








Heart healthy cities: genetics loads the gun but the environment pulls the trigger

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The world's population is estimated to reach 10 billion by 2050 and 75% of this population will live in cities. Two-third of the European population already live in urban areas and this proportion continues to grow. Between 60% and 80% of the global energy use is consumed by urban areas, with 70% of the greenhouse gas emissions produced within urban areas. The World Health Organization states that city planning is now recognized as a critical part of a comprehensive solution to tackle adverse health outcomes. In the present review, we address non-communicable diseases with a focus on cardiovascular disease and the urbanization process in relation to environmental risk exposures including noise, air pollution, temperature, and outdoor light. The present review reports why heat islands develop in urban areas, and how greening of cities can improve public health, and address climate concerns, sustainability, and liveability. In addition, we discuss urban planning, transport interventions, and novel technologies to assess external environmental exposures, e.g. using digital technologies, to promote heart healthy cities in the future. Lastly, we highlight new paradigms of integrative thinking such as the exposome and planetary health, challenging the one-exposure-one-health-outcome association and expand our understanding of the totality of human environmental exposures.

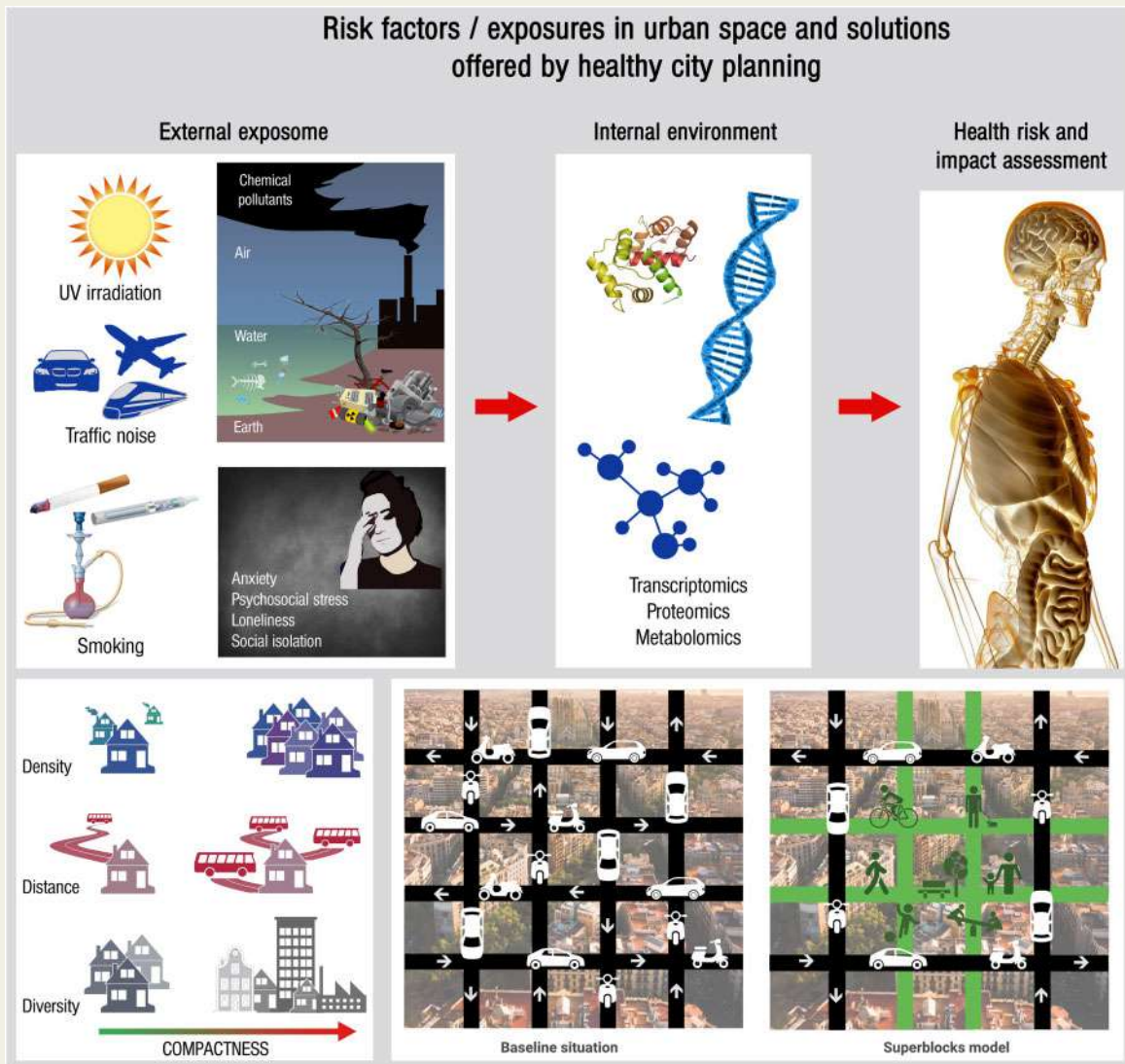
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Graphical Abstract



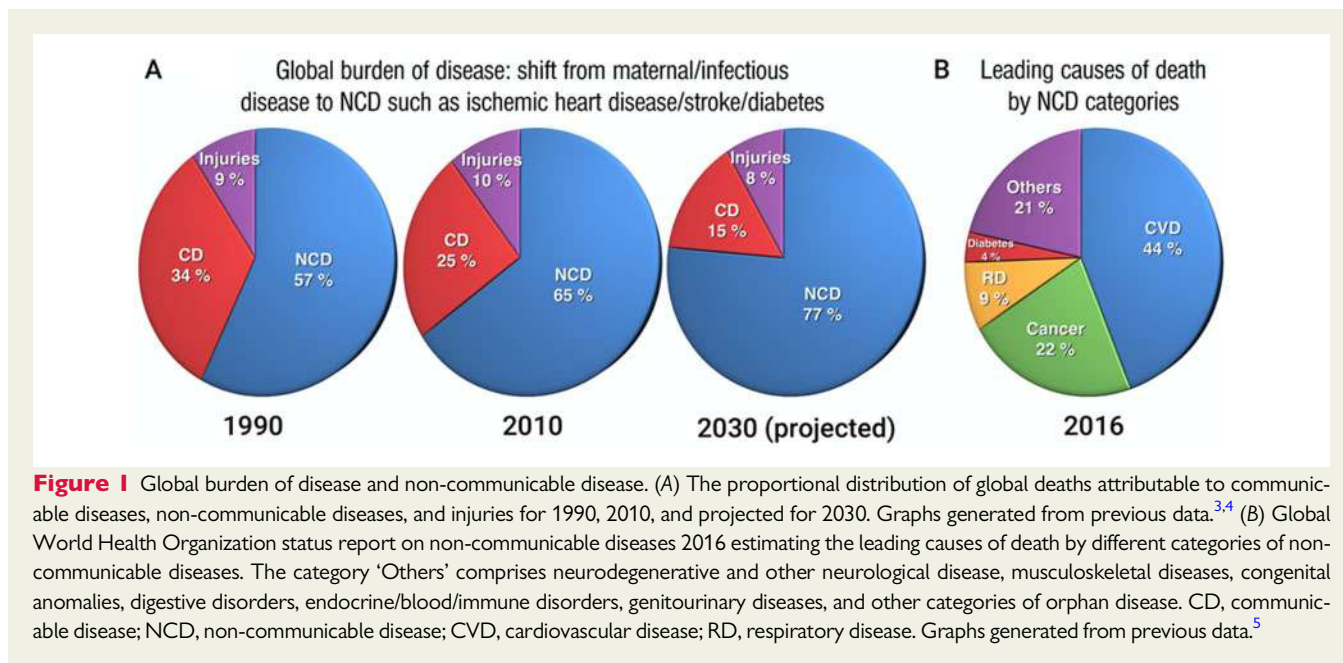
Keywords

Heart healthy city • Environmental stressors • Heat islands effects • Air pollution • Noise pollution • Light pollution • Urban and transport planning and design interventions

Introduction

Non-communicable diseases (NCDs) kill >38 million people each year, accounting for nearly 70% of deaths globally mostly attributable to cardiovascular disease (CVD), cancer, chronic respiratory disease, diabetes, and other system disorders. Among the victims are >14 million adults who in the words of the World Health Organization

(WHO), 'die too young'—that is, between the ages of 30 and 70.¹ Among NCDs, CVD accounts for the preponderant majority of deaths. In the Global Burden of Disease (GBD) 2019 study, the number of CVD deaths steadily increased from 12.1 million (95% confidence interval (CI): 1.4–12.6 million) in 1990, reaching 18.6 million (CI: 17.1–19.7 million) in 2019.² As depicted in Figure 1 in a mere three decades of global mortality accounting, there has been a



seismic shift from maternal, infectious diseases to NCDs, where CVD and diabetes predominate. Of note, the projection for 2030 does not consider the impact of COVID-19 pandemic. Despite the acute awareness paid to the growing health and economic consequences of NCDs, the substantial contribution of NCDs is generally not sufficiently acknowledged. This is surprising since in GBD publications, ambient air pollution consistently ranks within the top five causes of global mortality (rank number 4 in GBD 2019); a ranking that has not changed much over the years.² Environmental research, prevention, and treatment as it pertains to the development of NCDs are currently substantially underfunded.⁶ This is especially glaring, as the environment is a key facilitator of NCDs in general. Although 'creating active environments' is a priority for the WHO as articulated in its Global Action Plan on Physical Activity,⁷ the WHO Urban Health agenda,⁸ WHO NCD Global Action Plan¹ and the report 'Tackling NCDs'⁹ fail to adequately acknowledge the contribution of the environment to NCDs. Furthermore, the United Nations sustainable development goals (SDGs) have not been sufficiently incorporated the importance of appropriate and healthy urban development in cities.¹⁰ However, it should be noted that the SDGs track death from CVD, cancer, diabetes, and chronic respiratory diseases only in individuals aged 30–70 years and does not take into account the impact in children and adolescents and/or the contribution of chronic disease triggered by air pollution and other environmental factors.¹¹

While cities have been an engine of innovation and wealth, they are also a source of pollution and disease. Between 60% and 80% of the global energy use is consumed by urban areas,¹² with 70% of the greenhouse gas (GHG) emissions produced within urban areas.¹³ Two-third of the European population currently live in urban areas, and this share is expected to grow. Large parts of Asia are rapidly transforming to mega-cities. This unprecedented increase in urban populations has dramatically escalated the scale and scope of

complex urban exposures (Figure 2). Recently, Giles-Corti *et al.*¹⁵ defined environmental, social, and behavioural risk exposures related to urban and transport planning and design decisions, which have the potential to affect the risk of NCDs significantly. These exposures include traffic exposure, noise, air pollution, safety from crime, social isolation, physical inactivity, prolonged sitting, and unhealthy diet. Given that urban environments are a key aggregator of a number of environmental exposures such as air pollution, chemical toxins, noise pollution, psychosocial, and economic stressors, there is a substantial need to focus health efforts in reducing urban exposures.

With the present review we wish to focus on urbanization, its impact on cardiovascular NCDs, and the role that environmental risk exposures including noise, air pollution, temperature, and ambient light play in relation to the urban environment. We will address solutions to mitigate exposures pertinent to the urban environment such as urban planning, landscape reform, transport interventions, and finally novel technologies to address environmental exposures, which together will promote heart healthy behaviours and mitigate risk. Lastly, we will discuss new paradigms of thinking including the exposure, helping us to move away from simplistic paradigms of the 'one-exposure-one-health-outcome' association towards totality of human environmental exposures and human health.

Urbanization and air pollution

Air pollution constituents

Air pollution is the leading environmental risk factor for global health and the fourth largest risk factor for global mortality.² A large proportion of these deaths (>50%) are attributable to cardiovascular causes.¹⁶ Consistent associations between both short-term exposure in >652 cities across the world and cardiovascular mortality have been noted.¹⁷ Air pollution is a complex mixture of nano- to micro-sized particles and gaseous pollutants. Particulate

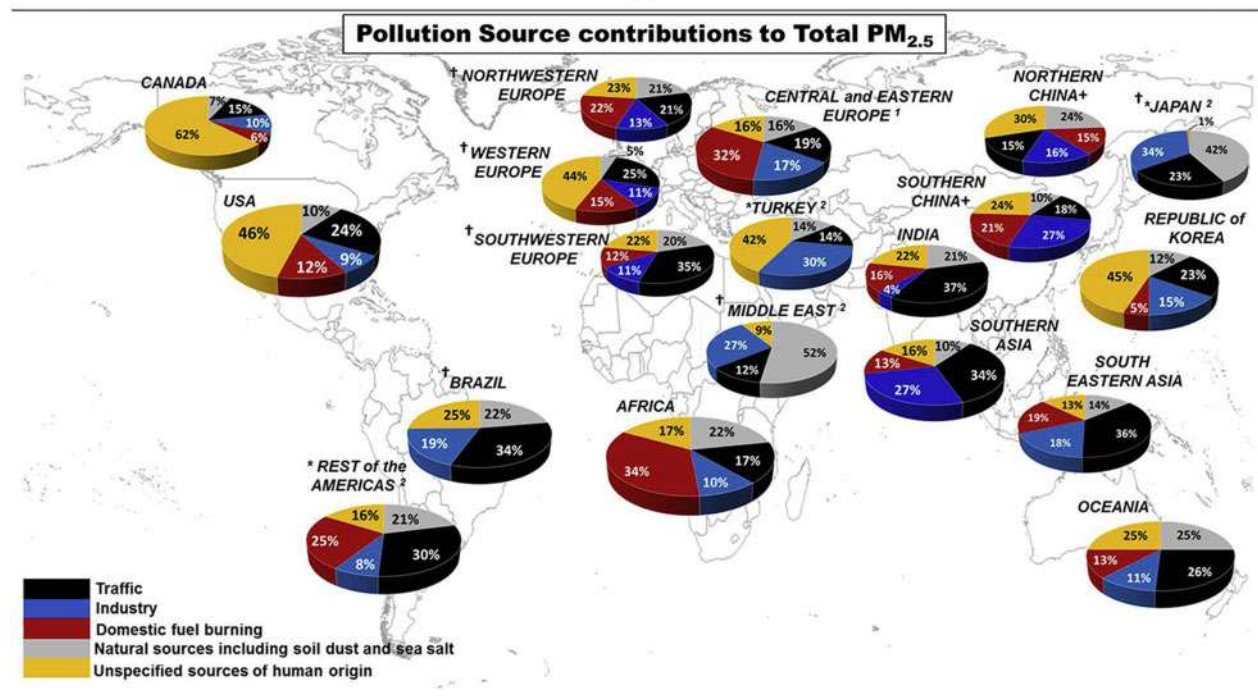
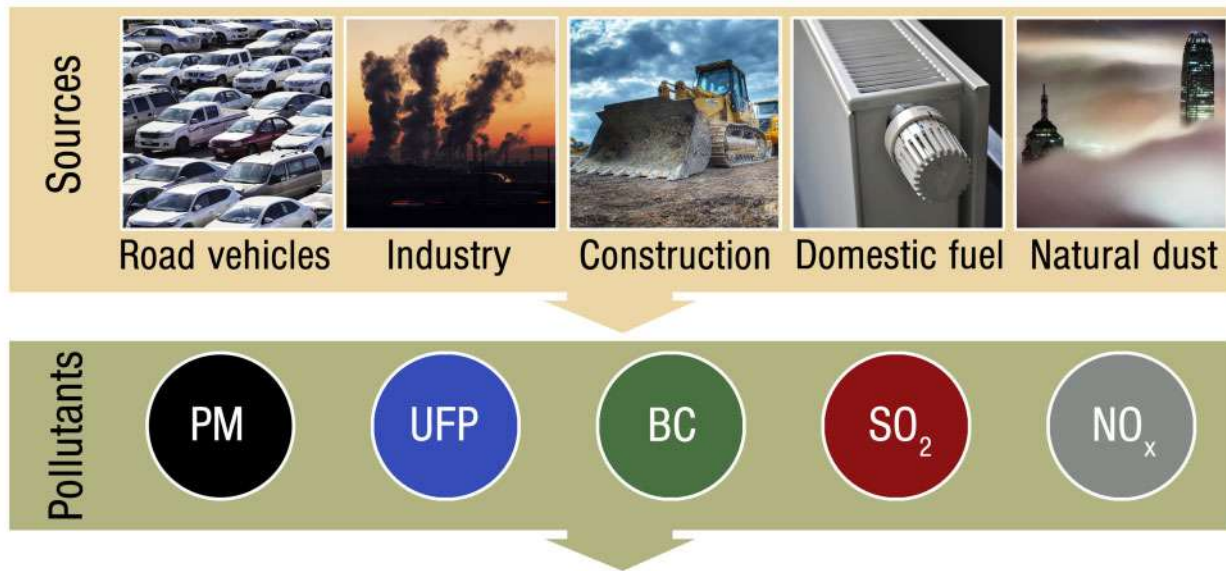


Figure 2 Sources of air pollution in cities and contribution of sources to PM_{2.5} air pollution. PM, particulate matter (e.g. PM_{2.5} and PM₁₀ with a diameter of <2.5 or 10 μm); UFP, ultrafine particles (diameter usually <0.1 μm); BC, black carbon; SO₂, sulphur dioxide; NO_x, nitrogen oxides (e.g. nitric oxide, nitrogen dioxide). Adapted from previous report with permission.¹⁴

matter of various size ranges (PM₁₀, PM_{2.5}, PM_{10-2.5} [coarse and fine particles ≤10 or 2.5 μm], and PM_{0.1} [ultrafine particles, UFP]) and gaseous pollutants (NO₂, SO₂, CO, and O₃) are some of the important pollutants in the urban environment.¹⁸ A limitation of the present work is that we exclusively discuss ambient (outdoor) air pollution, although people spend an appreciable part of their daily life indoors in their private homes and the work place. Accordingly, indoor air pollution represents an equally important risk factor, as highlighted by the GBD study with household air

pollution (mainly from heating and cooking) ranking among the top 10 risk factors for global mortality and morbidity.¹⁹ Likewise, indoor source emissions from unexpected sources such as laser printers may contribute to respiratory and cardiovascular NCDs at the work place or recently in home office.²⁰

Air pollution sources

Air pollution in mega-cities is attributable to a wide variety of mostly anthropogenic sources. These include: (i) mobile sources such as

cars, commercial vehicles, motorcycles and three-wheelers in developing countries, and non-vehicular traffic including shipping in coastal cities, airplanes, construction and agricultural equipment; (ii) stationary power sources such as factories, refineries, and power plants; and (iii) area sources such as industrial and commercial businesses, wastewater treatment and solid waste disposal plants, landfills, residential heating/cooling and fuel use, construction activities, mining operations, and agricultural activities. Natural (biogenic) sources include windblown soils, ocean salt spray, volcanoes, forest, and grassland.²¹ Transport emissions are by far the largest contributor to air pollution in cities around the world. In a global source apportionment review that examined 419 records from cities of 51 countries, 25% of urban ambient air pollution from PM_{2.5} was contributed by traffic, 15% by industrial activities, 20% by domestic fuel burning, 22% from unspecified sources of human origin, and 18% from natural dust and salt (Figure 2).¹⁴ Domestic fuel burning continues to be a significant source in some regions like Africa and Central and Eastern Europe. Biomass burning could be a large source of primary organic aerosols (POA) and could be a dominant source of black carbon. Biomass sources such as burning of crop residue (e.g. in cities in India such as New Delhi), residential wood burning for cooking and heating (e.g. in many cities in Africa), and biofuel for brick production may dominate air pollution levels in many cities in the world. Other sources that are important contributors to emissions include fireworks to celebrate New Year's Day, Diwali in India, and Spring Festival in China, as well as national holidays such as 4th of July in the USA and Bastille Day in France. Among natural sources, desert dust, pollen, and salt emission from agricultural use, especially PM_{2.5} from wildfires and volcano eruptions, may significantly contribute to PM levels and have been a concern with global warming.

Impact of sources on air pollution composition and particle 'loading'

The sources of PM_{2.5} have a substantial impact on its composition and health effects of PM_{2.5}. In this regard, urban PM_{2.5} differs substantially from rural or sub-urban PM_{2.5} in its composition. A substantial fraction of urban PM is comprised of organic aerosol (OA), which is composed of POA (organic compounds emitted directly in the particle phase) and secondary OA (SOA, formed from chemical reactions of precursor organic gases). In a recent study, at least in Europe, while secondary inorganic components, crustal material and SOA dominated the PM_{2.5} mass, the oxidative potential was associated mostly with anthropogenic sources, in particular with fine-mode SOA, from residential biomass burning and coarse-mode metals from vehicular non-exhaust emissions.²² Thus, mitigation strategies aimed at reducing PM_{2.5} mass alone may not suffice to reduce health complications with additional attention paid to specific urban sources. In addition to PM_{2.5}, urban environments demonstrate huge gradients in UFP (particles with diameter $\leq 0.1 \mu\text{m}$) produced predominantly from vehicular exhaust. These particles have both longer lifetimes, a higher probability of systemic effects and are increasingly acknowledged as a major health concern.²³ Recent evidence suggests that nanoparticles and transition metals, which are also associated with fossil fuel combustion, may play an important role in CVD.

Despite substantial reductions in ambient PM_{2.5} concentrations in North America and Europe, levels remain high throughout most of the world. Global annual average population weighted PM_{2.5} levels increased slightly from 40.8 $\mu\text{g}/\text{m}^3$ in 1990 to 42.6 $\mu\text{g}/\text{m}^3$ in 2019, with this increase almost entirely attributable to urbanization and increasing exposures in Asia, parts of the Middle East, and Africa. In the European Union (EU), air pollution-induced premature mortality is about 659 000 [95% CI 537 000–775 00] per year or even higher (790 000),¹⁶ of which approximately two-third are due to cardiovascular events, mainly ischaemic heart disease, stroke, diabetes, and arterial hypertension.

Projection model for air pollution by urbanization, population/economic growth

To assess the impact of different scenarios of exposure to air pollution in the urban population, a Shared Socioeconomic Pathway (SSP) model has been developed.²⁴ The contribution of emerging urbanization to exposure and premature mortality was estimated in this model assuming constant air pollution emissions representative of the year 2010 and population projections, combined with the health impact data from Lelieveld *et al.*¹⁶ Global calculations were performed at 1 km spatial resolution and then aggregated to country level. Four scenarios were compared: one that aimed at sustainability with environmentally friendly urban arrangements (SSP1), a 'middle-of-the-road' pathway with moderate urbanization (SSP2), a poor urban planning scenario (SSP3), and finally one with fast urbanization under rapid economic growth (SSP5). Figure 3A²⁴ presents the global population projections in urban areas under these four scenarios, and the fraction of the population exposed to PM_{2.5}, in excess of the WHO guideline concentration of 10 $\mu\text{g}/\text{m}^3$ annually. The projected population fractions exposed to degraded air quality in this model was 82–85%, representing about 7–8.5 billion people by 2050.

Figure 3B shows the consequences of urbanization on premature mortality from the exposure to PM_{2.5}, again assuming unchanged air pollution sources vs. the assumed hypothetical SSPs. Under all scenarios, premature mortality increases significantly following population development, while the projected urban fraction also grew but varied between 56% and 80% depending on SSP. Although such estimates will require considerable refinement based on emission projections, baseline mortality, population age structure, socioeconomic determinants of health, access to health services, etc., it nonetheless provides a framework to develop refined and evolving metrics to model scenarios. Baseline mortality for instance typically changes with societal development. Improved economic indices and access to healthcare is expected to shift mortality from communicable diseases to NCDs especially due to environmental risk factors.²⁵ In the coming decades, urbanization in low- and middle-income countries, especially in Africa and South Asia, is going to drive urbanization trends globally (Figure 3C). While this will undoubtedly create an unprecedented stress in urban environments, it will hopefully provide a fertile environment to model next generation zero carbon foot print cities replete with renewable energy sources, improved infrastructure, transportation, and urban landscape reform. These changes are not expected to happen overnight,

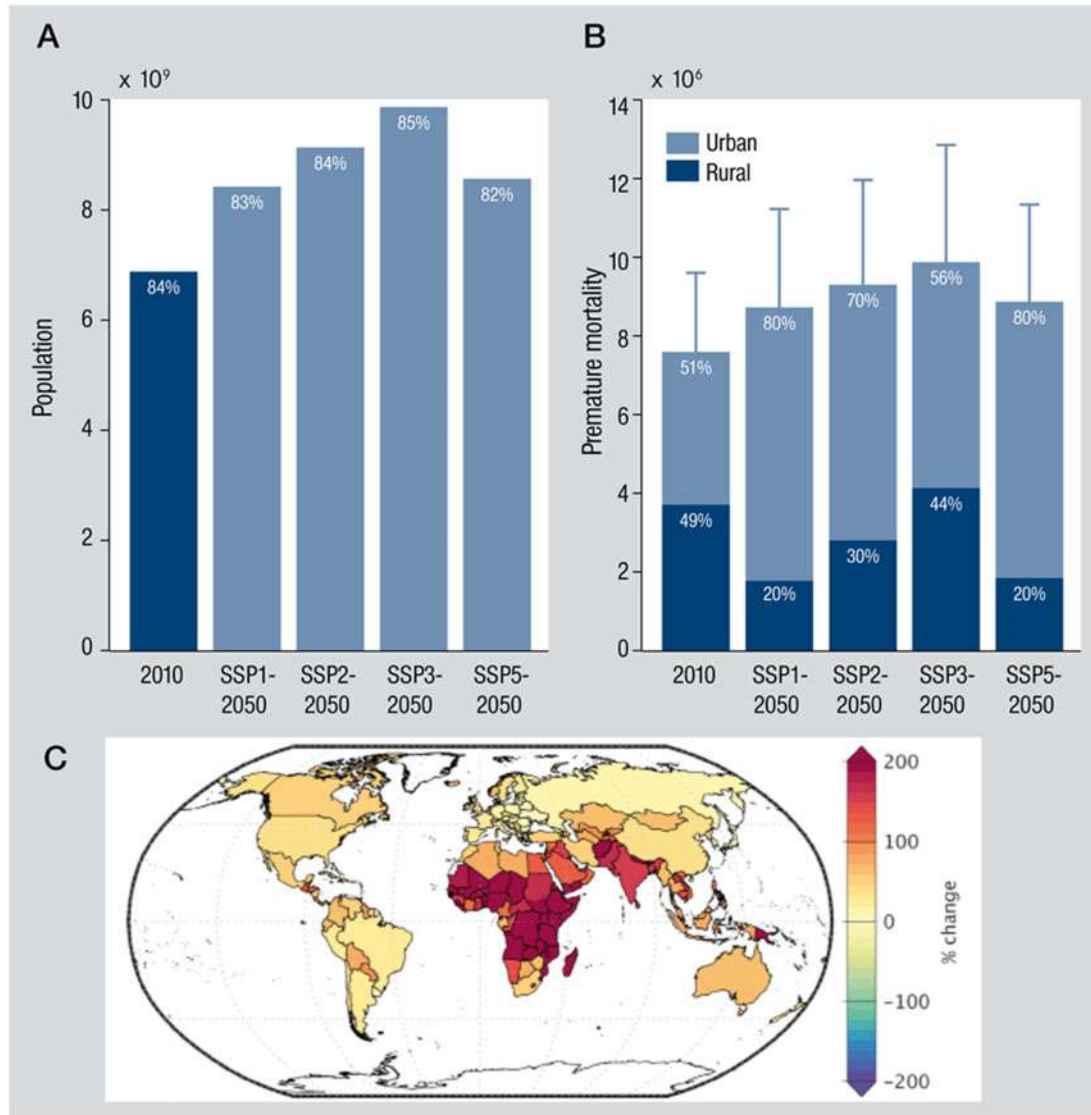


Figure 3 Projections for population growth, urbanization, and their health impact. (A) Global population in the year 2010 and projections for 2050 according to four shared socioeconomic pathway (SSP) models, and percentages exposed to unhealthy levels of PM_{2.5} (exceeding the World Health Organization guideline of 10 µg/m³), assuming that air pollution remains at the levels of 2010. (B) Global, annual premature mortality from the exposure to PM_{2.5}, assuming 2010 emissions and population developments according to four SPPs. The error bars indicate 95% confidence intervals. (C) Fractional change in urban population per country between 2010 and 2050 according to the 'middle-of-the-road' scenario SSP2. Graphs generated from data and using methods previously published.^{16,24}

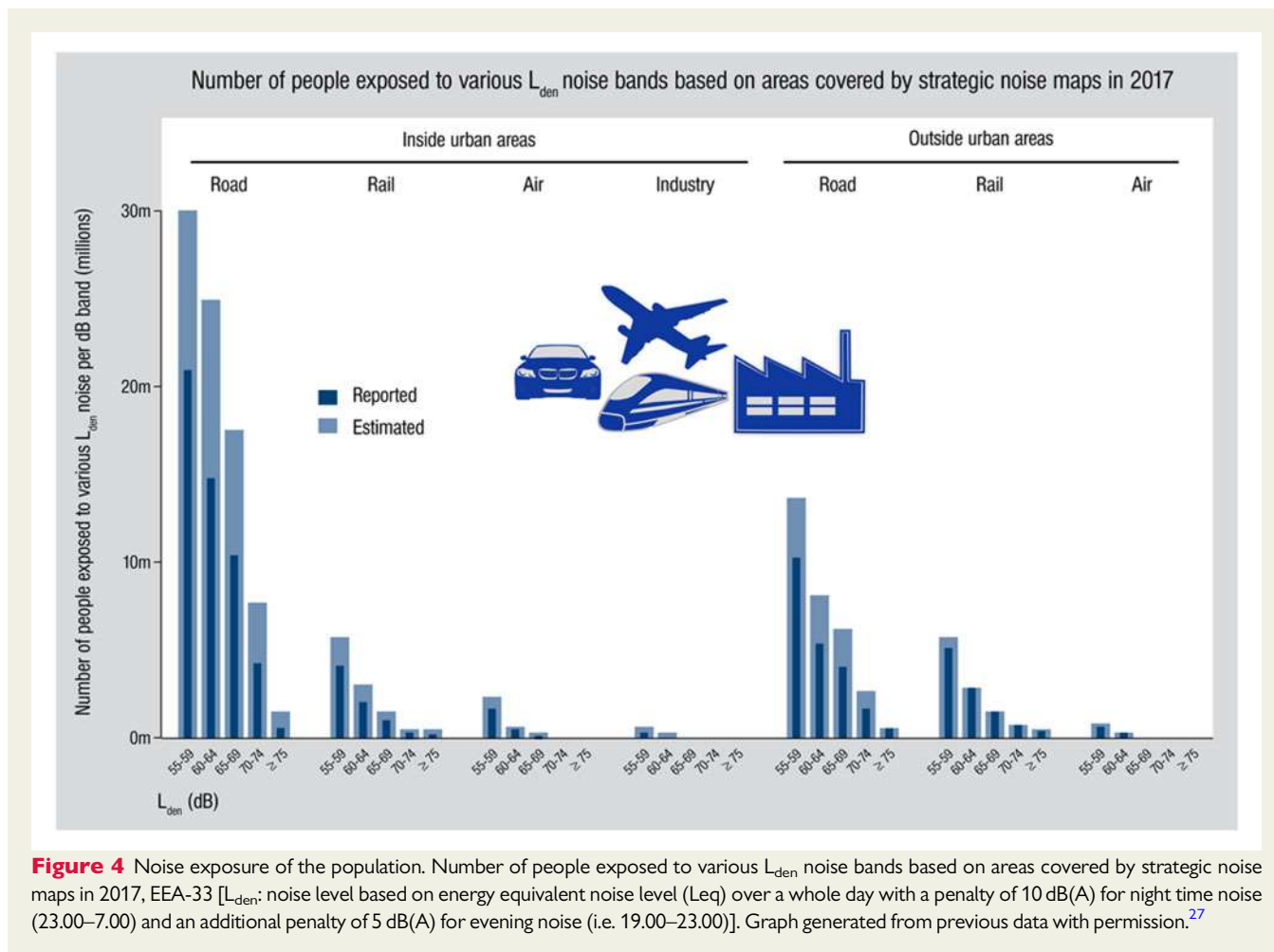
thus compelling a focus on personalized measures in the near-term, including use of N95 face masks, indoor air filtration devices, and common-sense pragmatic measures such as avoiding travel to heavily polluted environments, adoption of heart healthy behaviours such as exercise and adherence to healthy diets.²⁶

Urbanization and transportation noise

Urbanization and traffic growth have resulted in an increase in people exposed to high levels of transportation noise. The dominant source

of noise is road traffic, although trains, trams, and aircrafts also contribute to urban noise pollution. A recent mapping of the EU estimated that at least 20% of the population lives in areas where transportation noise is harmful to health (>55 decibel L_{den}); the majority of these are within urban areas (Figure 4).²⁷ As the EU mapping does not comprehensively cover urban areas, this proportion is most likely underestimated.²⁷

Exposure to transportation noise may affect the risk for cardiometabolic disease through an indirect pathway, with cognitive and emotional perception of noise, followed by activation of the sympathetic-adrenal-medullary, hypothalamic-pituitary-adrenal axes, and



disturbance of sleep, resulting in an increased level of stress hormones, heart rate, and blood pressure.^{28–30} Repeated and sustained activation of this pathway may increase risk for cardiometabolic disease. Exposure to noise during sleep is hypothesized to be particularly harmful,³¹ supported by translational studies, which have found nighttime exposure to transportation noise to be associated with cardiovascular risk factors, including vascular oxidative stress, endothelial dysfunction, and inflammatory markers.^{32–34} In 2018, a WHO expert group concluded that road traffic noise increases the risk for ischaemic heart disease³⁵ with subsequent epidemiological studies suggesting that transportation noise may also increase risk for stroke, obesity, and diabetes.^{36–41}

The European Environment Agency recently estimated that long-term exposure to transportation noise results in 6.5 million people suffering from chronic high sleep disturbance, 12 000 premature deaths, and 48 000 new cases of ischaemic heart disease per year in the EU.²⁷ Importantly, if future studies confirm the observed association between transportation noise and stroke and diabetes, the estimated disease burden from transportation noise will increase significantly.

Only few studies have investigated associations between transportation noise and CVD risk in urban vs. sub-urban and rural areas. A nationwide study from Switzerland investigating the effects of road

traffic noise on myocardial infarction mortality found risk estimates in sub-urban areas to be higher than risk estimates in urban areas.⁴² Interestingly, this pattern was more pronounced for noise at the least exposed façade (where people would normally place their bedroom) compared to noise at the most exposed façade. A potential explanation is masking of the association between transportation noise and myocardial infarction mortality by other surrounding noise sources, such as noise from neighbours, bars, and restaurants, which are ubiquitous in urban areas. Therefore, future studies aiming at estimating and disentangling both community and transportation noise are important.

Noise mitigation measures for urban settings include promotion of noise barriers, brake blocks for trains, continuous descendent approach (landing aircrafts descend later from 7000 to 3000 ft when approaching an airport, thereby decreasing noise exposure levels to housings around the airport) for airplanes, traffic curfews, low-noise tires, speed reductions, night bans for heavy traffic, trains and airplanes, quiet road surfaces, and thoughtful building design, e.g. by installation of soundproof double-glassed windows.²⁹ Reductions in road traffic intensity will only reduce noise levels slightly: as the decibel scale is logarithmic, a 50% reduction in traffic will only result in a 3-dB noise reduction. Moreover, introduction of electric cars will not contribute significantly to reduce noise, as the interaction

between the tires and the tarmac is the dominant source of noise at medium and high speeds (>30–40 km/h).⁴³ In addition to these upstream interventions, noise health effects can also be mitigated at the individual level by using ear plugs or noise-cancelling headphones.

Urbanization and outdoor light pollution

Light pollution is a ubiquitous environmental risk factor, defined by the changes in natural nighttime sky brightness induced by anthropogenic sources of light,^{44,45} which is most evident in big cities and large metropolitan areas. However, urban light pollution can also affect distant areas such as national parks, hundreds of kilometres from its source. Falchi *et al.*⁴⁴ reported that 83% of the world's population and >99% of the US and European populations live under light-polluted skies (>14 $\mu\text{cd}/\text{m}^2$ artificial nighttime sky illumination). In his review article, 'Missing the Dark: Health Effects of Light Pollution' in 2009, Chepesiuk⁴⁶ provides a compelling overview of electrified illumination at night supplemented by worrisome satellite images of evolution of light pollution in the USA starting in the 1950s, and ending with a projection for the year 2025, where he details a potential large impact of light pollution on NCDs.

Despite these alarming data, light pollution has only gained limited attention from environmental scientists until recently. Light pollution alters circadian rhythm of insects, animals, and birds causing premature mortality and loss of biodiversity. Misalignment in circadian rhythm is thought to be an important contributor to NCD.^{47–49} Mutations/altering expression of key circadian genes can cause obesity, hyperglycaemia, and defective beta-cell function leading to disease.^{50–52} Circadian preference and indeed sleep components and habits also referred to chronotype have been shown to have genetic components and indeed have been linked with metabolic complications such as obesity.^{53–58} A moderate increase in systolic and diastolic blood pressure by 4.3 and 3.0 mmHg, respectively, has been noted for a 5-lx increase (1 lx = 1 lumen/m²; 1 lumen is equivalent to ~0.1 W (bulb) or 0.01 W (LED)) in outdoor nighttime light pollution in elderly Japanese subjects.⁵⁹ A large body of evidence also supports a link between circadian rhythm disruption and insulin resistance and type 2 diabetes mellitus.^{60–64}

An association between outdoor nocturnal light pollution and risk of coronary heart disease (CHD) and mortality has been noted in the elderly.⁶⁵ Sun *et al.* demonstrated that nocturnal light pollution (change of 60.0 nW/cm²/s; units of radiance = watt per steradian per square metre. Outdoor illumination at night was obtained from satellite data with a precision of 1 km²) was associated with increased risk of CHD hospitalizations (hazard ratio of 1.11; 95% CI 1.03–1.18) and CHD deaths (hazard ratio 1.10; 95% CI 1.00–1.22), even after multivariable adjustment. Moreover, sensitivity analyses indicated that these associations were stable. Importantly, high PM_{2.5} exposure levels showed an additive interaction with CHD mortality in the highest light pollution quintiles (hazard ratio 1.32 and 1.39, respectively) (Figure 5).⁶⁵ In a recent comparative mechanistic study, both light exposure and chronic PM_{2.5} exposure were effective in inducing hyperinsulinaemia, brown adipose tissue dysfunction, and metabolic abnormalities such as reduced oxygen

consumption and energy expenditure. These phenotypic changes were associated with reprogramming of multiple pathways involved in lipid oxidation and gluconeogenesis, all without changes in body weight or visceral adipose deposition.⁷⁰ Both light and air pollution exposure, however, induced distinct epigenetic changes accompanied by their own unique pattern of circadian gene disruption.⁷⁰

The simplest mitigation measure to reduce light pollution is to turn off lights, especially in times when it may not be needed.^{44,46} Other mitigation strategies are based on the technical advances to reduce light pollution^{46,71} and comprise improved light shielding (sending light rather to the ground than to the horizon or outside the area to be lit), energy-efficient lights (use of low-pressure sodium lights emitting yellow light at the wavelength with the highest sensitivity of the human eye), and smart city techniques (e.g. sensor-controlled light shut-off when the area is not in use or adaption to meteorological conditions). Limiting the exposure to 'blue' light [light-emitting diodes have peak emission in the blue light range of 400–490 nm with more pronounced health effects (e.g. on circadian rhythm)] is of importance as it is more impactful in disrupting circadian rhythm.⁷¹ In the future, autonomous cars may make street illumination at night less important. Also, the safety aspects of nocturnal illumination of public metropolitan areas (e.g. preventing crimes) is not well supported by scientific studies, and it has been speculated that investing the money divined by turning of lights for actively solving socioeconomic problems may be much more effective in making metropolitan areas pseudosafe.⁴⁴ Finally, resetting the circadian clock by chronotherapeutic strategies (e.g. melatonin) may represent an approach to combat sleep disorders⁷² not only for light pollution but also for traffic noise at night³¹ and even air pollution.^{73,74}

Urbanization, temperature, heat islands, and green space

While cities facilitate economic prosperity and innovation as noted earlier, they also generate 70% of GHG emissions contributing to anthropogenic climate change.⁷⁵ Atmospheric concentrations of GHG emissions are rising, with carbon dioxide (the major GHG) reaching 411 ppm, the highest it has been in the past 800 000 years.⁷⁶ The 2018 Intergovernmental Panel on Climate Change has projected global temperatures rising by 1.5°C between 2030 and 2052 causing cataclysmic weather events.⁷⁶ These events will have both direct and indirect effects on human health with storms, drought, flood, and heatwaves affecting water quality, air pollution, land use changes, and pervasive damage to the eco-system.^{77–79} Climate events are relevant to rapidly urbanizing cities, as cities are at the epicentre for climate-induced disruptions while also contributing to increased GHG emissions. This is already apparent with cities experiencing trillions of dollars in costs related to destruction of infrastructure, health-related emergencies and increased mortality related to climatic events.^{77,78}

Dense compact urban development in new or established areas⁸⁰ to accommodate rapidly growing urban populations is typically accompanied by increasing amounts of impervious surfaces and significant loss of green space and tree canopy,^{80,81} leading to significant heat island effects. For example, in Hong Kong, intense heat island effects up to 4°C have been observed with adverse human health and biodiversity effects.⁸²

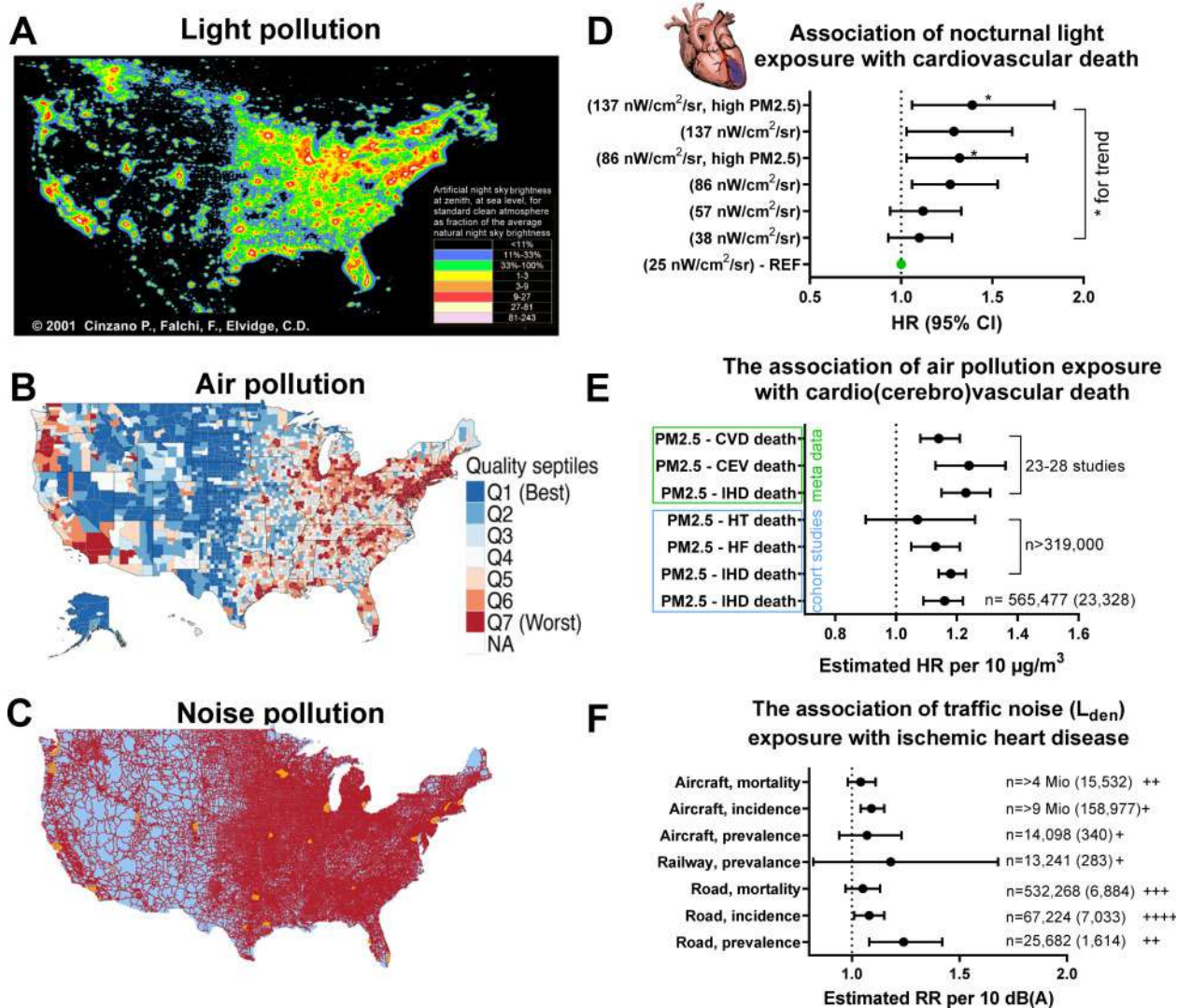


Figure 5 Co-localization of environmental pollutants. (A) Light pollution in the USA in the year 1997. Calculated according to Cinzano in 'Light Pollution: The Global View' (edited by H.E. Schwarz) and reused with permission by P. Cinzano, F. Falchi, C.D. Elvidge. VC 2001 ISTIL-Light Pollution Science and Technology Institute, Italy. Distribution of air pollution (B) and noise exposure levels (C) show a co-localization with light pollution in the USA. Air pollution map reused from previous data.⁶⁶ © 2019 Khan *et al.* under the Creative Commons Attribution License. Noise pollution map was qualitatively approximated from United States Department of Transportation, Bureau of Transportation Statistics (<https://maps.dot.gov/BTS/NationalTransportationNoiseMap/>) (Date accessed 19 April 2021)). Red colour = areas with higher noise exposure. Orange colour = noise exposure hot spots. (D) Hazard ratio for light pollution-mediated cardiovascular mortality. High particulate matter caused additive risk effects for coronary heart disease death. Graph was generated from previous tabular data.⁶⁵ (E) Hazard ratio for long-term air pollution-mediated cardiovascular mortality. Graph was generated from previous tabular data: upper three values,⁶⁷ values 4–6 from top,⁶⁸ and bottom value.⁶⁹ (F) Hazard ratio for long-term noise pollution-mediated ischaemic heart disease. Graph was generated from previous tabular data.³⁵ All tabular data used with permission. REF, reference value; CVD, cardiovascular disease; CEV, cerebrovascular; IHD, ischemic heart disease; HT, hypertension; HF, heart failure.

However, rising temperatures and heat island effects are also relevant to Europe. Following a spike in heat-related deaths in older adults during a 2003 heatwave in France, a case-control study found that urban design features that serve as risk factors for mortality include higher surface temperature within a 200-m radius of the home, while vegetation within 200 m was protective.⁸³ Apartment design features found to be important included lack of thermal insulation in dwelling units, living on the top floor of apartment buildings, the

number of windows per 50m², prolonged sunlight exposure into bedrooms, and keeping windows open throughout the afternoon. Conversely, the use of cooling devices such as air conditioners was found to be protective. The findings of this study suggested that heat-related deaths could be avoided if urban vegetative cover was increased around buildings, buildings insulation improved, and more reflective (and less absorbent) roofing materials used. Another European study of spatial variation in heat island effects found that

traditionally cooler northern cities were more at risk than southern cities, which had adapted to living in warmer climates.⁸⁴

Protecting and growing tree canopy, increasing access to green space, and carefully planned urban greening along wind corridors are critical to increasing urban cooling and enhancing the microclimates of high-density cities.^{80,82} However, urban greening not only provides important eco-system services in the face of a changing climate but access to green spaces may also enhance physical, mental, and community health.⁸⁵ Exposure to green space is associated with increased physical activity and enhances mental health and social capital. A recent systematic review and meta-analysis of longitudinal studies found a significantly decreased risk in all-cause mortality for those exposed to areas with more green space, objectively measured using a normalized difference vegetation index.⁸⁶ The authors concluded that increasing access to green space was a strategic public health intervention providing co-benefits for health and the environment. A recent study in Philadelphia showed that increasing tree canopy cover from 20% to 30% in the city could prevent >400 premature deaths annually with poorer neighbourhoods benefitting most.⁸⁷

Urban and transport planning and design interventions to create compact cities that enhance health and wellbeing

In addition to urbanization and rapid population growth, cities in the 21st century are confronting unparalleled challenges, including traffic congestion, air and noise pollution, climate change, lack of green space, heat islands, growing social inequity, and rising chronic disease. Hence, their future success will be shaped by decisions about how to accommodate the needs of growing urban populations. Transitioning to cities that promote local living and active and sustainable mobility is increasingly recognized as providing co-benefits for health and the environment by creating more sustainable and liveable cities.^{88,89}

There is now a vast body of evidence showing that city planning decisions affect multiple NCD pathways, not least of which is via increased physical activity through active transportation.^{7,90} A growing body of longitudinal evidence shows that urban sprawl and low walkability negatively affects cardiometabolic risk factors,^{91,92} while exposure to green space has been shown to lower all-cause mortality.⁸⁶

Urban planning and transport planning academics have long sought to understand how city and transport planning can be used to reduce motor vehicle kilometres travelled and encouraging public transport and active transportation such as walking and cycling. They identify five key built-form characteristics referred to as the 5Ds⁹³ including density, design, diversity of land use, distance to transit, design, and destination accessibility. Recently, these were expanded to the 8Ds to include demand management (e.g. the cost and availability of parking and road usage and congestion charging), the distribution of employment across a city affecting time spent commuting, and desirability (personal and traffic safety and attractiveness); and desirability (personal and traffic safety; the attractiveness of streetscapes and level of comfort to use public transport) with additional consideration of both local and regional planning.¹⁵

These city and transport planning interventions affect how people use and move around the city and impact whether using an active mode is possible and/or desirable.

Transport mode choices ultimately determine environmental risk exposures generated in a city (i.e. the amount of traffic, noise, air pollution) and people's levels of physical activity and stress. This in turn appears to determine morbidity and premature mortality. For example, building cities for cars and planning low density urban sprawl housing developments increases car use, traffic, traffic congestion, air pollution, and noise, which in turn increases stress, road trauma, physical inactivity, and prolonged sitting, leading to increased morbidity and premature mortality.¹⁵ Conversely, building more compact cities with high-quality public transport, bike-sharing systems, safe separated cycling infrastructure, and creating safe, convivial walkable neighbourhoods will provide access to local destinations and pedestrian infrastructure. This will not only increase bicycle use and walking, physical activity, as well as social contacts but also reduce air pollution, noise, stress, and road trauma, leading to decreased morbidity and premature mortality.^{94,95} The introduction of hybrid mobility solutions such as e-bike is clearly a trend, allowing one to easily cycle twice as far compared to a classic bike and to arrive without sweating. The speed pedelec (a fast electric bike that can reach up to 45 km/h) can enable a smooth connection between the countryside and the city.⁹⁶ However, as the popularity of e-bikes and e-scooters grows, providing safe and accessible infrastructure with rules about who, where and under what conditions people can ride, is vital to preventable road trauma.^{94,97}

Notably, ~20% of mortality could be prevented annually if international recommendations for physical activity, reduction in exposure to air pollution, noise and heat, and improved access to green space were followed.⁹⁸

New urban models

A number of new urban concepts are being introduced in various cities that address the above described problems to some degree, e.g. the Compact city, Superblocks, 15-min city, Car-free city, or a mixture of these. What these models have in common is that they aim to reduce private car use and increase public and active transportation (walking and cycling) and thereby reduce air pollution, noise, and heat island effects and increase physical activity and thereby promote the health of the heart.⁹² Cars take up a lot of public space [(road) network and parking] that can be used in a better way, for example by creating green space. In a city like Barcelona, 60% of public space is used for cars while cars account for only 25% of transport mode.⁸⁹ Also, the shorter distance between homes and destinations in the Compact or 15-min city will encourage walking, cycling, and physical activity while reducing CO₂ emissions.⁸⁹

The Compact city

Compact cities (*Figure 6A*) are cities with higher density, shorter travel distances, higher foliage, and biodiversity. Compared with low density sprawling cities, their CO₂ emissions are lower and they are healthier because of increased greenery, increased land use mix, and active transportation opportunities. Making cities 30% more compact and thereby increasing density and land use, reducing travel distances,

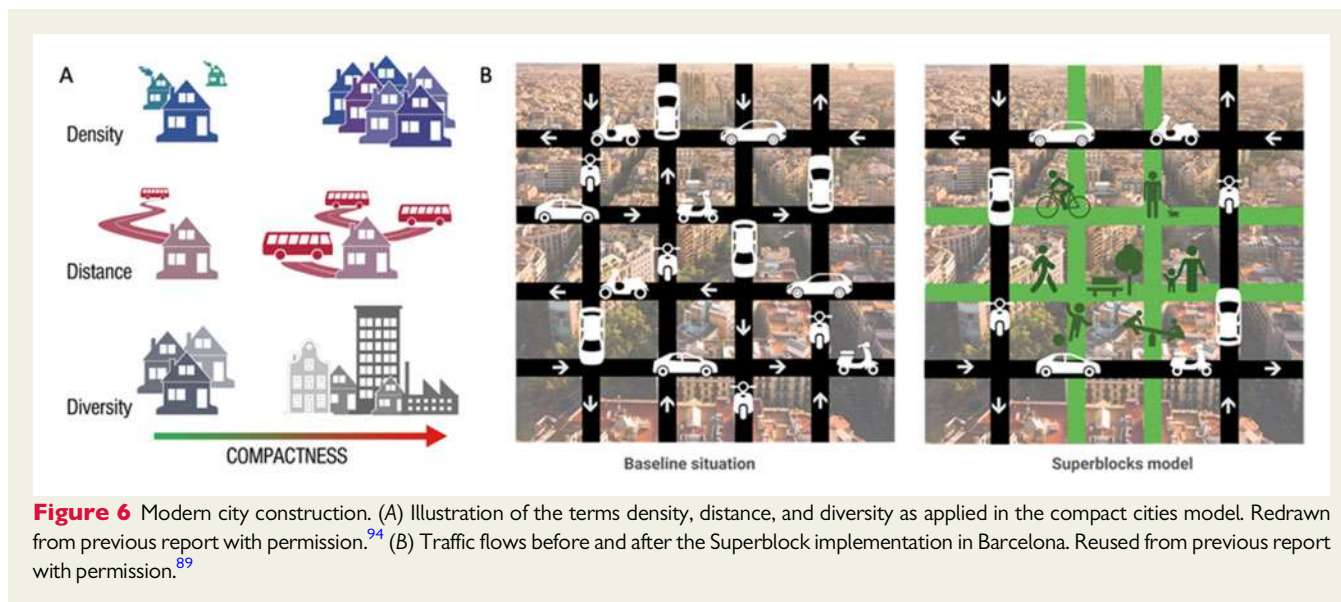


Figure 6 Modern city construction. (A) Illustration of the terms density, distance, and diversity as applied in the compact cities model. Redrawn from previous report with permission.⁹⁴ (B) Traffic flows before and after the Superblock implementation in Barcelona. Reused from previous report with permission.⁸⁹

increasing public and active transportation could avoid around 400–800 disability-adjusted life years per 100 000 people with respect to diabetes, CVD, and respiratory disease annually depending on the type of city.⁹⁴ Sprawled cities like Boston and Melbourne, where the transport mode share of cars is 80.1% and 85.1%, respectively, can hope to improve health by changes in land use and transport mode, developing walking and cycling infrastructure enhancing vegetation through policies to reduce sprawl and promote higher densities. This will be a long process but necessary for a sustainable and health future.

The Superblocks

Over 500 superblocks (Figure 6B) are planned in Barcelona, which reduce motorized traffic in some streets of a block and provide space for people, active travel, and green environs. This will reduce air pollution, noise heat island effects and increase green space and physical activity, thereby theoretically preventing nearly 700 premature deaths each year in Barcelona.⁹⁹ The largest number of deaths prevented come from a reduction in air pollution, followed by noise, heat island effects, and then green space. Similar principles are being applied in low traffic neighbourhoods.¹⁰⁰ The Superblock model can be implemented fairly easily in urban areas with a grid system and sufficient population and facility densities. Particularly in warmer climates, the greening of the area can considerably reduce temperatures, thereby limiting premature mortality. Initially, implementation of a Superblock in the Poblenou neighbourhood of Barcelona was met with considerable resistance from the local population, but later developments like the neighbourhoods of Sant Antoni and Horta are better received after improved consultation with the local population. A further expansion plan is currently under evaluation.¹⁰¹

The 15-min city

Paris is introducing the 15-min city, the brain child of Carlos Moreno, where work, school, entertainment, and other activities are

reachable within a 15-min walk of the home.^{102,103} The 15-min city involves the creation of a city of villages and a return to more traditional city design. The envisaged new trees and cycleways, community facilities and social housing, homes, and workplaces all reflect a potentially transformative vision for urban planning and is a concept being discussed by governments globally including in Australia (i.e. the 20-min neighbourhood). It will require a fairly radical rethink of our contemporary cities and a mixing of different population groups rather than the distribution of housing by socioeconomic status. The 15-min city will encourage more physical activity through more active transport and is likely to reduce urban inequalities and health inequities.¹⁰⁴ Critically, it will also reduce the need for long distance travel and thereby reduce CO₂ emissions, air pollution, and noise levels. The 15-minute city calls for a return to a more local and somewhat slower way of life, where commuting time is instead invested in richer local relationships. The COVID-19 pandemic has only accelerated this development in many cities in Europe.

The car-free city

Hamburg plans to be car free by 2034, partly to address the climate crisis. Car-free cities reduce unnecessary private motorized traffic, provide easy access to active and public transportation, reduce air pollution and noise, increase physical activity, and access to green space.¹⁰⁵ A successful example is Vauban in Freiburg, Germany, which is a neighbourhood without cars and with sustainable housing. Other cities like Oslo, Helsinki, and Madrid have recently announced their plans to become (partly) car free. Many cities have introduced different policies that aim to reduce motorized traffic including implementing car-free days. Some of the main challenges will be how to change existing infrastructure that was mainly designed for cars to infrastructure for active and public transport, and how to change people's perceptions, attitudes, and behaviours.¹⁰⁶ The transition to car-free cities may substantially improve the liveability of neighbourhoods—especially in those neighbourhoods that bear disproportional burdens of pollution, social disadvantage, crashes, and public

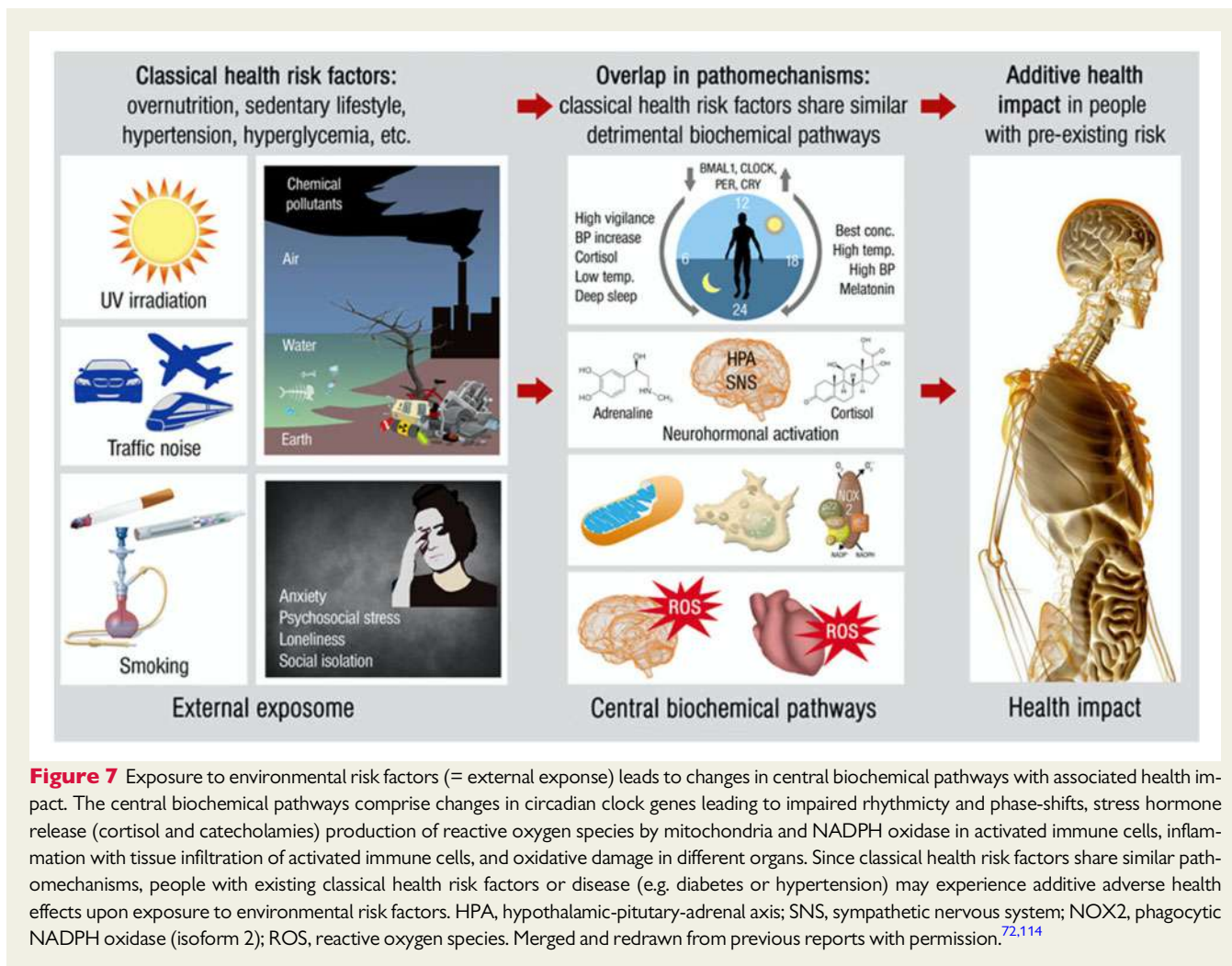


Figure 7 Exposure to environmental risk factors (= external exposure) leads to changes in central biochemical pathways with associated health impact. The central biochemical pathways comprise changes in circadian clock genes leading to impaired rhythmicity and phase-shifts, stress hormone release (cortisol and catecholamines) production of reactive oxygen species by mitochondria and NADPH oxidase in activated immune cells, inflammation with tissue infiltration of activated immune cells, and oxidative damage in different organs. Since classical health risk factors share similar pathomechanisms, people with existing classical health risk factors or disease (e.g. diabetes or hypertension) may experience additive adverse health effects upon exposure to environmental risk factors. HPA, hypothalamic-pituitary-adrenal axis; SNS, sympathetic nervous system; NOX2, phagocytic NADPH oxidase (isoform 2); ROS, reactive oxygen species. Merged and redrawn from previous reports with permission.^{72,114}

transport disinvestment. A transition from car-dominated urban landscapes and transport policies towards car-free cities that are considering the mobility needs of all people to access key destinations, regardless of their access to private cars would, therefore, constitute an important step towards a more inclusive and just urban environment that is also more sustainable and healthier.¹⁰⁶

The new paradigms and tools

The exposome and exposure outcomes

The exposome concept refers to the totality of exposures from a variety of external and internal sources, including chemical agents, biological agents, or radiation, over a complete lifetime (Figure 7). This rethink of simplistic models to complex network effects will allow one to decipher a plethora of influences on human health and understanding of the genesis of complex NCD.

Despite the general acknowledgement by the scientific community that 'Genetics loads the gun but the environment pulls the trigger', when it comes to the causation of major NCDs, there is persistent

uncertainty as to the global burden of disease attributable to environmental factors including lifestyle and the climate.¹⁰⁷ Deciphering the human exposome is a novel exciting way to improve health and to reduce the overall burden of disease.

So far, environmental epidemiology has mainly focused on hard outcomes, such as mortality, disease exacerbation, and hospitalizations. However, there are many other relevant outcomes related to environmental exposures that can be facilitated by an improved understanding of biomarkers of exposure and response to the exposome through the application of integrated omics technologies. Biomarkers and omics technologies may also allow better causal attribution, for example using instrumental variables in triangulation.¹⁰⁸

The work around the exposome in the urban context has shown us the large number of exposures we experience every day, how they are interconnected, and the relationship of other exposures such as socioeconomic measures.¹⁰⁹ Using geographic information systems, remote sensing and spatio-temporal modeling, environmental indicators such as meteorological factors, air pollutants, traffic noise, traffic indicators, natural space, the built environment, public transport, facilities, and walkability can be

assessed. Furthermore, these exposures can now also be assessed using wearables that can be worn by people for a long time and provide important information on their urban environment,¹¹⁰ but also health parameters like blood pressure and heart rate variability.¹¹¹

Planetary health

What is good for the planet is also good for human health. The recent Declaration of Helsinki emphasizes the urgency to act, as scientific evidence shows that human activities are causing climate change, biodiversity loss, land degradation, overuse of natural resources, and pollution.¹¹² They threaten the health and safety of humankind. A shift from fragmented approaches to policy and practice towards systematic actions will promote human and planetary health. Systems thinking will need to feed into conserving nature and biodiversity and into halting climate change. The Planetary Health paradigm, the health of human civilization, and the state of natural systems on which it depends must become the driver for all policies.

Sustainable Development Goals

Cities are an important driving force to implement the SDGs and the New Urban Agenda.¹⁰ The SDGs provide an operational framework to consider urbanization globally, while providing local mechanisms for action and careful attention to closing the gaps in the distribution of health gains. While health and wellbeing are explicitly addressed in SDG 3, health is also present as a precondition of SDG 11 that aims at inclusive, safe, resilient, and sustainable cities. Health in All Policies (HiAP) is an approach to public policy across sectors that systematically takes into account the health implications of decisions, seeks synergies, and avoids harmful health impacts to improve population health and health equity. HiAP is key in the context of urban policies to promote public health interventions aimed at achieving SDG targets. HiAP relies heavily on the use of scientific evidence and evaluation tools, such as health impact assessments.¹¹³ Health impact assessments may include city-level quantitative burden of disease, health economic assessments, and citizen and other stakeholders' involvement to inform the integration of health recommendations in urban policies. Citizen participation is essential to obtain desirable and acceptable outcomes.

Gaps in current knowledge, future research, and training needs

Considering the pervasive and often cumulative impact of environmental exposures in big cities and large urbanized areas, the health problems and disease burden attributable to the sum totality of exposures may exceed all previous estimations.^{72,114} There is a large spatial overlap of environmental stressors such as traffic noise, air pollution, nocturnal artificial light pollution, heavy metals and/or pesticides in soil and water, and exposure to psychosocial risk factors such as social isolation, work strain, and racial inequities. This reinforces the need for exposure assessment to include simultaneous assessment of stressors rather than as fragmented individual stressors to provide an accurate portrait on their health effects. Such an integrated assessment is further supported by epidemiological evidence

for the additive effects of different environmental stressors, such as air pollution, noise, and nocturnal light pollution on cardiovascular risk (Figure 7). Therefore, multi-exposure studies are urgently required to study these additive/synergistic effects of multiple environmental exposures, their interaction with other risk factors and finally their impact in facilitating and/or exaggerating pre-existing chronic NCD. We additionally need a dramatic shift in the city environments that are currently detrimental to health, because of increased air pollution, noise, heat, and light exposure through institution of a number of measures, including reducing space allocated to private motorized transport, increasing space to active and public transportation and finally increase in green space (trees, etc.). What we urgently need is studies to assess the health effects of these current interventions that are taking place in cities.¹¹⁵ These interventions must be evaluated to assess the 'dose' of the interventions delivered and any policy-implementation gaps; and the health effects of being exposed to more supportive environments.¹¹⁶ Vice versa, there is an obvious research need addressing why growing urbanisation has gone hand in hand with longevity. Did we miss some positive aspects of urbanisation that promote health, such as access to better health care that may be key to understand this obvious contradiction.

The COVID-19 pandemic may be an opportunity though to build better and more sustainable societies and cities.⁸⁹ It has provided opportunities for cities to capitalize on a desire for local living with more people working from home, more often, and increased active transportation enabling people to physically distance. However, it has presented challenges for those living in small apartments, particularly parents' home-schooling children; and a shift away from public transport for fear of transmission of infection. Recently, the WHO published a manifesto for a healthy recovery from COVID-19, including building healthy and liveable cities. These ideas, however, need support and investment. The European Green Deal is a comprehensive road map striving to make the EU more resource-efficient and sustainable, and a great opportunity to make cities carbon neutral, more liveable, and healthier through better urban and transport planning.¹¹⁷

This transformation required to create healthy liveable and sustainable cities undoubtedly will need to be facilitated by well informed, well-trained health professionals and health researchers who are able to work collaboratively with disciplines and sectors outside of health. This highlights a critical role for universities to train the next generation of researchers and policy and practice public health workers, to enable them to co-design research as equal partners with sectors outside of health.

What are the societal and political consequences?

Cities concentrate people and resources in one place, which creates both hazards and very real opportunities for improving health. In densely populated and highly urbanized areas, environmental exposures are prominent features of everyday living that may systemically interfere with human and planetary health. Although we have revolutionized the way we treat patients and health conditions on an individual basis over the last decades, serious and sustainable efforts to combat hazardous environmental exposures at the population level

are needed. This will serve as well to fight not only global pandemics such as COVID-19 but also successfully stem the tsunamis of NCDs and help protect planetary health.

Currently, ~96% of public health funding goes towards treatment and only 4% towards prevention. In addition, the monies allocated for prevention is predominantly directed at the individual with very little effort or dollars devoted to the collective social and physical environment to help mitigate environmental exposures. In this sense, investment to facilitate broad intersectoral action to improve our cities is a dire need, as it is indeed these cross disciplinary actions taken by urban, transport, and health planners that will have the largest impact on health. And in this sense, there is potential for them to be some of the best public health professionals, in the same way they were in the rapidly industrializing 19th century, tackling infectious and environmental diseases. Unfortunately these professionals often may not realize the impact of their work on human health and how they can improve health. Like the 19th century city reformers, it is critical that the health researchers gather evidence to inform policy and practice about how to create healthy liveable cities and that the health sector work closely with sectors outside their domain of expertise to encourage and ensure successful implementation.¹¹⁸

Successful implementation of these efforts to reduce NCD risk and create a healthy and sustainable future will require a radical re-think about how we organize the way we live in the future in order to protect human and planetary health. This is only achievable by engaging the individual and the community and through large-scale long-term macro interventions that include economic investment in smart cities, transformation of power generation, and elimination of fossil fuels.

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References

- World Health Organization. *Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020*. Geneva: WHO; 2013. https://apps.who.int/iris/bitstream/handle/10665/94384/9789241506236_eng.pdf;jsessionid=71BC EA94B3F85737AB42F3C84216E54A?. Date accessed 31 March 2021.
- GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;**396**(10258):1223–1249.
- Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, De Leo D, Degenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorsey ER, Driscoll T, Duber H, Ebel B, Erwin PJ, Espindola P, Ezzi M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabriel SE, Gakidou E, Gaspari F, Gillum RF, Gonzalez-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassebaum N, Keren A, Khoo JP, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabweijano J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mock C, Mocumbi AO, Mokdad AA, Moran A, Mulholland K, Nair MN, Naldi L, Narayan KM, Nasseri K, Norman P, O'Donnell M, Omer SB, Ortblad K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivero AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope CA, 3rd Porrini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De Leon FR, Rosenfeld LC, Rushton L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Sliwa K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Towbin JA, Truelsen T, Undurraga EA, Venketasubramanian N, Vijayakumar L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh PH, Yip P, Zabetian A, Zheng ZJ, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**:2095–2128.
- World Health Organization. Projections of mortality and causes of death, 2016 to 2060. https://www.who.int/healthinfo/global_burden_disease/projections/en/. Date accessed 31 March 2021.
- World Health Organization. Noncommunicable diseases: mortality. https://www.who.int/gho/ncd/mortality_morbidity/en/. Date accessed 31 March 2021.
- Frumkin H, Haines A. Global environmental change and noncommunicable disease risks. *Annu Rev Public Health* 2019;**40**:261–282.
- World Health Organization. Global action plan on physical activity 2018–2030: more active people for healthier world. <https://www.who.int/ncds/prevention/physical-activity/global-action-plan-2018-2030/en/>. Date accessed 19 April 2021.
- World Health Organization. Global report on urban health: equitable healthier cities for sustainable development. <https://apps.who.int/iris/handle/10665/204715> (Date accessed 19 April 2021).
- World Health Organization. Tackling NCDs Best buys. <https://apps.who.int/iris/bitstream/handle/10665/259232/WHO-NMH-NVI-17-9-eng.pdf;sequence=1&isAllowed=y>. Date accessed 31 March 2021.
- Ramirez-Rubio O, Daher C, Fanjul G, Gascon M, Mueller N, Pajin L, Plasencia A, Rojas-Rueda D, Thonoo M, Nieuwenhuijsen MJ. Urban health: an example of a "health in all policies" approach in the context of SDGs implementation. *Global Health* 2019;**15**:87.
- Bukhman G, Mocumbi AO, Atun R, Becker AE, Bhutta Z, Binagwaho A, Clinton C, Coates MM, Dain K, Ezzati M, Gottlieb G, Gupta I, Gupta N, Hyder AA, Jain Y, Kruk ME, Makani J, Marx A, Miranda JJ, Norheim OF, Nugent R, Roy N, Stefan C, Wallis L, Mayosi B; Lancet NCDI Poverty Commission Study Group. The Lancet NCDI Poverty Commission: bridging a gap in universal health coverage for the poorest billion. *Lancet* 2020;**396**:991–1044.
- Global Energy Assessment. *Global Energy Assessment: Toward a sustainable future*. Cambridge, UK: Cambridge University Press; 2012. p1888.
- International Energy Agency. *World Energy Outlook*. Paris: IEA; 2012. p700.
- Karagulian F, Belis CA, Dora CFC, Prüss-Ustün AM, Bonjour S, Adair-Rohani H, Amann M. Contributions to cities' ambient particulate matter (PM): a systematic review of local source contributions at global level. *Atmos Environ* 2015;**120**:475–483.
- Giles-Corti B, Vernez-Moudon A, Reis R, Turrell G, Dannenberg AL, Badland H, Foster S, Lowe M, Sallis JF, Stevenson M, Owen N. City planning and population health: a global challenge. *Lancet* 2016;**388**:2912–2924.
- Lelieveld J, Klingmüller K, Pozzer A, Poschl U, Forns H, Daiber A, Munzel T. Cardiovascular disease burden from ambient air pollution in Europe reassessed using novel hazard ratio functions. *Eur Heart J* 2019;**40**:1590–1596.
- Liu C, Chen R, Sera F, Vicedo-Cabrera AM, Guo Y, Tong S, Coelho M, Saldiva PHN, Lavigne E, Matus P, Valdes Ortega N, Osorio Garcia S, Pascal M, Stafoggia M, Scortichini M, Hashizume M, Honda Y, Hurtado-Diaz M, Cruz J, Nunes B, Teixeira JP, Kim H, Tobias A, Iniguez C, Forsberg B, Astrom C, Ragettli MS, Guo YL, Chen BY, Bell ML, Wright CY, Scovronick N, Garland RM, Milojevic A, Kyselý J, Urban A, Orru H, Indermitte E, Jaakkola JJK, Rytí NRI, Katsouyanni K, Analitis A, Zanutetti A, Schwartz J, Chen J, Wu T, Cohen A, Gasparrini A, Kan H. Ambient particulate air pollution and daily mortality in 652 cities. *N Engl J Med* 2019;**381**:705–715.

18. Münzel T, Gori T, Al-Kindi S, Deanfield J, Lelieveld J, Daiber A, Rajagopalan S. Effects of gaseous and solid constituents of air pollution on endothelial function. *Eur Heart J* 2018;**39**:3543–3550.
19. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, Atkinson C, Bacchus LJ, Bahalim AN, Balakrishnan K, Balmes J, Barker-Collo S, Baxter A, Bell ML, Blore JD, Blyth F, Bonner C, Borges G, Bourne R, Boussinesq M, Brauer M, Brooks P, Bruce NG, Brunekreef B, Bryan-Hancock C, Bucello C, Buchbinder R, Bull F, Burnett RT, Byers TE, Calabria B, Carapetis J, Carnahan E, Chafe Z, Charlson F, Chen H, Chen JS, Cheng AT, Child JC, Cohen A, Colson KE, Cowie BC, Darby S, Darling S, Davis A, Degenhardt L, Dentener F, Des Jarlais DC, Devries K, Dherani M, Ding EL, Dorsey ER, Driscoll T, Edmond K, Ali SE, Engell RE, Erwin PJ, Fahimi S, Falder G, Farzadfar F, Ferrari A, Finucane MM, Flaxman S, Fowkes FG, Freedman G, Freeman MK, Gakidou E, Ghosh S, Giovannucci E, Gmel G, Graham K, Grainger R, Grant B, Gunnell D, Gutierrez HR, Hall W, Hoek HW, Hogan A, Hosgood HD, 3rd Hoy D, Hu H, Hubbell BJ, Hutchings SJ, Ibeanusi SE, Jacklyn GL, Jasrasaria R, Jonas JB, Kan H, Kanis JA, Kassebaum N, Kawakami N, Khang YH, Khatibzadeh K, Khoo JP, Kok C, Laden F, Lalloo R, Lan Q, Lathlean S, Leasher JL, Leigh J, Li Y, Lin JK, Lipshultz SE, London S, Lozano R, Lu Y, Mak J, Malekzadeh R, Mallinger L, Marcenes W, March L, Marks R, Martin R, McGale P, McGrath J, Mehta S, Mensah GA, Merriman TR, Micha R, Michaud C, Mishra V, Mohd Hanafiah K, Mokdad AA, Morawska L, Mozaffarian D, Murphy T, Naghavi M, Neal B, Nelson PK, Nolla JM, Norman R, Olives C, Omer SB, Orchard J, Osborne R, Ostro B, Page A, Pandey KD, Parry CD, Passmore E, Patra J, Pearce N, Pelizzari PM, Petzold M, Phillips MR, Pope D, Pope CA, 3rd Powlson J, Rao M, Razavi H, Rehfuess EA, Rehm JT, Ritz B, Rivara FP, Roberts T, Robinson C, Rodriguez-Portales JA, Romieu I, Room R, Rosenfeld LC, Roy A, Rushton L, Salomon JA, Sampson U, Sanchez-Riera L, Sanman E, Sapkota A, Seedat S, Shi P, Shield K, Shivakoti R, Singh GM, Sleet DA, Smith E, Smith KR, Stapelberg NJ, Steenland K, Stockl H, Stovner LJ, Straif K, Straney L, Thurston GD, Tran JH, Van Dingenen R, van Donkelaar A, Veerman JL, Vijayakumar L, Weintraub R, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC, Williams W, Wilson N, Woolf AD, Yip P, Zielinski JM, Lopez AD, Murray GJ, Ezzati M, AlMazrou MA, Memish ZA. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**:2224–2260.
20. Pirela SV, Martin J, Bello D, Demokritou P. Nanoparticle exposures from nano-enabled toner-based printing equipment and human health: state of science and future research needs. *Crit Rev Toxicol* 2017;**47**:678–704.
21. Molina LT. Introductory lecture: air quality in megacities. *Faraday Discuss* 2021; **226**:9–52.
22. Daellenbach KR, Uzu G, Jiang J, Cassagnes L-E, Leni Z, Vlachou A, Stefanelli G, Canonaco F, Weber S, Segers A, Kuenen JJP, Schaap M, Favez O, Albinet A, Aksoyoglu S, Dommen J, Baltensperger U, Geiser M, El Haddad I, Jaffrezzo J-L, Prévôt ASH. Sources of particulate-matter air pollution and its oxidative potential in Europe. *Nature* 2020;**587**:414–419.
23. Al-Kindi SG, Brook RD, Biswal S, Rajagopalan S. Environmental determinants of cardiovascular disease: lessons learned from air pollution. *Nat Rev Cardiol* 2020; **17**:656–672.
24. Jiang LON, BC. Global urbanization projections for the shared socioeconomic pathways. *Glob Environ Change* 2017;**42**:193–199.
25. Landrigan PJ, Fuller R, Acosta NJR, Adeyi O, Arnold R, Basu NN, Balde AB, Bertollini R, Bose-O'Reilly S, Boufford JJ, Breyse PN, Chiles T, Mahidol C, Coll-Seck AM, Cropper ML, Fobil J, Fuster V, Greenstone M, Haines A, Hanrahan D, Hunter D, Khare M, Krupnick A, Lanphear B, Lohani B, Martin K, Mathiasen KV, McTeer MA, Murray CJL, Ndhimananjara JD, Perera F, Potocnik J, Preker AS, Ramesh J, Rockstrom J, Salinas C, Samson LD, Sandilya K, Sly PD, Smith KR, Steiner A, Stewart RB, Suk WA, van Schayck OCP, Yadama GN, Yumkella K, Zhong M. The Lancet Commission on pollution and health. *Lancet* 2018;**391**:462–512.
26. Rajagopalan S, Brauer M, Bhatnagar A, Bhatt DL, Brook JR, Huang W, Münzel T, Newby D, Siegel J, Brook RD; American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; and Stroke Council. Personal-level protective actions against particulate matter air pollution exposure: a scientific statement from the American Heart Association. *Circulation* 2020;**142**:e411–e431.
27. European Environment Agency. Environmental noise in Europe; 2020. <https://www.eea.europa.eu/publications/environmental-noise-in-europe>. Date accessed 31 March 2021.
28. Babisch W. The noise/stress concept, risk assessment and research needs. *Noise Health* 2002;**4**:1–11.
29. Münzel T, Schmidt FP, Steven S, Herzog J, Daiber A, Sorensen M. Environmental noise and the cardiovascular system. *J Am Coll Cardiol* 2018;**71**:688–697.
30. Basner M, McGuire S. WHO environmental noise guidelines for the European region: a systematic review on environmental noise and effects on sleep. *Int J Environ Res Public Health* 2018;**15**:519.
31. Münzel T, Kroller-Schon S, Oelze M, Gori T, Schmidt FP, Steven S, Hahad O, Roosli M, Wunderli JM, Daiber A, Sorensen M. Adverse cardiovascular effects of traffic noise with a focus on nighttime noise and the new WHO noise guidelines. *Annu Rev Public Health* 2020;**41**:309–328.
32. Schmidt FP, Basner M, Kroger G, Weck S, Schnorbus B, Muttray A, Sariyar M, Binder H, Gori T, Warnholtz A, Münzel T. Effect of nighttime aircraft noise exposure on endothelial function and stress hormone release in healthy adults. *Eur Heart J* 2013;**34**:3508–314a.
33. Schmidt F, Kolle K, Kreuder K, Schnorbus B, Wild P, Hechtner M, Binder H, Gori T, Münzel T. Nighttime aircraft noise impairs endothelial function and increases blood pressure in patients with or at high risk for coronary artery disease. *Clin Res Cardiol* 2015;**104**:23–30.
34. Herzog J, Schmidt FP, Hahad O, Mahmoudpour SH, Mangold AK, Garcia Andreo P, Prochaska J, Koeck T, Wild PS, Sorensen M, Daiber A, Münzel T. Acute exposure to nocturnal train noise induces endothelial dysfunction and pro-thrombotic changes of the plasma proteome in healthy subjects. *Basic Res Cardiol* 2019;**114**:46.
35. Kempen EV, Casas M, Pershagen G, Foraster M. WHO environmental noise guidelines for the European region: a systematic review on environmental noise and cardiovascular and metabolic effects: a summary. *Int J Environ Res Public Health* 2018;**15**:379.
36. Halonen JI, Hansell AL, Gulliver J, Morley D, Blangiardo M, Fecht D, Toledano MB, Beevers SD, Anderson HR, Kelly FJ, Tonne C. Road traffic noise is associated with increased cardiovascular morbidity and mortality and all-cause mortality in London. *Eur Heart J* 2015;**36**:2653–2661.
37. Heritier H, Vienneau D, Foraster M, Eze IC, Schaffner E, Thiesse L, Rudzik F, Habermacher M, Kopfli M, Pieren R, Brink M, Cajochen C, Wunderli JM, Probst-Hensch N, Roosli M; SNC Study Group. Transportation noise exposure and cardiovascular mortality: a nationwide cohort study from Switzerland. *Eur J Epidemiol* 2017;**32**:307–315.
38. Seidler AL, Hegewald J, Schubert M, Weihofen VM, Wagner M, Droge P, Swart E, Zeeb H, Seidler A. The effect of aircraft, road, and railway traffic noise on stroke—results of a case-control study based on secondary data. *Noise Health* 2018;**20**:152–161.
39. Sorensen M, Hvidberg M, Andersen ZJ, Nordsborg RB, Lillelund KG, Jakobsen J, Tjonneland A, Overvad K, Raaschou-Nielsen O. Road traffic noise and stroke: a prospective cohort study. *Eur Heart J* 2011;**32**:737–744.
40. Vienneau D, Eze IC, Probst-Hensch N, Roosli M. Association between transportation noise and cardio-metabolic diseases: an update of the WHO meta-analysis. In: *Proceedings of the 23rd International Conference on Acoustics*; 2019. p1543–1550.
41. Pyko A, Eriksson C, Lind T, Mitkovskaya N, Wallas A, Ogren M, Ostenson CG, Pershagen G. Long-term exposure to transportation noise in relation to development of obesity—a cohort study. *Environ Health Perspect* 2017;**125**:117005.
42. Vienneau D, Heritier H, Foraster M, Eze IC, Schaffner E, Thiesse L, Rudzik F, Habermacher M, Kopfli M, Pieren R, Brink M, Cajochen C, Wunderli JM, Probst-Hensch N, Roosli M; SNC Study Group. Facades, floors and maps—influence of exposure measurement error on the association between transportation noise and myocardial infarction. *Environ Int* 2019;**123**:399–406.
43. Münzel T, Miller MR, Sorensen M, Lelieveld J, Daiber A, Rajagopalan S. Reduction of environmental pollutants for prevention of cardiovascular disease: it's time to act. *Eur Heart J* 2020;**41**:3989–3997.
44. Falchi F, Cinzano P, Duriscoe D, Kyba CC, Elvidge CD, Baugh K, Portnov BA, Rybnikova NA, Furgoni R. The new world atlas of artificial night sky brightness. *Sci Adv* 2016;**2**:e1600377.
45. Falchi F, Furgoni R, Gallaway TA, Rybnikova NA, Portnov BA, Baugh K, Cinzano P, Elvidge CD. Light pollution in USA and Europe: the good, the bad and the ugly. *J Environ Manage* 2019;**248**:109227.
46. Chepesiuk R. Missing the dark: health effects of light pollution. *Environ Health Perspect* 2009;**117**:A20–7.
47. Crnko S, Du Pre BC, Sluiter J, Van Laake LW. Circadian rhythms and the molecular clock in cardiovascular biology and disease. *Nat Rev Cardiol* 2019;**16**:437–447.
48. Liu H, Chen A. Roles of sleep deprivation in cardiovascular dysfunctions. *Life Sci* 2019;**219**:231–237.
49. Steffens S, Winter C, Schloss MJ, Hidalgo A, Weber C, Soehnlein O. Circadian control of inflammatory processes in atherosclerosis and its complications. *Arterioscler Thromb Vasc Biol* 2017;**37**:1022–1028.
50. Kohsaka A, Laposky AD, Ramsey KM, Estrada C, Joshi C, Kobayashi Y, Turek FW, Bass J. High-fat diet disrupts behavioral and molecular circadian rhythms in mice. *Cell Metab* 2007;**6**:414–421.
51. Marcheva B, Ramsey KM, Buhr ED, Kobayashi Y, Su H, Ko CH, Ivanova G, Omura C, Mo S, Vitaterna MH, Lopez JP, Philipson LH, Bradfield CA, Crosby

- SD, JeBailey L, Wang X, Takahashi JS, Bass J. Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinaemia and diabetes. *Nature* 2010;**466**:627–631.
52. Turek FW, Joshi C, Kohsaka A, Lin E, Ivanova G, McDearmon E, Laposky A, Losee-Olson S, Easton A, Jensen DR, Eckel RH, Takahashi JS, Bass J. Obesity and metabolic syndrome in circadian Clock mutant mice. *Science* 2005;**308**:1043–1045.
53. Patterson F, Malone SK, Grandner MA, Lozano A, Perket M, Hanlon A. Interactive effects of sleep duration and morning/evening preference on cardiovascular risk factors. *Eur J Public Health* 2018;**28**:155–161.
54. Hu Y, Shmygelska A, Tran D, Eriksson N, Tung JY, Hinds DA. GWAS of 89,283 individuals identifies genetic variants associated with self-reporting of being a morning person. *Nat Commun* 2016;**7**:10448.
55. Lane JM, Vlasac I, Anderson SG, Kyle RD, Dixon WG, Bechtold DA, Gill S, Little MA, Luik A, Loudon A, Emsley R, Scheer FA, Lawlor DA, Redline S, Ray DW, Rutter MK, Saxena R. Genome-wide association analysis identifies novel loci for chronotype in 100,420 individuals from the UK Biobank. *Nat Commun* 2016;**7**:10889.
56. Jones SE, Tyrrell J, Wood AR, Beaumont RN, Ruth KS, Tuke MA, Yaghoobkar H, Hu Y, Teder-Laving M, Hayward C, Roenneberg T, Wilson JF, Del Greco F, Hicks AA, Shin C, Yun CH, Lee SK, Metspalu A, Byrne EM, Gehrman PR, Tiemeier H, Allebrandt KV, Freathy RM, Murray A, Hinds DA, Frayling TM, Weedon MN. Genome-wide association analyses in 128,266 individuals identifies new morningness and sleep duration loci. *PLoS Genet* 2016;**12**:e1006125.
57. Merikanto I, Lahti T, Puolijoki H, Vanhala M, Peltonen M, Laatikainen T, Vartiainen E, Salomaa V, Kronholm E, Partonen T. Associations of chronotype and sleep with cardiovascular diseases and type 2 diabetes. *Chronobiol Int* 2013;**30**:470–477.
58. Levandovski R, Dantas G, Fernandes LC, Caumo W, Torres I, Roenneberg T, Hidalgo MP, Allebrandt KV. Depression scores associate with chronotype and social jetlag in a rural population. *Chronobiol Int* 2011;**28**:771–778.
59. Obayashi K, Saeki K, Iwamoto J, Ikada Y, Kurumatani N. Association between light exposure at night and nighttime blood pressure in the elderly independent of nocturnal urinary melatonin excretion. *Chronobiol Int* 2014;**31**:779–786.
60. Gale JE, Cox HI, Qian J, Block GD, Colwell CS, Matveyenko AV. Disruption of circadian rhythms accelerates development of diabetes through pancreatic beta-cell loss and dysfunction. *J Biol Rhythms* 2011;**26**:423–433.
61. Kurose T, Yabe D, Inagaki N. Circadian rhythms and diabetes. *J Diabetes Investig* 2011;**2**:176–177.
62. Qian J, Yeh B, Rakshit K, Colwell CS, Matveyenko AV. Circadian disruption and diet-induced obesity synergize to promote development of beta-cell failure and diabetes in male rats. *Endocrinology* 2015;**156**:4426–4436.
63. Gamble KL, Berry R, Frank SJ, Young ME. Circadian clock control of endocrine factors. *Nat Rev Endocrinol* 2014;**10**:466–475.
64. Stenvers DJ, Scheer F, Schrauwen P, la Fleur SE, Kalsbeek A. Circadian clocks and insulin resistance. *Nat Rev Endocrinol* 2019;**15**:75–89.
65. Sun S, Cao W, Ge Y, Ran J, Sun F, Zeng Q, Guo M, Huang J, Lee RS, Tian L, Wellenius GA. Outdoor light at night and risk of coronary heart disease among older adults: a prospective cohort study. *Eur Heart J* 2021;**42**:822–830.
66. Khan A, Plana-Ripoll O, Antonsen S, Brandt J, Geels C, Landecker H, Sullivan PF, Pedersen CB, Rzhetsky A. Environmental pollution is associated with increased risk of psychiatric disorders in the US and Denmark. *PLoS Biol* 2019;**17**:e3000353.
67. Alexeeff SE, Liao NS, Liu X, Van Den Eeden SK, Sidney S. Long-Term PM2.5 Exposure and Risks of Ischemic Heart Disease and Stroke Events: Review and Meta-Analysis. *JAHA* 2021;**10**:e016890.
68. Pope CA, 3rd Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 2004;**109**:71–77.
69. Hayes RB, Lim C, Zhang Y, Cromar K, Shao Y, Reynolds HR, Silverman DT, Jones RR, Park Y, Jerrett M, Ahn J, Thurston GD. PM2.5 air pollution and cause-specific cardiovascular disease mortality. *Int J Epidemiol* 2020;**49**:25–35.
70. Palanivel R, Vinayachandran V, Biswal S, Deiluiis JA, Padmanabhan R, Park B, Gangwar RS, Durieux JC, Ebreo Cara EA, Das L, Bevan G, Fayad ZA, Tawakol A, Jain MK, Rao S, Rajagopalan S. Exposure to air pollution disrupts circadian rhythm through alterations in chromatin dynamics. *iScience* 2020;**23**:101728.
71. Falchi F, Cinzano P, Elvidge CD, Keith DM, Haim A. Limiting the impact of light pollution on human health, environment and stellar visibility. *J Environ Manage* 2011;**92**:2714–2722.
72. Li H, Kilgallen AB, Munzel T, Wolf E, Lecour S, Schulz R, Daiber A, Van Laake LW. Influence of mental stress and environmental toxins on circadian clocks: implications for redox regulation of the heart and cardioprotection. *Br J Pharmacol* 2020;**177**:5393–5412.
73. Nawrot TS, Saenen ND, Schenk J, Janssen BG, Motta V, Tarantini L, Cox B, Lefebvre W, Vanpoucke C, Maggioni C, Bollati V. Placental circadian pathway methylation and in utero exposure to fine particle air pollution. *Environ Int* 2018;**114**:231–241.
74. Song P, Li Z, Li X, Yang L, Zhang L, Li N, Guo C, Lu S, Wei Y. Transcriptome profiling of the lungs reveals molecular clock genes expression changes after chronic exposure to ambient air particles. *Int J Environ Res Public Health* 2017;**14**:90.
75. International Energy Agency. World Energy Outlook 2020. <https://www.iea.org/reports/world-energy-outlook-2020> [accessed 31 March 2021].
76. The Intergovernmental Panel on Climate Change. Managing the risks of extreme events and disasters to advance climate change adaptation. <https://www.ipcc.ch/report/managing-the-risks-of-extreme-events-and-disasters-to-advance-climate-change-adaptation/>. Date accessed 31 March 2021.
77. Fann N, Alman B, Broome RA, Morgan GG, Johnston FH, Pouliot G, Rappold AG. The health impacts and economic value of wildland fire episodes in the US: 2008–2012. *Sci Total Environ* 2018;**610–611**:802–809.
78. Yu P, Xu R, Abramson MJ, Li S, Guo Y. Bushfires in Australia: a serious health emergency under climate change. *Lancet Planet Health* 2020;**4**:e7–e8.
79. Tong S, Ebi K. Preventing and mitigating health risks of climate change. *Environ Res* 2019;**174**:9–13.
80. Amati M, Boruff B, Caccetta P, Devereux D, Kaspar J, Phelan K, Saunders A. *Where Should All the Trees Go? Investigating the Impact of Tree Canopy Cover on Socio-Economic Status and Wellbeing in LGA's*. Sydney, Australia: Horticulture Innovation Australia; 2017.
81. Ossola A, Staas L, Leishman M. *Urban Trees and People's Yards Mitigate Extreme Heat in Western Adelaide*. Sydney, Australia: Macquarie University; 2020.
82. Tan Z, Lau KK-L, Ng E. Urban tree design approaches for mitigating daytime urban heat island effects in a high-density urban environment. *Energy and Buildings* 2016;**114**:265–274.
83. Vandentorren SB, Zeghnoun A, Mandereau-Bruno L, Croisier A, Cochet C, Ribéron J, Siberan I. August 2003 heat wave in France: risk factors for death of elderly people living at home. *Eur J Public Health* 2006;**16**:583–591.
84. Ward K, Lauf S, Kleinschmit B, Endlicher W. Heat waves and urban heat islands in Europe: a review of relevant drivers. *Sci Total Environ* 2016;**569–570**:527–539.
85. Nieuwenhuijsen MJ, Khreis H, Triguero-Mas M, Gascon M, Davdand P. Fifty shades of green: pathway to healthy urban living. *Epidemiology* 2017;**28**:63–71.
86. Rojas-Rueda D, Nieuwenhuijsen MJ, Gascon M, Perez-Leon D, Mudu P. Green spaces and mortality: a systematic review and meta-analysis of cohort studies. *Lancet Planet Health* 2019;**3**:e469–e477.
87. Kondo MC, Mueller N, Locke DH, Roman LA, Rojas-Rueda D, Schinasi LH, Gascon M, Nieuwenhuijsen MJ. Health impact assessment of Philadelphia's 2025 tree canopy cover goals. *Lancet Planet Health* 2020;**4**:e149–e157.
88. The health benefits of tackling climate change. An executive summary of The Lancet Series. https://www.who.int/globalchange/publications/tackling_climate_change/en/ (Date accessed 19 April 2021).
89. Nieuwenhuijsen MJ. Urban and transport planning pathways to carbon neutral, liveable and healthy cities; a review of the current evidence. *Environ Int* 2020;**140**:105661.
90. Mueller N, Rojas-Rueda D, Cole-Hunter T, de Nazelle A, Dons E, Gerike R, Gotschi T, Int Panis L, Kahlmeier S, Nieuwenhuijsen M. Health impact assessment of active transportation: a systematic review. *Prev Med* 2015;**76**:103–114.
91. Chandrabose M, Rachele JN, Gunn L, Kavanagh A, Owen N, Turrell G, Giles-Corti B, Sugiyama T. Built environment and cardio-metabolic health: systematic review and meta-analysis of longitudinal studies. *Obes Rev* 2019;**20**:41–54.
92. Nieuwenhuijsen MJ. Influence of urban and transport planning and the city environment on cardiovascular disease. *Nat Rev Cardiol* 2018;**15**:432–438.
93. Ewing R, Cervero R. Travel and the built environment: a meta-analysis. *J Am Plann Assoc* 2010;**76**:265–294.
94. Stevenson M, Thompson J, de Sa TH, Ewing R, Mohan D, McClure R, Roberts I, Tiwari G, Giles-Corti B, Sun X, Wallace M, Woodcock J. Land use, transport, and population health: estimating the health benefits of compact cities. *Lancet* 2016;**388**:2925–2935.
95. Mueller N, Rojas-Rueda D, Salmon M, Martinez D, Ambros A, Brand C, de Nazelle A, Dons E, Gaupp-Berghausen M, Gerike R, Gotschi T, Iacorossi F, Int Panis L, Kahlmeier S, Raser E, Nieuwenhuijsen M; PASTA Consortium. Health impact assessment of cycling network expansions in European cities. *Prev Med* 2018;**109**:62–70.
96. Neven A, Verstraal A, Janssen A, Dendale P. Transport as a new avenue for CV prevention in city dwellers: how to kill two birds with one stone? *Eur Heart J* 2020;**41**:816–817.
97. Giles-Corti B, Zapata-Diomed B, Jafari A, Both A, Gunn L. Could smart research ensure healthy people in disrupted cities? *J Transp Health* 2020;**19**:100931.
98. Mueller N, Rojas-Rueda D, Basagana X, Cirach M, Cole-Hunter T, Davdand P, Donaïre-Gonzalez D, Foraster M, Gascon M, Martinez D, Tonne C, Triguero-Mas M, Valentin A, Nieuwenhuijsen M. Urban and transport planning related exposures and mortality: a health impact assessment for cities. *Environ Health Perspect* 2017;**125**:89–96.

99. Mueller N, Rojas-Rueda D, Khreis H, Cirach M, Andres D, Ballester J, Bartoll X, Daher C, Deluca A, Echave C, Mila C, Marquez S, Palou J, Perez K, Tonne C, Stevenson M, Rueda S, Nieuwenhuijsen M. Changing the urban design of cities for health: the superblock model. *Environ Int* 2020;**134**:105132.
100. London Living Streets. Campaigning for safe and vibrant streets, where people want to walk. <https://londonlivingstreets.com/low-traffic-liveable-neighbourhoods/>. Date accessed 31 March 2021.
101. Superisla Barcelona: nueva etapa. <https://ajuntament.barcelona.cat/superilles/es/>. Date accessed 31 March 2021.
102. Moreno C, The 15 minutes-city: for a new chrono-urbanism!. <http://www.moreno-web.net/the-15-minutes-city-for-a-new-chrono-urbanism-pr-carlos-moreno/>. Date accessed 31 March 2021.
103. Sisson P, How the '15-Minute City' could help post-pandemic recovery. https://www.bloomberg.com/news/articles/2020-07-15/mayors-tout-the-15-minute-city-as-covid-recovery?cmpid=BBDO71620_CITYLAB&utm_medium=email&utm_source=newsletter&utm_term=200716&utm_campaign=citylabdaily. Date accessed 31 March 2021.
104. Turrell G, Haynes M, Wilson LA, Giles-Corti B. Can the built environment reduce health inequalities? A study of neighbourhood socioeconomic disadvantage and walking for transport. *Health Place* 2013;**19**:89–98.
105. Nieuwenhuijsen MJ, Khreis H. Car free cities: pathway to healthy urban living. *Environ Int* 2016;**94**:251–262.
106. Nieuwenhuijsen M, Bastiaanssen J, Sersli S, Waygood EOD, Khreis H. Implementing car-free cities: rationale, requirements, barriers and facilitators. In: M Nieuwenhuijsen, H Khries, eds. *Integrating Human Health into Urban and Transport Planning*. Cham, Switzerland: Springer International Publishing; 2019. p199–219.
107. Olden K, Wilson S. Environmental health and genomics: visions and implications. *Nat Rev Genet* 2000;**1**:149–153.
108. Vineis P, Robinson O, Chadeau-Hyam M, Dehghan A, Mudway I, Dagnino S. What is new in the exposome? *Environ Int* 2020;**143**:105887.
109. Robinson O, Tamayo I, de Castro M, Valentin A, Giorgis-Allemand L, Hjertager Krog N, Marit Aasvang G, Ambros A, Ballester F, Bird P, Chatzi L, Cirach M, Dedele A, Donaire-Gonzalez D, Grazuleviciene R, Iakovidis M, Ibarluzea J, Kampouri M, Lepeule J, Maitre L, McEachan R, Oftedal B, Siroux V, Slama R, Stephanou EG, Sunyer J, Urquiza J, Vegard Weyde K, Wright J, Vrijheid M, Nieuwenhuijsen M, Basagana X. The urban exposome during pregnancy and its socioeconomic determinants. *Environ Health Perspect* 2018;**126**:077005.
110. Donaire-Gonzalez D, Curto A, Valentin A, Andrusaityte S, Basagana X, Casas M, Chatzi L, de Bont J, de Castro M, Dedele A, Granum B, Grazuleviciene R, Kampouri M, Lyon-Caen S, Manzano-Salgado CB, Aasvang GM, McEachan R, Meinhard-Kjellstad CH, Michalaki E, Panella P, Petravičienė I, Schwarze PE, Slama R, Robinson O, Tamayo-Uria I, Vafeiadi M, Waiblinger D, Wright J, Vrijheid M, Nieuwenhuijsen MJ. Personal assessment of the external exposome during pregnancy and childhood in Europe. *Environ Res* 2019;**174**:95–104.
111. Nieuwenhuijsen MJ, Donaire-Gonzalez D, Foraster M, Martinez D, Cisneros A. Using personal sensors to assess the exposome and acute health effects. *Int J Environ Res Public Health* 2014;**11**:7805–7819.
112. Halonen JI, Erhola M, Furman E, Haahtela T, Jousilahti P, Barouki R, Bergman A, Billo NE, Fuller R, Haines A, Kogevinas M, Kolossa-Gehring M, Krauze K, Lanki T, Vicente JL, Messerli P, Nieuwenhuijsen M, Paloniemi R, Peters A, Posch KH, Timonen P, Vermeulen R, Virtanen SM, Bousquet J, Anto JM. A call for urgent action to safeguard our planet and our health in line with the Helsinki Declaration. *Environ Res* 2020;**193**:110600.
113. Nieuwenhuijsen MJ, Khreis H, Verlinghieri E, Mueller N, Rojas-Rueda D. Participatory quantitative health impact assessment of urban and transport planning in cities: a review and research needs. *Environ Int* 2017;**103**:61–72.
114. Daiber A, Munzel T. Special issue "Impact of environmental pollution and stress on redox signaling and oxidative stress pathways". *Redox Biol* 2020;101621.
115. Craig P, Cooper C, Gunnell D, Haw S, Lawson K, Macintyre S, Ogilvie D, Petticrew M, Reeves B, Sutton M, Thompson S. Using natural experiments to evaluate population health interventions: new Medical Research Council guidance. *J Epidemiol Community Health* 2012;**66**:1182–1186.
116. Hooper P, Foster S, Bull F, Knuiman M, Christian H, Timperio A, Wood L, Trapp G, Boruff B, Francis J, Strange C, Badland H, Gunn L, Falconer R, Learnihan V, McCormack G, Sugiyama T, Giles-Corti B. Living liveable? RESIDE's evaluation of the "Liveable Neighborhoods" planning policy on the health supportive behaviors and wellbeing of residents in Perth, Western Australia. *SSM Popul Health* 2020;**10**:100538.
117. Reiner DM, Hannula I, Koljonen T, Allen M, Lucht W, Guillen-Gosalbez G, Mac Dowell N. Europe's 'green deal' and carbon dioxide removal. *Nature* 2021;**589**:19.
118. Giles-Corti B, Lowe M, Arundel J. Achieving the SDGs: evaluating indicators to be used to benchmark and monitor progress towards creating healthy and sustainable cities. *Health Policy* 2020;**124**:581–590.