We also argue for finer-grained information that characterizes localities and populations most affected. Previous research has identified that people who are poor or African-American, live in coastal and low-lying areas or are outdoor workers are at increased risk of climate-change health effects due to intersecting vulnerabilities[8–10]. A multi-country multi-city study of suicide and temperature that identified nonlinear associations in northeast Asia and more linear associations in several Western countries (including the USA)[11] also indicates the need to explore the possibility of varying patterns of injury–temperature associations in different settings.

Climate-change policy presents unprecedented opportunities for implementing equity-focused public-health plans that address the synergistic and intergenerational effects of multiple risk factors and social determinants that influence injuries[6,12]. The need to address this is particularly urgent in low- and middle-income countries that experience over 80% of the global injury burden and are generally more vulnerable to the effects of extreme weather. ❐

Shanthi Ameratunga* and Alistair Woodward
Section of Epidemiology & Biostatistics, School of Population Health, Faculty of Medical & Health Sciences, University of Auckland, Auckland, New Zealand.
*e-mail: s.ameratunga@auckland.ac.nz

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Competing interests
The authors declare no competing interests.

PUBLIC HEALTH

Implications of legacy lead for children's brain development

Children at a higher risk of lead exposure develop smaller brain cortical surface area and volume, but only if they are from low-income families.

Aaron Reuben, Maxwell Elliott and Avshalom Caspi

Although lead has largely been banned from gasoline, pipes, paint, and other consumer products in most countries, legacy lead in the environment remains an ongoing hazard for children around the world[1]. Exposure to lead, a neurotoxicant, is associated with disrupted cognitive and behavioral development[2]. Despite decades of study, not enough is known about the structural changes in the brain that underlie these disruptions, or to what extent they are lasting, modifiable, or likely to worsen over time. In this issue, Marshall et al. report that US children living in neighborhoods with higher risks of lead exposure develop smaller cortical volumes and surface areas if they are from low-income families but not if they are from middle- or high-income families[3]. The authors interpret these brain morphology differences, which were accompanied by deficits in cognitive test performance, as suggesting that the children from low-income families are possibly more vulnerable to lead's neurotoxic effects than are their more affluent peers.

No level of lead exposure has been deemed safe for children. While humans have been interacting with lead for millennia[4], not enough is known about how its harms are mediated. Animal studies have shown that lead mimics calcium at the cellular level[5]. It is absorbed through the gastrointestinal and respiratory tracts, binds to erythrocyte proteins in the blood, and may pass through the blood–brain barrier via calcium ATPase pumps[5]. Once in the brain, lead enters glia and neurons through voltage-sensitive calcium channels and, there, perturbs calcium homeostasis, disrupts mitochondrial function, and suppresses neurotransmitter storage and release[5]. Lead's half-life in the brain is 2 years, and its presence at even low levels during development may disrupt neuronal proliferation, differentiation, and synapse formation[5]. However, it is not clear how to generalize such findings to humans, whose toxicodynamics of lead metabolism, removal and vulnerability vary by age, sex, and genetics. Owing to its known toxicity and persistent use in metalworking, food preparation, building materials, and fuel, lead——as well as its removal——has been invoked to explain a number of historical events and trends, from the fall of the Roman Empire[6], to the rise in IQ across the second half of the 20th century[7], to the drop in urban crime rates in the 1990s[8]. Such arguments have been controversial because, among other issues, lead exposure is typically entwined with adversities related to socio-economic deprivation, including lack of access to high-quality housing, nutrition, education, and healthcare[9]. This has led to an at times acrimonious area of research, sometimes fueled by opinionated financial interest from lead-related industries[10].

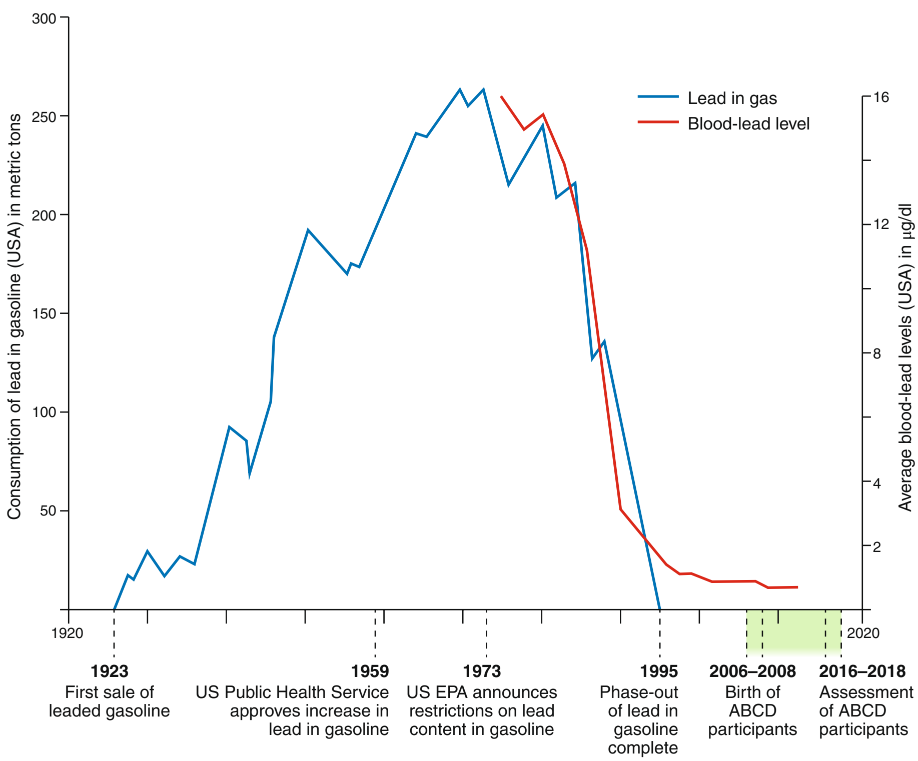

Fig. 1 | Timeline of consumption of lead in gasoline in the USA and mean population blood-lead levels across the past 100 years. This plot shows the changes in lead in gasoline that may have affected the lead levels in the census tracts in the study by Marshall et al.[3]., presented as the timeline of US consumption of lead in gasoline (metric tons) and mean US population blood-lead levels (in µg/dl). Data points are approximations derived from refs. [13–15].

Marshall et al.[3] used cross-sectional data from the Adolescent Brain Cognitive Development (ABCD) Study, one of the world's largest studies of brain development, with 11,878 US participants 9–10 years of age. The exposure of the children in the ABCD cohort to lead was estimated on the basis of a proxy measure of risk of exposure, calculated as a composite of poverty rate and average home age within each child's residential census tract. The authors tested whether children's risk of lead exposure is associated with differences in their brain structure, which was assessed by magnetic resonance imaging of the thickness, surface area, and volume of the cortex, and their cognitive performance, which was assessed by cognitive tests from the NIH Toolbox, and, if so, whether lead-related outcomes would be more pronounced in low-income families. They found that, on average, children from low-income families growing up in neighborhoods at high risk for lead exposure developed brains with smaller cortical surface areas and volumes than those of their peers from low-income families growing up in neighborhoods at lower risk for lead exposure. These brain differences were paralleled by deficits in cognitive performance. For children from middle- or high-income families, there was no significant association between lead-exposure risk and brain morphology or cognitive performance.

Taken together, these results suggest that children from low-income families may be at higher risk for developmental harm from living in high-lead-risk census tracts than are their more affluent peers. These results warrant further attention but for now must be interpreted with caution. The children in the ABCD cohort have yet to be tested for lead. The risk-of-exposure measure used by Marshall et al.[3] has been shown to associate statistically with actual blood-lead levels among participants in other studies ($b = 0.32$; $P < .001$). However, the authors acknowledge that this proxy measure does not directly assess lead toxicity among children enrolled in the ABCD Study. This proxy measure may assess lead exposure but may also capture the influence of multiple developmental risks of growing up poor in census tracts with high poverty rates and old homes, including, potentially, greater exposure to crime, low access to high-quality schools and healthcare, lack of parks and open spaces, and even exposure to other pollutants, such as air pollution.

Marshall et al. have proposed adding lead testing to the ABCD cohort[3]. This would add to the understanding of how early-life exposure to lead influences brain development and just how low blood-lead levels need to be to ensure healthy development. Levels of lead exposure in the USA have been decreasing steadily for the past 50 years. Correspondingly, recommendations for what constitutes a worrisome level of lead exposure have dropped from 60 micrograms of lead per deciliter of blood (60 µg/dl) to 5 µg/dl over the same time period (Fig. 1).This means that any lead associations found in the ABCD cohort reflect the consequences of relatively low levels of lead exposure among today's children and may thus underestimate the effects that lead has probably had on the brain development of yesterday's children. The parents and grandparents of children in the ABCD cohort were exposed to the highest levels of lead in their own childhoods. There is reason to believe they will now be at risk for novel brain impairments, such as accelerated brain aging and neurodegenerative disease[11,12], owing to several factors, including novel neurotoxicity from lead remobilized from bone during menopause and osteoporosis, lowered neural and cognitive reserve, and dormant epigenetic modifications that foster protein pathology in late life. The study by Marshall et al.[3] is an important reminder about the potential immediate and lasting vulnerability of the brain to childhood lead exposure. ❐

Aaron Reuben[1], Maxwell Elliott[1] and Avshalom Caspi[1,2,3,4]*

[1]Department of Psychology & Neuroscience, Duke University, Durham, NC, USA. [2]Department of Psychiatry & Behavioral Sciences, Duke University School of Medicine, Durham, NC, USA. [3]Center for Genomic and Computational Biology, Duke University, Durham, NC, USA. [4]Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK.

*e-mail: ac115@duke.edu

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Competing interests

The authors declare no competing interests.

DIGITAL HEALTH

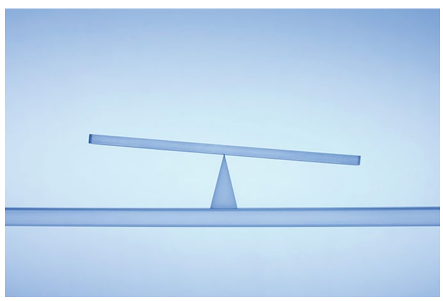
Diagnosing bias in data-driven algorithms for healthcare

A recent analysis highlighting the potential for algorithms to perpetuate existing racial biases in healthcare underscores the importance of thinking carefully about the labels used during algorithm development.

Jenna Wiens, W. Nicholson Price II and Michael W. Sjoding

Many data-driven algorithms in healthcare map a set of patient characteristics to the patients' estimated risk of experiencing a future outcome[1–3]. Such algorithms are often used to identify high-risk patients for targeted interventions. Recently, Obermeyer et al. examined one such algorithm currently used by health systems in the USA to target patients for high-risk care management[4]. Analyzing the algorithm's predictions by race, where race was self-reported and extracted from hospital records, they identified racial bias in the algorithm. Specifically, black patients were less likely to be identified by the algorithm as candidates for potentially beneficial care programs than were white patients who had the same number of chronic illnesses.

The commercial algorithm analyzed by Obermeyer et al. was trained in a supervised learning framework to predict a patient's total medical expenditures in the following year, using their age, sex, prescribed medications, medical encounters and billed amounts during the current year; notably, the algorithm did not include race[4]. Patients predicted by the algorithm to be in the 97th percentile or above in terms of future expenditures were automatically enrolled in a care program in which patients with complex health needs receive additional resources, and the primary care physicians of patients in the 55th percentile and above were asked to consider enrolling the patients in this care program. As the top 5% of patients account for 50% of health spending[5], many health systems now use similar algorithms to guide care-management interventions.



Credit: Le Club Symphonie/Cultura/Getty

The algorithm was marketed as able to identify patients with the highest healthcare needs, under the assumption that medical expenditures equate to healthcare needs, and used in such a way that assumes that patients with the highest medical expenditures are most likely to benefit from the intervention. As the authors demonstrate, these assumptions result in a biased algorithm. They find that among individuals predicted to have the same level of medical expenditures, black individuals actually had more active chronic medical conditions than white individuals. Left unchecked, this kind of bias becomes systematized by the algorithm when used by healthcare providers, as black patients are disproportionately under-referred to additional care programs.

The first assumption, that medical expenditures equate to healthcare needs, results in label bias in which the label used to train the algorithm is only a proxy for the true outcome that one ultimately cares about. Although assessing total healthcare costs is one method that has been recommended by the National Academy of Medicine for identifying high-need patients[6], cost is an imperfect proxy for health needs. Patients of lower socioeconomic status are less likely to access healthcare services, and a "lack of trust" or, more precisely, "a lack of trustworthiness on the part of the medical industry"[7] is hypothesized to result in a lack of engagement with healthcare by black individuals and, hence, in racial disparities in healthcare spending.

Rather than changing the statistical approach to developing the algorithm, to reduce potential bias, Obermeyer et al. suggest changing the labels used during training[4]. Working with the original developers of the algorithm, they experimented with different labels, including a formulation that combined an estimate of future active medical conditions and future costs. This reformulation led to a reduction in bias by over 80%. When developing data-driven algorithms for healthcare, we should think carefully about the labels used during training.

Beyond cost, many other labels are vulnerable to bias, including other commonly considered outcomes such as sepsis or healthcare-associated infections[8]. These labels rely on clinical tests that require a clinician to recognize symptoms and place an order. This can result in delays if symptoms go unnoticed, or false negatives if patients are never tested. If certain subpopulations are systematically