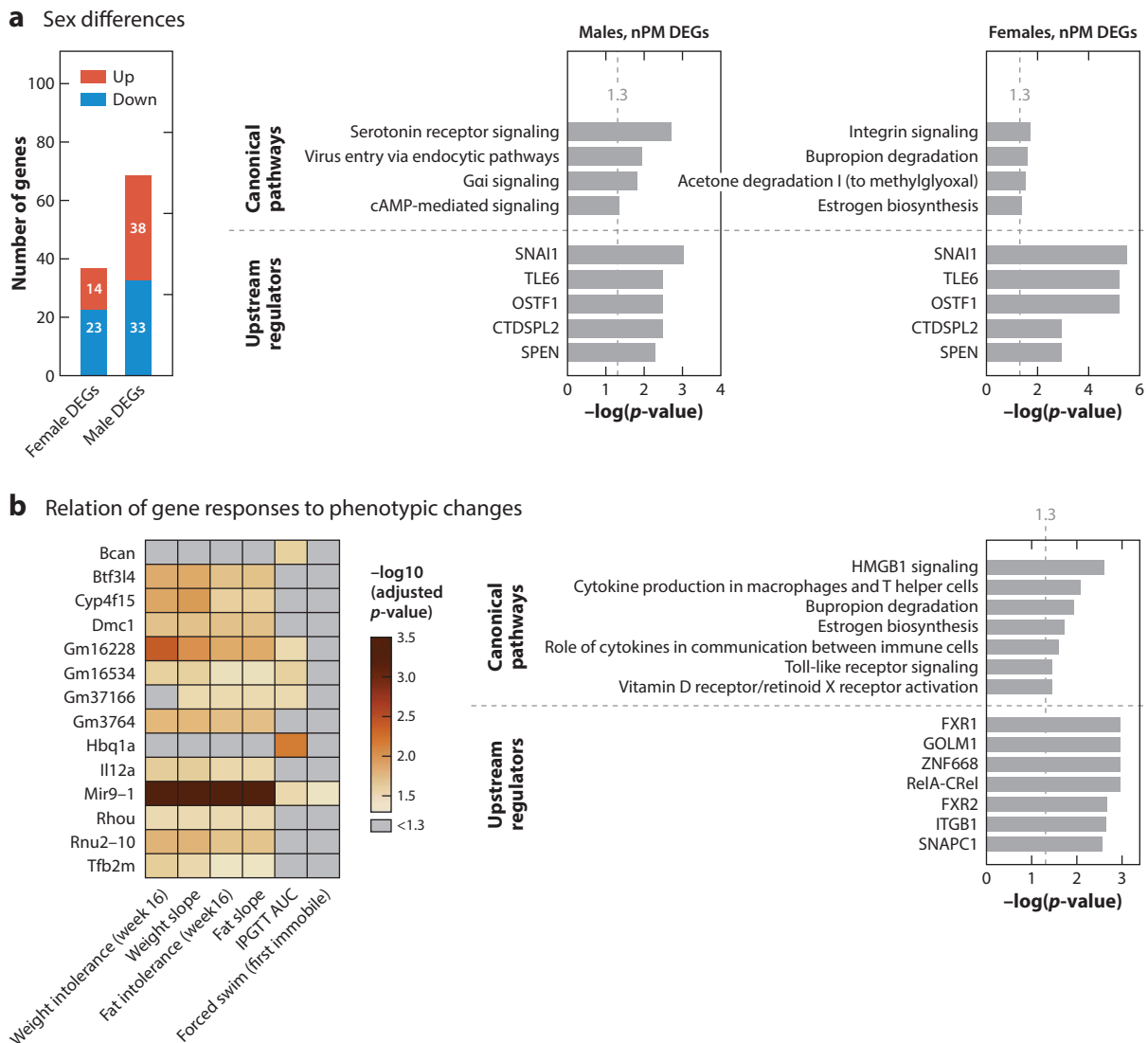
a Sex differences

b Relation of gene responses to phenotypic changes

Gestational AirPoll exposure (nPM) alters gene expression in the hippocampus of adult mice by analysis of the Rseq transcriptome. (*a*) Sex-specific hippocampal RNA responses. The number of DEGs at $p < 0.005$ significance is indicated on the bar chart. (*b*) DEGs are associated with depressive behaviors, glucose intolerance, and body fat. Canonical pathways and upstream regulators were identified by ingenuity pathway analysis. Abbreviations: AirPoll, air pollution; AUC, area under curve; DEGs, differentially expressed genes; IPGTT, intraperitoneal glucose tolerance test; nPM, nanosized particulate matter. Figure adapted from Haghani et al. (2020b) (CC BY).

was correlated with depressive behavior and with adiposity and glucose intolerance (heat map, **Figure 6b**). Other body-wide interactions with brain gene expression are anticipated.

Relevance to humans. Behavioral and genomic responses to developmental AirPoll may cause a predisposition to ASD, adiposity, and accelerated brain aging. The male excess of ASD in humans parallels the male excess of anxiety, impulsivity, social isolation-aggression, and reduced

social interactions in developmentally exposed rodents, described in the section titled Neurogenesis, Myelination, and Neurotransmitters. Increased levels of IL17 are a potential link to ASD (Gumusoglu et al. 2020, Reed et al. 2020). The microRNA Mir9-1 was associated with sex-specific depressive behavior and systemic metabolic changes that have adverse interactions with brain aging and AD risk. Mir9-1 also regulates NFκB1 and other transcriptional mediators of neurodegeneration and stress responses.

The large neuronal deficits in the nucleus accumbens from postnatal exposure to concentrated PM0.2 (**Figure 3b**) should encourage study of other brain regions for altered neuron density. The 50% loss of adult neurogenesis from developmental exposure could accelerate the loss of neural stem cells (NSCs) during aging. A smaller initial NSC pool would be more rapidly depleted during the exponential decline of NSC during normal aging (Kuhn et al. 1996). Other experimental reductions of NSC impaired learning and increased vulnerability to depression and stroke (Peng & Bonaguidi 2018).

Adult gene expression of at least 10 glutamate and monoamine-related enzymes and receptors was altered by developmental exposure. We anticipate interactions of the glutamate deficits with adult exposure to AirPoll, which have damaged glutamatergic neurons in multiple studies. For example, nPM AirPoll exposure consistently decreased GluR1 subunit (Cacciottolo et al. 2017, Morgan et al. 2011) and neurite atrophy of CA1 pyramidal neurons, while sparing neurites of the dentate gyrus (Woodward et al. 2017b). This selective vulnerability to AirPoll of adult CA1 neurites corresponds to the selective CA1 neurodegeneration during AD. Gestational nPM did not alter expression of amyloid pathway genes, with the possible exception of Presenilin 2. Future studies will examine the impact of developmental AirPoll on lipid rafts, in which amyloid peptide production is increased by adult exposure (Cacciottolo et al. 2020).

The increased fat and glucose intolerance of developmentally exposed male rodents parallels the obesogenic impact of AirPoll on children. The persistence of adiposity for three generations suggests that prefertilization oocytes are vulnerable to AirPoll. Grandmaternal CigS also has multigenerational effects.

TOBACCO

CigS is associated with excess global mortality and morbidity throughout life, on the same scale as AirPoll (**Table 1**). Both cause similar diseases and accelerate aging, from the lung to heart to artery to brain. Despite the recent reduction of CigS, more than 30% of US pregnancies are exposed to CigS: 7% of gravid women actively smoke (Drake et al. 2018), while 25% of pregnancies are exposed to SHS (Homa et al. 2015). Altogether, SHS impacts 4 of 10 US children aged 3–11 years (Homa et al. 2015). Maternal CigS is considered the main preventable cause of growth retardation, neonatal deaths, stillbirth, and miscarriage (Diamanti et al. 2019). However, few studies have examined neurodevelopmental consequences (Moore et al. 2020). SES factors were included as covariates in these examples but are not resolved for distinct impact. Little is known of SES interactions with the combination of CigS and AirPoll, which may synergize with childhood obesity and age-related conditions in the heart, lung, and brain (**Table 2**).

CigS and AirPoll share PAHs and other chemicals arising from the combustion of organic materials, although the chemical overlap varies by local AirPoll. Because CigS has a short path from combustion to direct inhalation, CigS typically has much higher levels of carbon monoxide (CO), nitric oxides, and PAHs than does AirPoll, as discussed for brain development (**Figure 2**). The PAHs include at least 16 proven human carcinogens and hundreds of other potential carcinogens and toxins (Hecht 2012, Intern. Agency Res. Cancer 2004). Both AirPoll and CigS also have free radicals that can damage DNA and that are implicated in lung cancer (Pryor 1997). Both share Pb
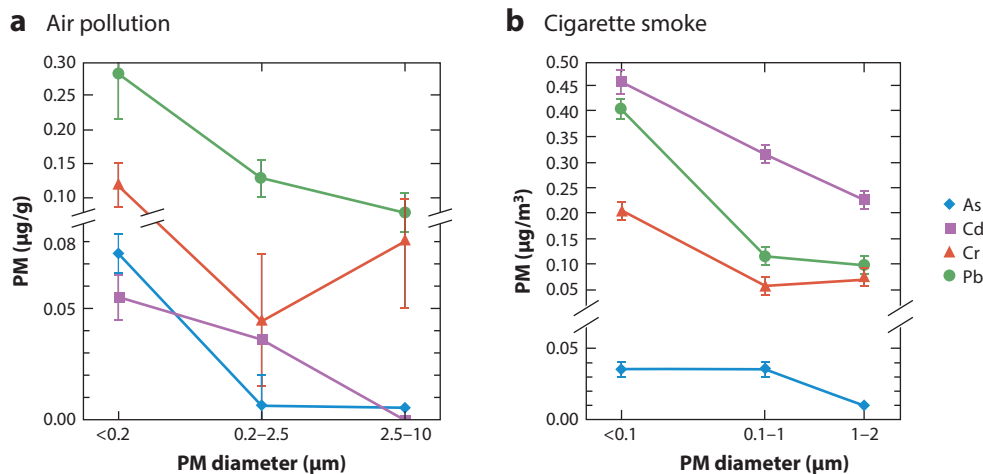
a Air pollution

b Cigarette smoke

Figure 7

(*a,b*) Heavy metals in particulate matter (PM) of air pollution (AirPoll) and cigarette smoke (CigS). The smallest class, <0.2 μm, has the most lead (Pb) for AirPoll (μg/g) and CigS (μg/m³). Metals for AirPoll calculated by Dr. Arian Saffari (University of Southern California) based on near-roadway samples in Los Angeles, CA, USA, 2012–2014 (Shirmohammadi et al. 2015, 2016). Iron and copper were not available by PM size. Abbreviations: As, arsenic; Cd, cadmium; Cr, chromium. Panel *a* adapted from Forman & Finch (2018), and data in panel *b* from Wang et al. (2016).

and other heavy metals: 1–2 μg of Pb is inhaled per pack of 20 cigarettes (Ashraf 2012). The Pb content of smaller PM is enriched for both AirPoll and CigS (Forman & Finch 2018) (**Figure 7**), both of which penetrate deeply into the lungs. Sources of AirPoll Pb in the roadway samples in **Figure 7** include leaded fuel (still allowed for piston aircraft), chemical industries, batteries, paint, roadways, and soil (Frank et al. 2019).

Developmental Exposure to CigS

Fetal growth is consistently impaired by maternal CigS. For example, in the Generation R Study of 10,000 Rotterdam pregnancies, risk of prematurity with 200 g smaller birthweight was three-fold higher from maternal daily smoking of nine or more cigarettes; the third trimester was most vulnerable (Jaddoe et al. 2008a,b). Similarly, the third trimester shows dose dependence of CigS for head size (skull width), femur length, and abdominal circumference (**Figure 8**) (Abraham et al. 2017).

The prospective Behavior and Mood in Babies and Mothers Study associated maternal CigS with neurological dysfunctions. Prenatally, the spontaneous body movement activity was 30% higher in smoking mothers (Stroud et al. 2018). Postnatally, this higher spontaneous prenatal activity predicted with lower attention and self-regulation. Exposed infants had 60% lower cortisol stress responses. Epigenetic effects of maternal CigS included that the promoter for the placental glucocorticoid receptor (NR3C1 gene) had >50% less DNA methylation (DNAme) at two CpG sites (Stroud et al. 2014).

Maternal smoking adversely impacts brain development, consistent with the smaller skull width (**Figure 8**). Impaired cerebral cortex development is suggested by computerized tomography scans from the huge UK Biobank sample (Salminen et al. 2019): At age 62, perinatal CigS was associated with smaller parietal and pericalcerine cerebral cortexes. This sample had 30% more psychiatric
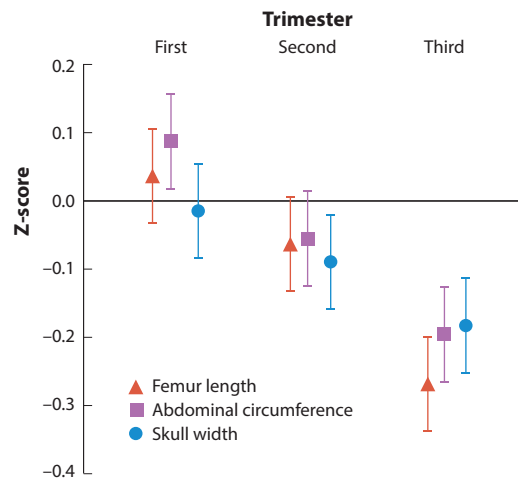
Figure 8

Meta-analysis of 10,000 pregnancies from 16 studies showing that maternal cigarette smoke impairs fetal growth. Z-scores for abdominal circumference, femur length, and skull width (biparietal diameter). Figure adapted from Abraham et al. (2017) (CC BY).

disorders; the smaller cortical areas could have arisen during development or from accelerated aging. In the PIPARI Study of preterm infants, maternal CigS decreased the volumes of the frontal lobe and cerebellum (Ekblad et al. 2010). Cognitive impairments of CigS are indicated but, like the impact on brain size, may interact with maternal alcohol and drug use and other SES-related factors (Gibson & Porter 2018, Palmer et al. 2016).

Longitudinal studies document cognitive-behavioral consequences of maternal CigS with increased risk of conduct disorder, lower IQ, and substance abuse for young adults (Kristjansson et al. 2018, Lotfipour et al. 2014, Obel et al. 2009). These findings are consistent with increased severity of attention deficit hyperactivity disorder (ADHD) and other behavioral problems from gestational CigS found in several studies (Hartman & Craig 2018, Thakur et al. 2013). SES differences include 40% higher smoking by lower income African American women than Hispanic women. The postnatal impact of maternal CigS gives strong rationale to study the interactions of CigS with maternal alcohol and drug use and diet.

Contrary to AirPoll associations with autism (see the section titled AirPoll and Brain Development), CigS exposure has not consistently shown associations with ASD. For the Danish population of one million siblings from 1991 to 2011, ASD did not differ by CigS exposure when analyzed for family factors (Kalkbrenner et al. 2020). Nonetheless, ASD risk may be 50% higher for the F2 generation of grandmaternal smoking lineages without F1 maternal smoking; this study also did not find any F1 association of ASD with F0 maternal smoking (Golding et al. 2017). A grandmaternal effect could arise from maternal smoking effects on the daughter ovary, which develops before birth (Finch & Loehlin 1998). The divergence of CigS with AirPoll for autism could be due to different neural targets, but it also raises the unexpected possibility that the higher levels of CO and nitric oxide in CigS might protect against the shared neurotoxic components of AirPoll.

Childhood BMI is also increased by postnatal exposure to SHS, exacerbated by AirPoll (**Figure 2**) (McConnell et al. 2015), and in the US-wide sample from The National Health and Nutrition Examination Survey (NHANES) (Kim et al. 2014). The SHS impact is further

augmented by residence near major roadways, which increases exposure to AirPoll (near roadway air pollution curve, **Figure 2**). The synergy of this combination (**Table 2**) has major implications for accelerated aging of arteries and brain. Higher childhood BMI increases risk for adult dyslipidemias (elevated triglycerides and LDL cholesterol) that, in turn, increase risk of heart attack (Yan et al. 2019). Midlife dyslipidemias also increase AD (Reitz 2013). Triglyceridemia at midlife was associated with the presence of pathological amyloid and tau 20 years later (bioFINDER, Sweden; Nägga et al. 2018). Cohorts of developmental CigS exposure should be studied at midlife for blood lipids and cognition.

Adult CigS is strongly associated with increased AD risk in multiple studies, e.g., the Atherosclerosis Risk in Community (ARIC) study (population based; Deal et al. 2020) and the Alzheimer's Disease Neuroimaging Initiative (ADNI) (clinical cohorts; Durazzo et al. 2014). Mouse models show that CigS is proamyloidogenic (increased the amyloid load of AD-transgenic mice; Moreno-Gonzalez et al. 2013) and neuroinflammatory for adult offspring with maternal CigS exposure (increased IL1R, IL6, and TLR4; Chan et al. 2016).

Maternal CigS also has epigenetic effects that are observed in neonatal blood cells (Joubert et al. 2012). A recent study of large samples showed association of neonatal blood DNAme with birthweight for 900 CpG sites (meta-analysis of 24 birth cohorts, 8,825 neonates) (Küpers et al. 2019). Per 10% change in DNAme, birth weight differed by 180 g. Genes with the largest associations are *MAP4K2* (increased DNAme, immune functions) and *DHCR24* (decreased DNAme, cholesterol metabolism, decreased expression in AD). The four Hispanic and two African American cohorts also showed modest persistence of DNAme into childhood. By adulthood, the associations of DNAme with birthweight dwindled, and these genes lacked consistent association of DNAme with mRNA in other studies. The relation of DNAme to birthweight is undefined and could be a consequence of retarded growth (Fragou et al. 2019). Paternal smoking may also alter children's DNAme (Mørkve Knudsen et al. 2019).

Animal studies of CigS use reference cigarettes (Johnson et al. 2009) to generate defined levels of nicotine and PM2.5 per micrograms per cubic meter, paralleling mouse AirPoll exposure. Growing evidence shows adult deficits in memory and behaviors. Mice exposed from gestation through weaning spent more time in an open field, suggesting less anxiety, and had impaired spatial memory in Morris and Cincinnati water maze tests (Amos-Kroohs et al. 2013). At age 6 months, the hippocampal proteome of gestationally exposed mice had changes in 34 proteins, including 50% loss of SIRT1, a key regulator of glucose metabolism, and changes of up to 25% changes in enzymes of glucose metabolism (Neal et al. 2014, 2016). These authors hypothesize that memory deficits from gestational CigS arise from energy limitations. Other studies show synaptic deficits in circuits that mediate cognition and behavior. The hippocampal glutamatergic synapses in CA1 neurons had deficits of GluA2 receptors in association with increased postnatal impulsivity and impaired attention (Polli et al. 2020). Neonatal CigS exposure also impaired hippocampal synaptic development through deficits of synaptic proteins (PSD95, synaptophysin), in correspondence with impaired spatial memory (Torres et al. 2015).

Among the hundreds of chemical toxins in CigS, nicotine and benzo[a]pyrene (BaP) are strong candidates for developmental neuroteratogens. Two notable studies show the impact of nicotine ingestion by rodents during pregnancy, approximating the nicotine of a daily pack of cigarettes. Electrophysiological studies showed selective impairments of glutamatergic GluA2 and GluN2A receptor functions in hippocampal CA1 neurons (Polli et al. 2020). Behavioral deficits included impaired attention, hyperactivity, and increased impulsivity, which are core symptoms of human clinical ADHD. Grandmaternal nicotine ingestion (F0) had two generations of impact on behavior, causing greater nicotine preference, hyperactivity, and cholinergic receptor function (Buck et al. 2019). Moreover, the F1 and F2 generations without nicotine exposure had 30–50% lower

levels of the enzymes that epigenetically regulate gene expression, including MECP2, DNMT3A, and HDAC2 in cerebral cortex, in addition to twofold higher phosphorylation of HDAC2 (Buck et al. 2020). These findings are relevant to the increasing use of smokeless cigarettes (vaping), which may reduce exposure to tobacco carcinogens but does not blunt the nicotine addiction. Thus, the twofold higher risk of smoking in children of parental smokers (Leonardi-Bee et al. 2011) has neurobiological as well as cultural components.

Gestational exposure to BaP, an infamous carcinogen in CigS, caused sex-specific behavioral impairments, e.g., increased hyperactivity by 25% in both sexes and decreased fear responses by 20% in males (Hawkey et al. 2019). As noted earlier, BaP is variably present in AirPoll. Maternal ingestion of BaP at gestation days 14–17 also impaired cortical neuron responses to whisker stimulation with 50% decrease of the glutamate receptor subunit NMDA-NR2b (McCallister et al. 2008).

CO is also produced at high levels in CigS that can impair fetal growth in rodents (Carmines & Rajendran 2008). The RESPIRE Study of Guatemalan villages associated household CO from open-hearth fires with childhood deficits of motor control and short-term memory; the third trimester had the strongest associations (Dix-Cooper et al. 2012). Household CO is a global neurotoxin (Levy 2017).

Toxic metals in CigS include Pb (**Figure 7**), and smokers have elevated blood levels of Pb, 30–70% above nonsmokers (NHANES; Agency Toxic Subst. Dis. Registry 2019, table 5). However, neonatal cord blood levels of Pb and other heavy metals have not shown consistent elevations with maternal smoking (authors' survey of Agency Toxic Subst. Dis. Registry 2019).

Despite pervasive medical and societal sanctions, smoking during pregnancy continues in at least 10% of the pregnant population in the United States and transatlantic countries, led by Ireland with 38% (Lange et al. 2018). The growing use of e-cigarettes (US Dep. Health Hum. Serv. 2016) is compounding the apparently intractable hazard of nicotine to public health. We anticipate that e-cigarettes will contribute to maternal effects of smoking beyond the effects of nicotine through Pb and other toxic emanations (Olmedo et al. 2018). Next, we consider ambient sources of Pb for overlapping toxicity with AirPoll and CigS.

LEAD TOXICITY: PLUMBING THE BRAIN

The element Pb is highly toxic and has no role in any enzyme activity or biochemical process. One million deaths/year are attributed to Pb exposure, 50% more than are attributed to SHS (**Table 1**). Pb exposure is also associated with intellectual disability, distinct from known genetic factors, accounting for >60% of the global burden (Inst. Health Metrics Eval. 2018). Lower SES is associated with increased Pb exposure, e.g., non-Hispanic African American children are sevenfold more likely than non-Hispanic white children to have blood Pb of 10–20 µg/dL (Bernard & McGeehin 2003). Nationwide, African American children are at least fourfold more likely to have elevated Pb ≥5 µg/dL (Yeter et al. 2020). Many populations of low-income countries have even greater Pb exposure.

Pb enters the body by three main routes: inhalation, ingestion, and skin absorption (Agency Toxic Subst. Dis. Registry 2019). This monograph from the US Department of Health and Human Services gives a critical and comprehensive summary of Pb toxicity. Inhalation of ambient Pb increased for several generations with the expanding addition of tetraethyl Pb to gasoline to improve its combustion starting in the 1920s. During the past 70 years, the most developed countries have legislatively decreased exposure to traffic-derived Pb. The highest phase of airborne Pb exposure was before 1975 in the United States, followed by >90% reductions by 1990 (Dignam et al. 2019). In 1973, a gallon of gasoline typically contained 2–3 g of Pb. Average blood Pb levels dropped 50% by 1981, followed by gradual further reduction of 94% since 2000. Pb's toxicity

Table 4   Neurobehavioral associations of blood lead 1–10 µg/dL

Entity affected	Children	Adults
Decreased cognition, including full-scale IQ	Yes	Yes
Decreased attention	Yes	Yes
Impaired fine motor skills	Yes	Yes
Impaired visual-motor integration	Yes	Yes
Increased risk	Autism spectrum behaviors	Amyotrophic lateral sclerosis

Data from Agency Toxic Subst. Dis. Registry (2019, pp. 127–28).

was known to early manufacturers, but legislative restrictions were only gradually achieved; the Clean Air Act of 1996 finally banned its on-road use (EPA 1996). This seven-decade delay equals a life span. The declining exposure to Pb did not have immediate benefits because of its multiyear retention. Most Pb is retained in bone, with a long half-life of 5–10 years, while the brain receives a minor portion (<1%), with a half-life of 2 years (Leggett 1993).

Blood Pb from ≤10 to >50 µg/dL adversely impacts cognitive, motor, and sensory functions across all ages (**Table 4**). Children's full-scale IQ showed log-linear response to blood Pb, decreasing by 2.9 IQ points per µg/dL, over a range of 0.9–7.4 µg/dL. Brain MRI volume decreased with blood Pb >10 µg/dL. The cognitive impact for full-scale IQ in children may extend below 1.0 µg Pb/dL (meta-analysis of seven studies) (Budtz-Jørgensen et al. 2013; updated in Agency Toxic Subst. Dis. Registry 2019, p. 155). Prenatal Pb effects include higher risk of prematurity in prospective birth cohort studies from China (Cheng et al. 2017), Massachusetts (Perkins et al. 2014), and England (Taylor et al. 2014).

The Cincinnati Lead Study (1979–2016) enrolled a birth cohort of 90% African Americans from the inner city exposed to high levels of Pb, even >50 µg/dL. At age 6 years, frontal lobe gray matter MRI volumes varied inversely with blood Pb (Cecil et al. 2008). Although both sexes had similar blood Pb, only boys had Pb-brain association. Their IQ and fine motor coordination also varied inversely with blood Pb. By age 22, criminal arrests varied directly with blood levels for men; women had many fewer arrests despite the same range of blood Pb (Wright et al. 2008). These associations cannot be direct effects of Pb and may be understood as impulsive behaviors from impaired executive functions. Behavioral consequences of Pb are being further analyzed in the multiethnic and US-wide Adolescent Brain Cognitive Development Study of children aged 9–10 years (Marshall et al. 2020). High Pb exposure was associated with smaller cerebral cortex volume and lower cognitive scores in low SES families (**Figure 9**), extending below 5 µg Pb/dL. The highest risk group had 10% deficits in cortical volume and cognition. There is no safe lower threshold for Pb, paralleling AirPoll and CigS.

Developmental exposure to Pb also increases risk factors for heart disease and later-life neurodegenerative disease. Prenatal Pb exposure increased postnatal blood pressure with log-linearity: At age 5 years, systolic blood pressure increased by 0.58 mm Hg for doubled maternal Pb, according to the New Hampshire Birth Cohort Study (NHBCS) (Farzan et al. 2018). The NHBCS also showed smaller head size and body weight in top quartiles of toenail Pb (Signes-Pastor et al. 2019).

Middle-age cognitive deficits at age 38 years varied inversely with blood Pb at age 11 in the range of 4 to 28 µg Pb/dL, according to the Dunedin Multidisciplinary Health and Development Study, 1972–1973 birth cohort (Reuben et al. 2017): Per 5 µg/dL of childhood blood Pb, Wechsler Adult Intelligence Scale scores were depressed by 1.6 points. Higher childhood blood Pb was also associated with downward SES mobility and more psychopathology; the IQ decline contributed
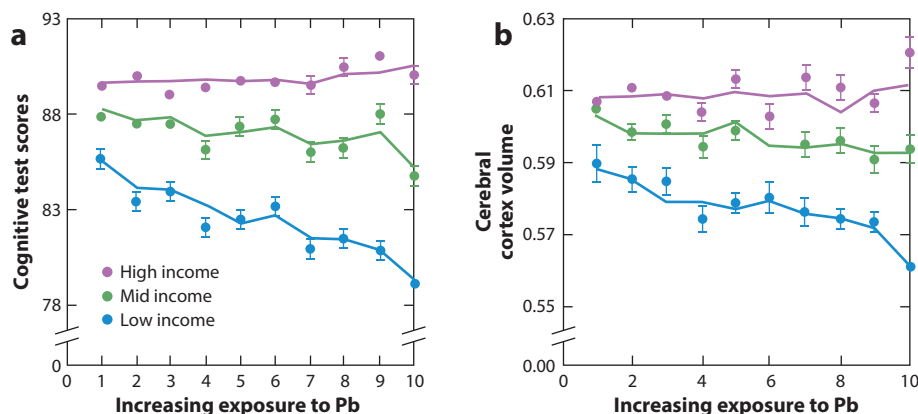
Figure 9

Socioeconomic status alters vulnerability of children aged 9–10 to lead (Pb) exposure. The Adolescent Brain Cognitive Development Study, a multiethnic US-wide sample of 10,000, evenly distributed by sex and income: Asian, 2%; African American, 15%; Hispanic, 20%; White, 53%; other, 10%. (*a*) Cognitive test scores using the NIH Toolbox. Data from Weintraub et al. (2013). (*b*) Cerebral cortex volume measured with magnetic resonance imaging. Exposure to Pb is a risk scale assessment based on census tract data validated for blood Pb in select populations. Data from Marshall et al. (2020).

40% of the SES association with blood Pb. Reuben et al. (2019) proposed pathways from experimental models by which high childhood Pb exposure could increase risk of AD and Parkinson's. We further suggest that the lower SES vulnerability to Pb may arise from poor diet and multiple stressors experienced by lower SES individuals, together with supra-additive synergies of Pb with AirPoll and CigS.

ApoE may also modulate Pb toxicity. In the VA Normative Aging Study, bone Pb was associated with faster cognitive aging at age 67: Per quartile of Pb, cognitive loss was accelerated 5 years (Weisskopf et al. 2004). Only *ApoE4* carriers had associations of Pb with cognitive loss based on allele dose (Prada et al. 2016). *ApoE* alleles may also influence the body load of mercury (Hg), another toxic heavy metal and industrial pollutant that may co-occur with Pb. In rural Brazilians, *ApoE2* carriers had lower Hg levels in hair than *ApoE4* carriers (Arrifano et al. 2018). Their Hg exposure is attributed to upstream gold mining, which contaminated their dietary fish and drinking water. Globally, dental fillings are a source of blood Hg. Dental patients with neuro-psychiatric issues symptomatic of Hg toxicity had 50% excess of *ApoE4* (Godfrey et al. 2003). We anticipate G×E interactions of Pb with AirPoll and CigS for risk of heart disease and later-life neurodegenerative disease. Epigenetic effects are also expected because white blood cell DNAme is influenced by Pb, Hg, and other metals (Martin & Fry 2018).

Animal responses to Pb also show its long-term neurotoxicity. An intriguing example is accelerated brain aging phenotypes in macaque monkeys fed Pb. Two groups were fed Pb on different schedules. The infantile fed group ingested Pb from birth to 14 months, yielding 32–36 µg/dL versus control 3–6 µg/dL; another group was fed continuously. By age 8 years, the continuous Pb group had more perseverative errors and other cognitive impairments than the infantile Pb group (Rice 1992). The modest cognitive impact of Pb in young adults did not anticipate remarkable acceleration of brain aging phenotypes at middle age in the infantile fed group (Wu et al. 2008). At age 23, the infantile Pb group had larger amyloid plaques in the frontal cortex, with 50% more amyloid β-peptides (**Figure 10*a***) and 50% more total tau and P-tau (**Figure 10*b,c***). DNA oxidative damage was modestly increased (8-oxo-dG, +20%), and there
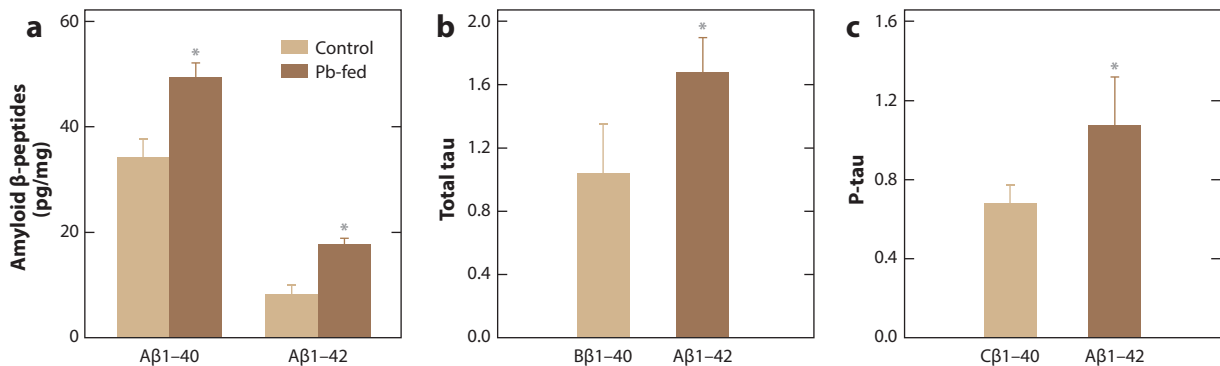
Figure 10

Accelerated brain aging phenotypes of monkeys fed lead (Pb) from birth to age 14 months (1.5 mg/kg, daily) and examined at age 23 years. (*a*) Frontal cortex amyloid β-peptides (total Aβ soluble and fibrillary Aβ, guanidinium extract). (*b*) Total tau protein. (*c*) Phospho-tau (P-tau). No Pb was detected in controls and Pb-treated monkeys (<0.1 ng/g brain). Figure adapted from Wu et al. (2008); copyright 2008 Society for Neuroscience.

were modest neurofibrillary changes in the frontal cortex. No behavioral or cognitive observations were reported, and the continuously fed Pb group was not mentioned. Although lacking cognitive or behavioral data, this unique study of monkeys shows that early Pb exposure can accelerate brain aging in a primate. As a caveat, these findings do not suffice for AD diagnosis. While monkeys normally accumulate brain amyloid and P-tau at more advanced ages, these usual aging changes do not reach clinical-grade AD cognitive or neurodegenerative changes (Finch & Austad 2012).

Mouse models of Pb ingestion show that Pb neurotoxicity parallels some aspects of CigS (Du et al. 2015). Adult mice of several genotypes had impaired memory and exploratory behavior, with male excess. The relatively low blood Pb levels of 2–5 µg/dL confirm conclusions from human studies: There is no safe lower threshold for Pb exposure (Singh et al. 2018, Tena et al. 2019). Within 6 weeks of oral Pb, AD transgenic mice had doubled amyloid plaque loads and worsened spatial learning (Gu et al. 2012). The higher Pb content in amyloid plaques is consistent with the proaggregating activity of Pb for amyloid β-peptides (Meleleo et al. 2019). The *ApoE4* allele also increased cognitive deficits from Pb in mice (Engstrom et al. 2017).

Gestational Pb exposure impacts behaviors for three generations of C57BL/6 mice, as shown in rigorous studies by Cory-Slechta and colleagues (Cory-Slechta et al. 2017; Sobolewski et al. 2018, 2020; Weston et al. 2014). Mice were fed Pb 2 months before mating and continued through weaning. The neonatal Pb levels of 10–15 µg/dL serum met the Centers for Disease Control and Prevention 2012 level of concern but were below Pb serum levels prevalent in the United States before 1980. Half the F0 mice were subjected to brief restraint stress in later gestation. Adults of the F1 generation progeny without further Pb had altered cognition, behavior, and stress responses, together with DNAme. Some effects of maternal Pb differed by sex: At 2 months, only F1 males had altered corticosterone regulation, with 50% lower basal levels and larger response to brief social stress. Subsequent generations were formed from male and female lines of the maternally exposed F1, generating eight lineages of the F3 generation (160 litters). The F3 generation had normal blood and bone Pb. The litter size and weaning weight were normal, but sporadic runting appeared in the F3 generation.

The grandmaternal Pb effects varied among the male and female lineages for conditioned responses (fixed-interval schedule of reward), for glucocorticoid receptors in the hippocampus and

cerebral cortex, and for DNAme of the *Bdnf* and *Th* genes, which modulate synaptic plasticity and neurotransmission. Interactions of grandmaternal Pb and restraint stress differed by sex across the eight lines: Lines of F3 females had lower corticosterone and more locomotor activity. Combined Pb and restraint stress strongly altered DNAme of the *Bdnf* and *Th* genes in the frontal cortex and hippocampus.

These rigorous studies should stimulate further analysis of mechanisms on the roles of epigenetic influences that may include methylation of histones and DNA and behavioral influences from maternal nurture. Later-life neurobehavioral effects are anticipated from grandmaternal Pb by findings from other labs that developmental Pb exposure decreased histone methylation and DNA methyltransferases up through age 2 years, the mouse life span (Dou et al. 2019; Eid et al. 2016, 2018). Exposure of macaques to Pb during nursing increased tau mRNA and protein (Bihaqi et al. 2014), which may anticipate the acceleration of neurofibrillary changes in monkeys discussed above.

Studies on Pb developmental impact, like those on AirPoll, are in an earlier stage than those on CigS. Other trace elements that may interact with Pb neurotoxicity include arsenic, cadmium, and Hg. Genetic vulnerability to Pb and Hg is indicated for *ApoE4* carriers. Does the resistance to arsenic in some populations (Apata & Pfeifer 2020) extend to Pb and Hg? Currently, genetic technology and single-cell analysis could identify cell- and tissue-specific gene networks and targets of intervention. For example, RNA sequencing of human brain progenitor cells during Pb exposure in vitro shows modulation of cell cycle, mTOR signaling, and nerve growth factors (Reis et al. 2019). Single-cell genomics on brain regions affected by Pb may identify neural circuit level dynamics of Pb toxicity across the life span.

SUMMARY AND SYNTHESIS

The comparison of AirPoll, CigS, and Pb summarized from the previous sections shows many shared pathological phenotypes from developmental and adult exposure (**Table 5a,b**). The extent of these shared responses has not been widely noted. Their concurrence suggests shared toxic and teratogenic pathways.

We perceive a multigenerational continuum of environmental influences including the grandmaternal uterus wherein our mother's ovaries form eggs for the next generation (Finch & Loehlin 1998). AirPoll can adversely impact eggs before fertilization, as shown for maternal transmission of obesity for three generations after a single preconceptual exposure to AirPoll (Xu et al. 2019). Moreover, ovarian follicles are decreased by prenatal exposure to diesel exhaust (Ogliari et al. 2013). The potential for multigenerational epigenetic effects on longevity is shown by altering histone methylation, which increased life span for three generations in the worm *Caenorhabditis elegans* (Greer et al. 2011). Three-way interactions are undefined for AirPoll, CigS, and Pb, and complex G×E interactions are anticipated.

Birth cohorts exposed to ambient Pb from leaded gas from 1970 to 1980 may show a corresponding gradient of risk for neurodegenerative disease after age 50 in our current year. Genomic responses by the brain include systemic influences and lung to brain, together with direct toxic effects. The stronger impact of Pb on brain development in lower SES individuals (**Figure 9**) may include synergies of AirPoll, CigS, and Pb. This potential three-way interaction is missing from **Table 2** and is not discussed elsewhere to our knowledge.

A mechanistic framework for G×E may be developed from forthcoming epigenetic data for diverse human populations. Beyond their developmental impact on young adults, AirPoll, CigS, and Pb may be considered as gerogens that accelerate aging processes in brain, arteries, and systemic metabolism. Some accelerated aging changes are also risk factors for brain and vascular

Table 5   Air pollution, cigarette smoke, and lead compared for shared responses

Entity affected	Air pollution	Cigarette smoke	Lead
a. Developmental exposure			
Birth prematurity	++	Human++	++
Head size	NR	Human++	++
Autism spectrum	+++	Human no link++	+++
Other abnormal behaviors	+++	Rodent++	+++
Cognitive deficits	+++	NR	++
Gray matter deficit	++	NR	+++
White matter deficit	Rodent++	NR	NR
Adult neurogenesis deficits	Rodent++	NR	NR
Blood pressure (systolic)	+++	+++	+
Blood dyslipidemias	NR	Human++	NR
Atherosclerosis	+++	+++	NR
Glucose intolerance	+++	NR	NR
Adiposity	+++	+++	+++
Male excess adiposity	+++	NR	NR
Accelerated brain aging	+++	+++	++
ApoE allele differences	NR	NR	NR
DNA methylation	+++	+++	+++
Transgenerational impact	Rodent++	+++	Rodent++
b. Adult exposure			
Adult neuronal stem cells	Rodent+	NR	NR
Alzheimer's disease	+++	+++	NR
Ischemic events	Human++	+++	NR
Glucose intolerance	Human++	Human++	Rodent++
ApoE allele differences	+++	++	+
DNA methylation	+++	+++	+++

Strength of evidence: NR, no reports; +, single report; ++, multiple studies; +++ shown for humans and animal models.

disease. The lineage- and sex-specific effects of grandmaternal exposure to Pb indicate epigenetic processes of relevance to future generations from our current and recent exposure to airborne toxins.

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