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Effects of urban-induced mutations on ecology, evolution and health

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Increasing evidence suggests that urbanization is associated with higher mutation rates, which can affect the health and evolution of organisms that inhabit cities. Elevated pollution levels in urban areas can induce DNA damage, leading to de novo mutations. Studies on mutations induced by urban pollution are most prevalent in humans and microorganisms, whereas studies of non-human eukaryotes are rare, even though increased mutation rates have the potential to affect organisms and their populations in contemporary time. Our Perspective explores how higher mutation rates in urban environments could impact the fitness, ecology and evolution of populations. Most mutations will be neutral or deleterious, and higher mutation rates associated with elevated pollution in urban populations can increase the risk of cancer in humans and potentially other species. We highlight the potential for urban-driven increased deleterious mutational loads in some organisms, which could lead to a decline in population growth of a wide diversity of organisms. Although beneficial mutations are expected to be rare, we argue that higher mutation rates in urban areas could influence adaptive evolution, especially in organisms with short generation times. Finally, we explore avenues for future research to better understand the effects of urban-induced mutations on the fitness, ecology and evolution of city-dwelling organisms.

Mutation is the original source of all genetic variation. Despite its importance, variation in mutation rates is often overlooked or considered of negligible significance in empirical studies of ecology and evolution, particularly in eukaryotes[1]. Mutation rates can be influenced by the environment[2,3] and can evolve through time[4,5]. Neglecting to consider mutation may be especially problematic in cities, where emerging evidence suggests that pollution elevates mutation rates[6,7].

One of the most consistent differences between urban and non-urban environments that could influence mutation rates is chemical pollution. Transportation, industry, wastewater management, home heating, landfills and pesticide application are all activities in urban areas commonly associated with elevated air, water and soil pollution[8–10]. Although less frequent in urban areas, nuclear plants, nuclear testing and warfare can also result in highly mutagenic ionizing radiation[11]. Studies on the mutagenic effects of radiation also provide general insight into how highly mutagenic pollutants can influence organisms in cities. Although pollution is not unique to urban areas, the concentration and diversity of pollutants are often highest in cities, exposing organisms to harmful stressors in unprecedented ways[8–10].

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Table 1 | Common urban chemical mutagens and carcinogens

Pollutant	Chemical species	Sources	Medium	Refs.
PM	$PM_{2.5}$ PM_{10}: inorganic ionic compounds, metal oxides, organic and elemental carbon	Combustion by-products from traffic and industrial emissions, residential heating and reactions between pollutants	Air	8,18
Volatile organic compounds	Aldehydes, ketones, aromatics and alkanes	Household products, building materials and combustion sources	Air	18,132
PAHs	Examples include benzo[a]pyrene, benzo[a] anthracene, chrysene, benzo[b]fluoranthene, benzo[k]fluoranthene	Combustion by-products from industrial, residential and transport emissions	Air/water/soil	33,133–135
Sulfur oxides (SO_x)	SO_2, sulfur trioxide (SO_3)	Fossil fuel combustion, other industrial processes	Air	8,18
CO	–	Fossil fuel combustion, transport emissions	Air	8,136
NO_x	Nitrous oxide (NO), nitrogen dioxide (NO_2)	Transport and industrial emissions	Air	8,137,138
Pesticides	Organophosphates, pyrethroids, carbamates, polychlorinated biphenyls, polybrominated biphenyls, persistent organic pollutants	Pesticide use in urban areas	Water/soil	139
Heavy metals	Mercury, arsenic, cadmium, chromium and lead	Industrial processes, mining	Water/soil	9,137
High salt	Salt (NaCl)	Road salting	Soil/water	140

For each pollutant, we indicate the chemical species, the most common anthropogenic sources, the medium in which the pollutant is typically encountered (air, water or soil) and references.

Urban chemical pollutants can cause physiological and genotoxic stress to organisms that may result in mutations. Such pollution is known to result in respiratory illnesses in humans[12], reduced photosynthesis and cell damage in plants[13], higher mortality in fishes and amphibians[14], and decreased fledgling success in birds[15]. Exposure to some pollutants can damage DNA and induce de novo mutations (hereafter simply called 'mutations')[16–19]. Although carcinogenic pollutants are known to cause somatic mutations (mutations in non-reproductive germ cell tissue), the fitness effects of these mutations and the prevalence of pollution-induced germline mutations are poorly understood outside of laboratory settings. Moreover, whether urban-induced higher mutation rates lead to an increased number of deleterious mutations, population decline or accelerated adaptive evolution has not been previously considered (but see ref. 20).

Our goal is to provide a forward-looking Perspective on the potential for elevated mutation rates in cities to influence the ecology and evolution of populations. Studies of the effects of urbanization on evolution have focused on genetic drift, gene flow and natural selection, and the potential for elevated mutation rates in cities to influence the ecology and evolution of populations is largely unexplored and of high priority for future research[21–24]. We begin by reviewing urban pollutants and the damage they cause to DNA. Next, we consider how pollution affects somatic and germline mutations and the potential importance of these mutations for ecology and evolution. Although urban pollution can affect all organisms in cities, most existing examples come from research on humans. We consider the effects of pollution on humans and non-human organisms throughout this Perspective, and we use the extensive literature on humans as a model to understand the wider ecological and evolutionary impacts for all organisms. Looking beyond humans is important because although cities reduce and homogenize species diversity, urban habitats still harbour substantial biodiversity[25–27], and many of these species in cities are of conservation concern or have fundamental ecosystem roles[28]. We end by discussing existing knowledge gaps and directions for future research.

Urban pollutants and damage to DNA

Air, water and soil in cities are consistently associated with a diverse mixture of pollutants (Table 1 and Box 1). The sources of most outdoor air pollutants in cities are combustion by-products from transportation, power generation, home heating/cooking and industry[29,30]. These by-products include pollutants such as polycyclic aromatic hydrocarbons (PAHs), nitrogen oxides (NO_x), sulfur dioxide (SO_2), carbon monoxide (CO) and various metal species (for example, Hg, Cu, Pb and Sn). These compounds can bind to particulate matter (PM), which can then be deposited in soil[18,31–33]. Soil can also become contaminated with genotoxicants from industrial by-products, manufacturing, mining and road salting[30]. Air pollutants, soil leaching, run-off and sewage all contribute to water pollution[34], which can lead to elevated levels of pesticides[35,36], polychlorinated biphenyls[37], pharmaceutical products[38–40] and microplastics[30,41,42] in aquatic habitats.

Pollution in urban settings varies in both time and space in complex ways. The levels and types of urban pollution have changed throughout the history of industrial and urban growth. For example, during the past 20 years, the level of $PM_{2.5}$ (PM with diameters <2.5 µm) in Shanghai, China, has increased by over 200%, yet it decreased by nearly 30% in New York, USA, and remained consistently low in Melbourne, Australia (Fig. 1). These changes through time are often influenced by changes in governmental policies (for example, the United States' Clean Air Act and the European Union's Ambient Air Quality Directive) and technological change, such as conversion from leaded to unleaded fuels. Urban pollutants also vary spatially in their concentrations and composition (Fig. 1 insets). For example, industrial steel production often leads to some of the highest concentrations of PAHs[43], whereas high vehicle traffic is typically associated with higher PM, ozone, CO and NO_x (Table 1). Socio-economic variation among neighbourhoods often covaries with pollution levels, whereby poorer neighbourhoods are frequently in the most polluted areas, causing disparity in exposure to potentially harmful genotoxicants[44,45]. Non-urban areas also frequently experience pollution due to anthropogenic activities, including resource extraction, agriculture, forestry and nuclear radiation. However, we focus on urban areas because they are the fastest-growing ecosystem on Earth, and they are consistently associated with elevated pollution made up of diverse mixtures of chemicals that potentially harm organisms including causing damage to DNA (genotoxicants) (Box 1).

The genotoxic effects of pollutants include chemical interactions that form DNA adducts (chemicals that bind to DNA) and reactive oxygen species that damage DNA (Box 1). When such damage is improperly repaired, it can cause small-scale and large-scale mutations. Small-scale mutations include single nucleotide substitutions and small insertions/deletions (indels). Large-scale mutations involve large indels, duplications, translocations, inversions and aneuploidy[46–48].

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BOX 1

Genotoxicity of urban pollutants and induction of mutations

Chemical pollutants are the primary cause of DNA damage induced by urban pollution. Ionizing radiation is less common but is a more extreme mechanism of DNA damage in and around cities. When an organism is exposed to a chemical pollutant, the pollutant can cause DNA damage and mutation through several steps:

(1) Pollutants can enter the cell via diffusion[157] or receptor-mediated endocytosis[158]
(2) Once inside the cell:
   (a) Pollutants (for example, PAHs) can form bonds with nitrogenous DNA bases, resulting in DNA adducts[159]
   (b) Presence and interaction of pollutants with cellular processes or proteins causes increases in reactive oxygen species that can oxidize DNA and proteins[160,161]
(3) Chemically induced DNA lesions may be subject to error-prone DNA repair processes that cause mutations, or if the amount of damage exceeds the cell's capacity for DNA repair, it can result in mutations or chromosome damage[162]
(4) Air pollutants can also cause oxidative stress via chronic inflammation and subsequent formation of reactive oxygen species[18]

Ionizing radiation and radiomimetic compounds can alter DNA sequences through a different mechanism:

(1) Radiation directly deposits energy in DNA, causing strand breaks, or it creates free radicals that damage DNA and proteins[163,164]
(2) Free radical DNA damage includes apurinic/apyrimidinic sites and deamination of DNA bases (among others), both of which have unique mutagenic mechanisms[165]
(3) Lack of repair or error-prone repair of this damage can cause chromosomal aberrations and mutations

DNA replication errors such as unequal crossovers that can result in gene duplication and deletion are also possible. The location of DNA damage (coding versus non-coding regions), the molecular function of damaged DNA (regulatory versus structural) and whether coding mutations are synonymous or non-synonymous all can influence the molecular, physiological and fitness consequences of damage. The fitness effects of mutation can in turn impact the ecology and evolution of populations[49–51] (see 'Ecological and evolutionary consequences').

The effects of urban-induced mutations may differ between species because of variation in ploidy, cellular complexity, mutation rate, reproductive system, population size and generation time. For example, many animals, higher plants and some eukaryotic microorganisms live primarily as diploids or polyploids, which can mask the fitness effects of recessive mutations at low frequencies[52,53]. Similarly, many multicellular organisms have differentiated germ and somatic cells, such that pollution-induced mutations in somatic cells will not generally be passed on to subsequent generations. By contrast, organisms with no distinction between germ and soma, such as some plants and fungi, may accumulate inherited mutations more rapidly if mutations arise in the cells that ultimately form gametic tissue[54,55]. Moreover, mutation rates vary by orders of magnitude, with bacteria and microbial eukaryotes having the lowest rates, vascular plants and animals having moderate rates, and viruses having the highest mutation rates[4,56]. Recombination in sexual organisms can allow more efficient purging of harmful mutations by selection than in asexual populations[57,58]. Finally, large populations with rapid generation times are expected to purge or fix environmentally induced mutations that affect fitness more rapidly than small long-lived populations[59]. In the sections that follow, we expand on how such variation among species may lead to different ecological and evolutionary consequences of urban-induced mutations.

Somatic mutations

The primary consequence of genotoxic exposure is the induction of somatic mutations that can adversely affect molecular, cellular and tissue function. Somatic mutations are not transmitted to the next generation unless they occur in germ cell progenitors, such as plant apical meristems[60], so they typically affect only the exposed individual's health and fitness. The causal role of chemically induced mutations in cancer development is well known in certain cases, such as lung cancer due to tobacco smoke[61] (Table 2). These examples show that exposure to genotoxicants can cause mutations in tumour suppressor genes or proto-oncogenes that can function as cancer drivers, causing cellular proliferation, tumour development and genetic instability[62]. Moreover, exposure to mutagens during key life stages, especially embryogenesis and organogenesis, may increase the probability of clonal expansion of mutation-bearing cells[17,63,64]. Data supporting the association between environmentally induced mutations and non-cancerous diseases are almost entirely lacking, despite knowledge of mutations across the genome caused by genotoxicant exposure and a growing understanding of the role of somatic cell mutagenicity in disease more generally (for example, ageing, neurological and cardiac diseases)[65,66]. Thus, there is currently no knowledge on the rates and functional consequences of pollution-induced somatic mutations for individuals, populations and species beyond the established association with cancer.

The study of mutagenesis is challenging because mutations are rare events at a genomic scale. This difficulty is compounded in the case of somatic mutations because the occurrence of mutations varies among tissues within a single individual. However, a variety of studies provide empirical evidence supporting an association between specific urban pollutants and elevated somatic cell mutation rates. The invention of the *Salmonella* mutation assay, often called the 'Ames assay', has been a transformative tool in the study of environmental mutagenesis[67,68]. In brief, the assay assesses how frequently *Salmonella* strains lacking the ability to metabolize histidine—due to engineered base-pair substitutions or frameshift mutations—exhibit revertant mutations to restore histidine metabolism when challenged by a toxicant[17,67]. This simple bacterial assay has revealed that the air, soil and water in urban environments is replete with mutagens[67]. Beyond *Salmonella*, observational and experimental cytogenetic studies show that numerous chemical pollutants cause chromosomal abnormalities in diverse organisms, including structural aberrations and aneuploidy[16,17,69]. Additional lines of evidence are based on the types and distribution of mutations (the mutation spectrum) observed in human cancers used to infer mutagenic exposures[70] as well as the COSMIC database[71]. Overall, laboratory models (for example, *Salmonella*, mice and plants) exposed to environmental media or extracts demonstrate the widespread mutagenicity of many chemical pollutants in urban areas[70].

The most extensive evidence of pollution-induced somatic cell mutagenicity is from studies on combustion-related by-products found in urban air pollution, contaminated soils and sediments. The weight of evidence for the mutagenicity of outdoor air pollution is high, with many specific agents declared "carcinogenic to humans" by the International Agency for Research on Cancer[18]. This agency's monographs thoroughly describe how these urban pollutants cause mutagenicity in laboratory organisms as diverse as bacteria, plants and rodents[18,72]. For example, the mutation spectrum observed in lung tumours of

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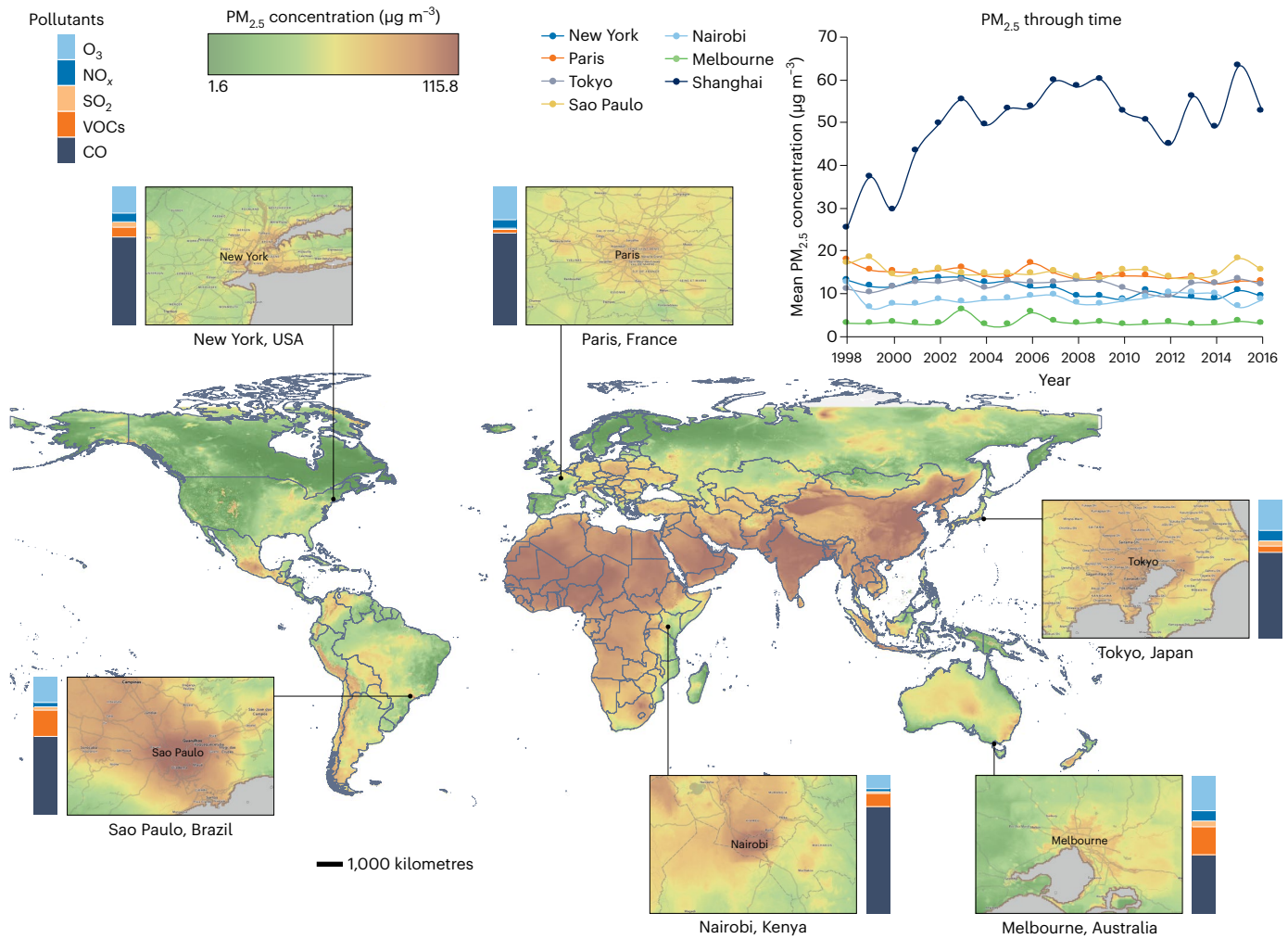

Fig. 1 | Global concentrations and composition of mutagenic and carcinogenic pollutants. Concentrations of $PM_{2.5}$ across terrestrial Earth in 2019–2020, with inset panels illustrating that concentrations are frequently highest in and around cities[152,153]. $PM_{2.5}$ concentrations have been changing through time (top right inset), increasing in some cities (for example, Shanghai, China) and decreasing in others (for example, New York, USA)[154]. The stacked bar charts show how the composition of major carcinogenic pollutants (CO, volatile organic compounds (VOCs), SO_2, NO_x and ozone (O_3)) in urban areas varies among countries[155,156]. High concentrations of $PM_{2.5}$ outside urban areas are caused by a combination of anthropogenic sources such as long-distance dispersal of industrial pollution, burning of crops in agricultural regions, forest fires and naturally occurring fine dust picked up by strong winds from bare soil, especially in arid regions (for example, Saharan and sub-Saharan Africa).

non-smokers associated with air pollution is broadly consistent with exposure to bulky-DNA-adduct-forming chemicals such as benzo[a]pyrene[73,74]. Additional evidence for the mutagenicity of air pollution comes from humans exposed to high levels of combustion by-products in residential and occupational settings, whereby individuals exhibit cytogenetic damage to various cell types[75,76], and the urine from such individuals is mutagenic to bacterial cells[77,78]. Moreover, soil and sediments that contain combustion-related contaminants are mutagenic to organisms that frequently come into contact with these substrates, such as bacteria and plants[17,69]. Undoubtedly, inhabitants of any urban ecosystem are exposed to mutagenic particulate pollutants associated with combustion emissions.

There are many other examples of mutagenic contaminants found in urban settings, from metals to pesticides, organochlorines and benzene (Table 1). These genotoxicants have the potential to impact the somatic cell mutation burden, contributing to the decreased health of individuals and populations[18,79]. The vast majority of mutagenicity testing is conducted in the laboratory on individual chemicals at high doses[19], leading to a major gap in our understanding of how lifelong, low-dose exposures to mixtures of mutagens affect mutation rates and disease outcomes. Moreover, the complex interactions between sociodemographic factors and mutagenic environmental mixtures inherent to cities have yet to be explored.

The study of environmentally induced somatic cell mutations has been considerably hampered by the lack of tools available outside of the laboratory. Although single-cell deep-sequencing[80] and error-corrected sequencing[81,82] methodologies exist, these have mostly been applied in clinical settings and have yet to be extended to studies on environmental exposures in natural populations. The high levels of pollution in urban areas offer an opportunity to address these obstacles using field experiments, in addition to laboratory experiments, that apply genomic technologies to directly quantify mutation frequency and spectrum in a diverse array of organisms (see 'Future directions').

Germline mutations

Unlike somatic mutations, germline mutations are inherited between generations. For this reason, it is primarily germline mutations that can influence the evolution of populations. Although germline mutations are rare at the individual level, even the smallest increase in the mutation rate can have large consequences for populations[83].

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Table 2 | Cancers associated with urban-induced mutations

Health effect	Region of study	Pollutant	Description of findings	Refs.
Childhood cancers (leukaemia, neuroblastoma, renal and bone tumours)	Spain	Air pollution	Risk of cancer increased with closer proximity to industrial and urban areas	141–143
Lung cancer	China	PM (PM_{10}: SO_2)	Lung cancer incidence and mortality increased with increased PM_{10}; SO_2 also positively correlated with cancer	144
	USA	PM (PM_{10}: SO_2, ozone)	Lung cancer was most strongly correlated with PM_{10} exposure, followed by SO_2 and ozone in male individuals; in female individuals, lung cancer correlated with SO_2, followed by PM_{10}	145
	Canada	Air pollution ($PM_{2.5}$)	$PM_{2.5}$ associated with increased risk of lung cancer	146,147
	Sweden	Air pollution (NO_2)	NO_2 exposure correlated to increased lung cancer	148
Stomach cancer	China	Soil pollution (heavy metals; Cd, Cr, Pb, Hg, As)	Heavy metals in soils correlated with higher stomach cancer incidence	149
Breast cancer	USA	Air pollution (NO_x)	Increased risk of breast cancer following NO_x exposure in women living near major roads	150
Digestive system cancers	China	Water pollution	Large-scale study identifying covariation between decreasing water quality and increased incidence of digestive cancers	151

Examples of the most common cancers associated with urban-induced mutations, including changes in rates of cancer in urban and non-urban populations. For each example, we indicate the study region, the pollutant studied and the main findings.

Laboratory and field studies suggest that exposure to many common urban pollutants can induce germline mutations. For example, over 80 chemical agents have been identified as germline mutagens in laboratory mice[19]. In humans, the best evidence of the impact of pollutants on germ cell mutagenesis comes from studies demonstrating an increased incidence of chromosomal abnormalities in human sperm[19]. Such abnormalities may explain the significant correlation between paternal blood dioxin levels due to occupational exposure and increased mutation rates in their offspring[84]. When considering exposure to radiation as an example of extreme exposure to a mutagen, children of parents exposed to ionizing radiation following the Chernobyl nuclear plant accident exhibited increased rates of tandem repeat mutations[85]. Similar inherited mutations have been observed in plants[86] and barn swallows[87]. However, increases in inherited single nucleotide variants have yet to be conclusively demonstrated for humans exposed to radiation[88]. In non-polluted areas, a recent study reported a reduced mutation rate in an Amish population, which has been interpreted as traditional rural lifestyles leading to low mutation rates because of reduced exposure to chemical mutagens[89]. Very few studies have examined non-human populations outside of laboratory conditions, and they show that birds and rodents exhibit increased heritable mutation rates in repetitive DNA regions when exposed to ambient industrial air pollution[6,7,90,91].

In addition to pollution, urban and rural human populations diverge in their demographic patterns in ways that are expected to influence germline mutation rates. In recent decades, there has been a trend for delayed childbearing in many countries. In both developed and developing nations, this delay is more pronounced in urban settings than in rural settings[92,93]. Studies of human parents and offspring over the past decade have consistently demonstrated an age-related increase in mutation rates, especially in fathers[94]. It is estimated that fathers transmit ~1.2 additional mutations for each year of age, versus ~0.4 new mutations per year of age in the mother. The higher paternal contribution is partially ascribed to the continuous production of sperm as men age, whereas no new oocytes are generated once a female individual is born. Surprisingly, the urban-biased shift towards delaying the age of reproduction is the only clear example of how urban living is associated with elevated germline mutation rates, other than urban pollution inducing mutations in repetitive regions of birds and mice. The consistency of divergence in parental age between urban and rural populations in developed and developing nations requires further investigation, as this major source of increased mutation rates could also result from differences in socio-economic factors and cultural differences throughout the world. There is also evidence that non-human organisms exhibit demographic shifts in urban habitats[95], but whether this is associated with changes in mutation rates requires investigation.

Despite the circumstantial evidence mentioned above for an effect of urban pollution and demographics on increased germline mutation rates, a direct link between urban pollution and mutations has yet to be definitively demonstrated using modern genome sequencing techniques. We therefore lack information on how and when urban pollution increases germline mutation rates, the targets of mutation and especially their phenotypic and fitness effects.

Ecological and evolutionary consequences

Alterations to the rate and spectrum of both somatic and germline mutations due to urban pollution could have important ecological and evolutionary repercussions. Theoretical and empirical studies show that the majority of new functionally significant mutations are deleterious and removed by purifying selection[96]. If deleterious mutations are elevated in urban settings, either due to a higher rate or as a larger fraction of deleterious mutations, we expect an increased mutation load (reduced fitness due to the burden of deleterious mutations relative to an unmutated individual) that will decrease population mean fitness[97,98]. Whether urban species in fact suffer a demographic decline depends on several factors including the strength of selection, effective population size (N_e) and generation time (Fig. 2). Keightley[99] estimated that the decline in human fitness due to mutation could reach 0.01% per generation, and the decline would change linearly with changes in mutation rate. This estimate does not include the countering force of purifying selection. It is therefore likely that organisms with long generation times will experience little effect on population mean fitness in the short term. Conversely, organisms such as microorganisms that have short generation times may experience changes in fitness over contemporary timescales.

Although evolutionary responses depend on inherited germline mutations, somatic mutations also have important consequences for the health and fitness of individuals that contribute to long-term population viability. In multicellular organisms, somatic mutations can create a mosaic of cells with slightly different genotypes[100]. These mutations can lead to developmental instability, which is particularly detrimental in organisms with strict body plans such as animals[101] (Table 2). The genomic diversity within an individual can also produce competition among cell lineages that can be harmful, as in the case

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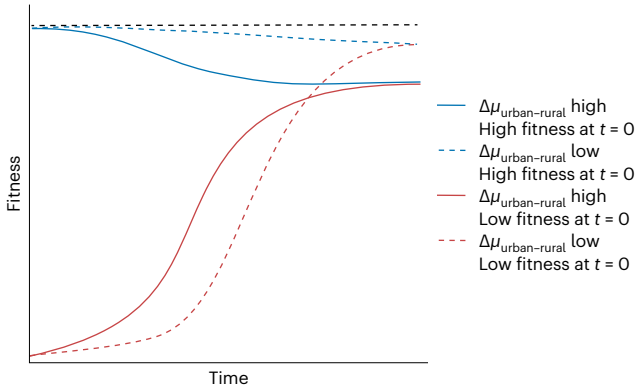

Fig. 2 | The potential for elevated mutation rates in cities to affect the evolution of a population relative to a fitness optimum. When a population starts at a fitness optimum (dashed horizontal black line) in an urban environment (blue lines), any increase in the mutation rate ($\Delta\mu$) can lead to a net increase in deleterious mutations within a population, moving the population further from the fitness optimum. If urban pollution elevates mutation rates in urban areas (that is, high $\Delta\mu$, indicated by the solid blue line), then we predict a population will move further from the fitness optimum through time. If $\Delta\mu$ is low but still >0, then this effect can be relatively small. By contrast, when a population is initially maladapted to an urban environment (red lines), such that it starts far away from the fitness optimum, then higher mutation rates in urban areas (solid red line) can lead to rapid adaptation such that the population quickly evolves towards the fitness optimum. The rate of this evolution will be slower when $\Delta\mu$ is lower (red dashed line). Such adaptive evolution could lead to evolutionary rescue, but such dynamics are only likely over contemporary time when N_e is high and generation times are short (as in viruses, bacteria and eukaryotic microorganisms). At equilibrium, populations are below the fitness optimum because elevated mutation rates in urban areas increase a population's mutation load. Moreover, populations experiencing higher $\Delta\mu$ are predicted to have lower fitness than those with lower $\Delta\mu$ because most new mutations will be deleterious when a population is close to its fitness optimum. A population may remain maladapted (scenario not shown) when N_e is low and generation times are long, which could lead to extinction if population growth rates are negative.

of cancers. There is also clear evidence for intra-organismal selection for healthy cell lineages that can reduce the overall impact of deleterious mutations, including in marine tunicates and long-lived perennial plants[100,101]. These different phenomena hint at complex interactions between development, life history and genetic systems when determining the relative impact of elevated somatic mutation rates in urban settings. Given the evidence that urban habitats have elevated concentrations of numerous mutagens (Table 1), the impact of somatic mutations may become very important to predicting the sustainability of some urban populations (see 'Applied impacts').

Theory generally predicts an advantage for reduced mutation rates because most non-neutral mutations are deleterious[102,103]. We might therefore expect that urban populations will be under selection to reduce mutation rates in the presence of mutagens. The ability and time it takes for selection to reduce mutation rates will depend on numerous factors such as the mating system, N_e and target size (the amount of nucleotide sequence that can reduce mutation rate) for mutation modifiers[104]. The drift-barrier hypothesis[105] predicts that directional selection will reduce mutation rates until a point at which the strength of genetic drift ($1/N_e$) overcomes the selective advantage (s) of smaller improvements in mutation rate (when $N_e s < 1$). This hypothesis is supported by recent comparative genomic analyses that show that species with higher long-term N_e and shorter generation times tend to have lower mutation rates per generation[5]. There is an equilibrium point beyond which if mutation rates are sufficiently high, selection to reduce the mutation rate should overcome drift. Nevertheless, if urban environments reduce an organism's N_e, resulting in a loss of genetic diversity[22], we may expect a higher equilibrium mutation rate.

Despite the genetic load created by deleterious mutations, mutation also provides the raw variation necessary for adaptation. These contrasting effects of mutation lead to the possibility that mutation-fuelled adaptation can result in an "evolutionary rescue"[98,106] (that is, an increase in the population growth rate of small populations due to adaptation) of populations subject to environmental challenges in urban environments (Fig. 2). For example, pathogens whose fitness in a new host is so low as to preclude persistence may benefit from higher mutation rates, where the higher the mutation rate, the larger the probability of evolutionary rescue[107]. However, this situation is highly context-dependent—once a population approaches its fitness optimum, any new mutations are likely to be deleterious. It is reasonable to speculate that urban environments will pose such strong selective pressures that some populations will benefit from elevated mutational input during initial establishment (Fig. 2). The extent to which mutation will provide variation to tackle new selective challenges will depend on how elevated the mutation rate is in urban areas, how close a population is to a fitness optimum, N_e and generation time (Fig. 2). If elevated mutation rates have beneficial implications for species colonizing urban environments, it may also mean that cities could facilitate rapid adaptation to pesticides, herbicides and antibiotics or provide the raw variation needed for pathogens to switch hosts.

It is plausible that elevated patterns of mutation in cities could facilitate speciation, especially if mutations induced by urban pollution cause chromosomal changes that affect mating compatibility, ecology or physiology. Elevated mutation rates in cities could help to fuel population divergence among urban and non-urban populations via local adaptation and accelerate genetic drift due to population fragmentation[108]. Under these conditions, higher mutation rates in urban settings would increase the possibility of generating mutations that are compatible with population-specific local alleles at other loci but incompatible with alleles in populations adapted to non-urban environments. Alleles that are compatible only with the genetic background in which they arose are called Bateson–Dobzhansky–Muller incompatibilities and often form the genetic basis of speciation[109]. Such incompatibilities may be particularly likely to occur if urban pollutants increase the frequency of chromosomal abnormalities or large structural mutations, including inversions, translocations, polyploidy or elevated activity of transposable elements. It is these types of large-scale structural mutations that are most commonly associated with genes that influence reproductive isolation and large changes in ecology and physiology[110]. Even in the absence of reproductive isolation, reduced vigour of urban and non-urban hybrids could alter the fitness of nearby populations. Overall, because elevated mutation rates in urban areas have the potential to lead to increased divergence[108], we believe that cities offer unique opportunities to study the process of speciation in real time.

Applied impacts

Given that urbanization can increase mutation rates, we expect numerous applied consequences associated with the health and conservation of organisms inhabiting cities. The anticipated health effects on humans and non-human species include cancers and other diseases linked to somatic and germline mutations. The conservation consequences relate to how elevated mutation rates are expected to influence the fitness and long-term population growth of urban-dwelling species (Fig. 2).

Urban pollution causes numerous types of cancer in humans and other organisms. Contemporary urban pollution elevates lung[74,111], breast[112] and other forms of cancer[113] by 10% to 1,000% above baseline incidence rates (Table 2). The magnitude of these effects varies among cities and over time because of variation in the types and concentrations of pollutants (Fig. 1). Admittedly, most research on the health

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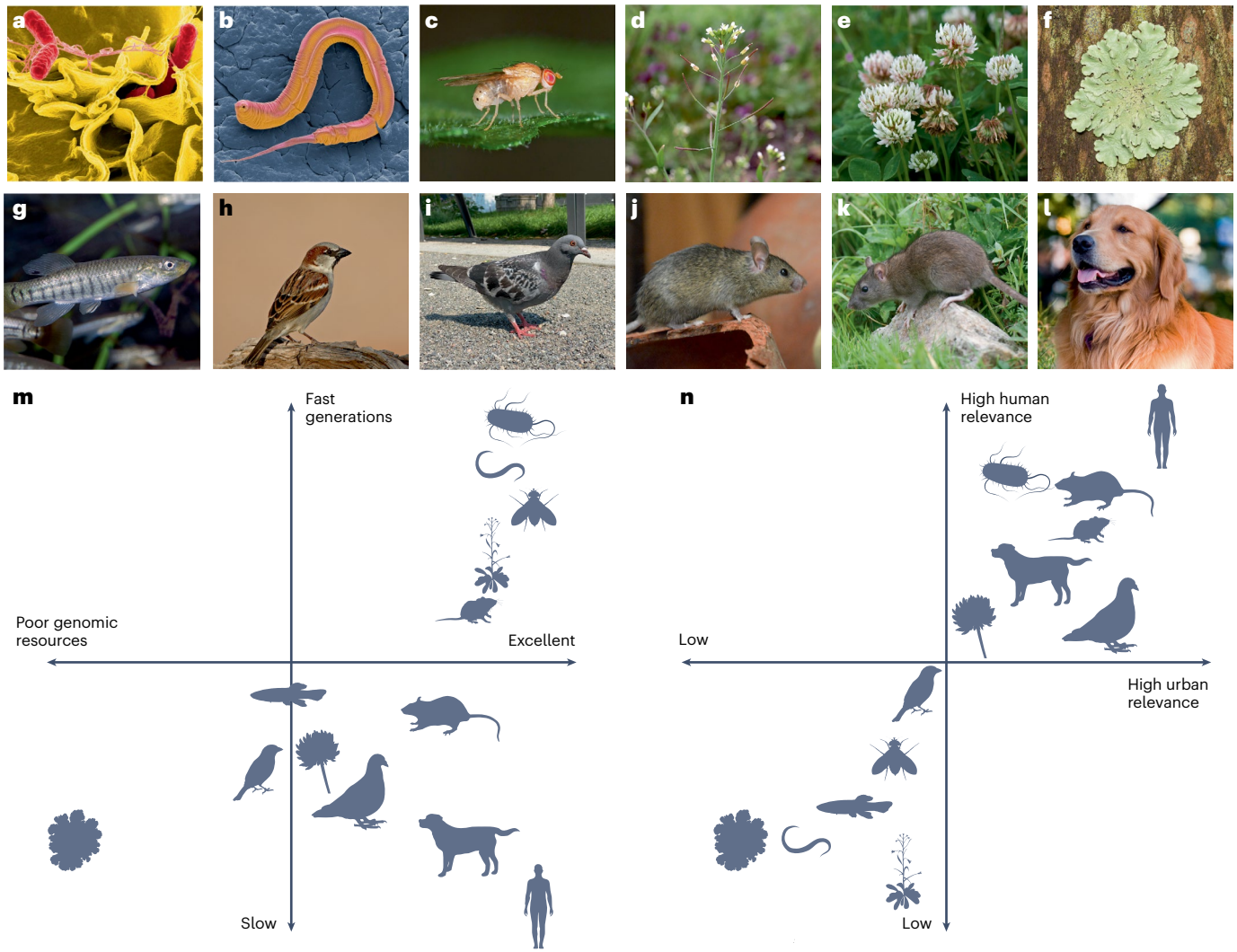

Fig. 3 | Potential biosentinel species for studying urban-associated mutations. a–**l**, Proposed biosentinels include *Salmonella enterica* (**a**), *Caenorhabditis elegans* (**b**), *Drosophila melanogaster* (**c**), *Arabidopsis thaliana* (**d**), *Trifolium repens* (**e**), *Flavoparmelia caperata* (a lichen) (**f**), *Fundulus majalis* (**g**), *Passer domesticus* (**h**), *Columba livia* (**i**), *Mus musculus* (**j**), *Rattus norvegicus* (**k**) and *Canis lupus familiaris* (**l**). An image of humans (*Homo sapiens*) is not shown but is included in the schematics below. These species represent a range of traditional laboratory model organisms used for studying genetic and evolutionary processes, as well as emerging models for studying ecological responses to pollution or evolution in urban areas. **m**,**n**, Some species offer a combination of fast generation time and excellent genomic resources for mutagenic studies (**m**), whereas others are more directly relevant to humans (that is, with respect to health and well-being) and urbanization (that is, owing to their relative abundance in urban versus non-urban habitats) given their commensal status with humans (**n**). Credits: Phanie - Sipa Press/Alamy Stock Photo (**a**), Science Photo Library/Alamy Stock Photo (**b**), Itsik Marom/Alamy Stock Photo (**c**), thrillerfillerspiller/Alamy Stock Photo (**d**), Nigel Cattlin/Alamy Stock Photo (**e**), Clarence Holmes Wildlife/Alamy Stock Photo (**f**), Robert S. Michelson/Tom Stack & Assoc./Alamy Stock Photo (**g**), robertharding/Alamy Stock Photo (**h**), M. Johnson (**i**), Tim Mander/Alamy Stock Photo (**j**), Dave Bevan/Alamy Stock Photo (**k**), K. L. Howard/Alamy Stock Photo (**l**).

effects of urban pollution has been done on humans and rodents. How urban pollution affects somatic mutations and cancers in non-model organisms is poorly understood, especially outside of laboratory settings, and represents a gap in knowledge[114–116] (see 'Future directions'). Although heritable germline mutations have the potential to magnify cancer risk in offspring due to pollution exposure in parents, there is currently no evidence outside the laboratory of environmentally induced heritable mutations causing cancer, even for ionizing radiation[19,88,117]. However, observational studies of birds[7] and laboratory studies of rodents[6,91] confirm that air pollution from steel mills can induce heritable germline mutations in repetitive DNA regions, which suggests that urban-induced mutations in cancer driver genes could also be inherited. Understanding how, when and where urban pollution leads to inherited mutations that influence cancer risk is an important goal for future research (see 'Future directions').

Multiple socio-ecological factors associated with urban lifestyles could interact with pollution to elevate mutation rates. The previously mentioned shift to older parental age among people in urban compared with non-urban communities is the best-known cause of higher germline mutation rates in urban populations[94]. Urban mutagenic pollution probably interacts with and amplifies this demographic effect on mutation rates. Human urban populations also exhibit increased rates of obesity and associated cancers due to a large proportion of processed foods in urban diets and relatively sedentary lifestyles[118]. Wildlife species also exhibit altered diets in cities that incorporate more anthropogenic food sources such as sugar, corn and wheat. Such diet shifts have been linked to higher body mass and hyperglycaemia in some species[119–121]. Food additives and contaminants in processed foods may influence germline mutation rates[122], as could shifts in urban gut microbiomes[123]. Exposure to environmental pollutants and lack

of access to high-quality diets may be biased towards certain urban demographics. Analysing urban mutagenesis and other evolutionary processes is thus an important step to address concerns about environmental justice[24,124,125].

Elevated mutation rates in cities have the potential to influence the dynamics of urban populations (Fig. 2). Given that most mutations are neutral or deleterious, it is likely that urban-induced mutations will frequently negatively affect individual fitness and population growth rate[97,98]. Determining whether such negative demographic effects will be sufficiently large to outweigh the influence of other factors requires careful quantification and modelling. We expect that the urban pollution-induced mutational load will be one of many factors threatening the persistence of populations and may become a conservation concern for rare or declining native species in cities. By contrast, we predict that populations of pests and other organisms that maintain large populations are less likely to be negatively affected by elevated mutation rates.

It is unlikely that urban-induced mutations will positively influence conservation through evolutionary rescue for most species. Only organisms with rapid generation times and high N_e are expected to experience positive long-term fitness effects of elevated mutation rates, and even then, only when selection is strong (Fig. 2). Such scenarios are most likely to apply to viruses, bacteria and some eukaryotic microorganisms (for example, yeast and algae), raising the possibility that elevated mutation rates in cities could promote the spread of pathogenic organisms[107]. Field and laboratory experiments that examine how urban-induced changes in mutation rates affect known and emerging diseases and pests could have important implications for public health.

Future directions

Our Perspective illustrates that water, soil and air pollution in urban areas increases mutation rates, but the magnitude and mutational spectrum of this increase, as well as its ecological and evolutionary consequences, remain unresolved. These gaps represent important problems requiring attention, which we outline as research questions below.

What is the magnitude of increase in somatic and germline mutation rates, and what are the types of mutations caused by urban pollution?

Although it is important to refine how somatic mutation rates are influenced by urban pollution, the greatest need remains establishing whether and under what circumstances urban pollution causes germline mutations in wild populations[19]. Conventional genomic technologies are poorly suited for quickly surveying the mutagenic properties of changing environments such as urban areas. New error-corrected sequencing approaches enable the study of rare mutations within a heterogenous population of cells[126,127]. These methods can facilitate more rapid and definitive tests of how urban pollution affects mutation rates because they rely on uniquely labelling individual DNA molecules prior to sequencing, which allows the removal of PCR and sequencing errors associated with standard next-generation sequencing. This enables, for the first time, the accurate quantification of rare mutations directly in the exposed organism.

What are the fitness effects of urban-induced mutations, and how do these influence the ecology and evolution of populations?

Answering this question will require a combination of laboratory and field experiments, coupled with genome sequencing. Laboratory experiments could establish how mutations caused by specific urban pollutants influence individual fitness, population growth and (mal) adaptation. Field experiments could follow the fitness of individuals that exhibit the presence or absence of mutations. Such experiments could be expanded on by experimentally recreating mutations via transgenic or CRISPR manipulations. Finally, identification of somatic and germline mutations from human and wild urban populations of diverse organisms (Fig. 3) could be used to infer fitness and health effects on the basis of how the types and locations of mutations are expected to disrupt homeostasis using deep learning models of DNA sequence evolution across thousands of species[128].

How do urban-induced mutations vary among species?

There is a need to expand the investigation of mutations caused by pollution to a wider diversity of organisms beyond humans given the indiscriminate threats of urban pollutants to all species. We propose a global research programme that uses a range of organisms as biosentinels (organisms to assay mutations induced by pollution), where the species chosen would vary in their relevance to humans, prevalence in urban areas, generation time and genomic resources (Fig. 3). A biosentinel programme could detect mutagenic effects even when specific mutagens are difficult to identify[129,130]. Bacteria, plants and human cell lines have all been proposed as urban biosentinels[131]. *Salmonella* has been the vanguard biosentinel because it responds readily to both known and unknown mutagens[68], and we see it as a possible bacterial model moving forward (Fig. 3). Existing plant (*Arabidopsis*) and animal (*Drosophila* and *Caenorhabditis elegans*) model organisms offer a rich genomic toolkit, although given their marginal importance to humans and/or prevalence in urban areas, non-model organisms that have been the focus of studies in urban areas should also be included, such as white clover, dogs and various birds. Rodents, particularly house mouse (*Mus musculus*) and Norway rat (*Rattus norvegicus*), are important pests in urban areas that are commonly used in laboratories, offering a biosentinel model that more closely resembles human physiology[16]. The deployment of such biosentinels could provide a rapid and accurate view of how urban-induced mutations affect the biology of urban-dwelling species, including humans.

Conclusions

Our Perspective highlights the potential broad-ranging mutagenic effects of urban pollution on virtually all life in cities. These mutagenic effects are expected to influence the fitness, ecology and evolution of wild populations, but these effects are largely unstudied outside of laboratory settings, and even there, only a small subset of species have been studied. Given the many mutagens that are prevalent in urban areas and their potentially large impacts on human and wildlife fitness, we argue that the study of urban mutagenesis is in urgent need of attention and should be prioritized in future research on health, ecology and evolution.

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Author contributions

M.T.J.J. conceived and led the project. All authors (M.T.J.J., I.A., F.M., J.M.-S., R.W.N., M.S., B.C.V., C.L.Y., D.N.A., W.B., A.E.C., E.J.C., A.D., J.G., C.G.L., M.O., M.P.-R., D.J.R., M.S.R. and K.M.W.) contributed to brainstorming the ideas covered in the paper, and the original outline was written by the lead team members (F.M., J.M.-S., R.W.N., M.S., B.C.V. and C.L.Y.). I.A., M.T.J.J., F.M., J.M.-S., R.W.N., M.S., B.C.V., K.M.W. and C.L.Y. led the writing of specific sections and/or the preparation of the figures and tables. All remaining authors (D.N.A., W.B., A.E.C., E.J.C., A.D., J.G., C.G.L., M.O., M.P.-R., D.J.R., M.S.R. and K.M.W.) contributed to one or more sections, and all authors (M.T.J.J., I.A., F.M., J.M.-S., R.W.N., M.S., B.C.V., C.L.Y., D.N.A., W.B., A.E.C., E.J.C., A.D., J.G., C.G.L., M.O., M.P.-R., D.J.R., M.S.R. and K.M.W.) edited the final drafts of the paper.

Competing interests

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Additional information

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