Environment International 133 (2019) 105187

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Urban-associated diseases: Candidate diseases, environmental risk factors, and a path forward

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ARTICLE INFO

Handling Editor: Hanna Boogaard

Keywords:
Urban
Health
Environmental microbiome
Environmental risk factors
Disease
Ecology

ABSTRACT

Background: Cities are home to over half the global population; that proportion is expected to rise to 70% by mid-century. The urban environment differs greatly from that in which humans evolved, with potentially important consequences for health. Rates for allergic, inflammatory and auto-immune diseases appear to rise with urbanization and be higher in the more urbanized nations of the world which has led some to suggest that cities promote the occurrence of these diseases. However, there are no syntheses outlining what urban-associated diseases are and what characteristics of cities promote their occurrence.

Objectives: To synthesize the current understanding of "urban-associated diseases", and discover the common, potentially modifiable features of cities that may be driving these associations.

Methods: We focus on any diseases that have been associated with cities or are particularly prominent in today's urban societies. We draw on expertise across diverse health fields to examine the evidence for urban connections and drivers.

Discussion: We found evidence for urban associations across allergic, auto-immune, inflammatory, lifestyle and infectious disease categories. Some conditions (e.g. obesity and diabetes) have complex relationships with cities that have been insufficiently explored. Other conditions (e.g. allergies and asthma) have more evidence demonstrating their relationship with cities and the mechanisms driving that association. Unsurprisingly, air pollution was the characteristic of cities most frequently associated with disease. Other identified urban risk factors are not as widely known: altered microbial exposure and a disconnect from environmental microbiomes, vitamin D deficiency, noise and light pollution, and a transient, over-crowded, impoverished population. However, many complexities and caveats to these relationships beg clarification; we highlight the current knowledge gaps and outline ways to fill those gaps. Identifying urban-associated diseases and their drivers will allow us to prepare for the urban-disease burden of the future and create healthy cities that mitigate that disease burden.

1. Introduction

Since the advent of farming, human society has become increasingly concentrated within high-density communities. These 'cities', with their mix of living, working and commercial environments, are a defining attribute of modern civilization. Although cities have long been the hubs of commerce and government, their character and importance has changed dramatically in recent centuries, starting with the industrial revolution. Today, more people live in cities than not, and this trend towards urbanization is set to continue throughout the 21st century. City residents live within a largely artificial setting, disconnected from the natural world and far removed from the environmental surroundings of human evolution. In this context, it is important to understand the health impact of humanity's shift into cities.

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https://doi.org/10.1016/j.envint.2019.105187
Received 11 July 2019; Received in revised form 13 September 2019; Accepted 13 September 2019
Available online 21 October 2019

Fig. 1. There is great heterogeneity among cities and within cities across time and space. The environmental and health experiences would be very different for a person living along Mulberry Street in New York City, USA in the early 1900s (a) versus Mulberry Street today (b). Similarly, people the affluent parts of Cairo (c) face very different health challenges than people living in Cairo's slums (d) or in New York City (b).

Cities are spatially and temporally dynamic (Fig. 1) and so are the health challenges they bring. In the mid-1300s in Europe, cities were a dangerous place to live – violence, crime and plague ravaged their populations. Today, many developing cities and impoverished areas in developed cities still face similar challenges. In developed nations housing regulations, air and water quality protection, sanitation systems, indoor plumbing and smokeless heating have alleviated historic urban scourges. Employment, income, and health care quality and access tend to be higher in urban versus non-urban areas resulting in an "urban health advantage" for city residents in developed nations (AIHW, 2017; Eberhardt et al., 2001; Mainous and Kohrs, 1995; Morgan, 2002; WHO and Metropolis, 2014). For example, in Australia, people living in rural areas have lower life expectancy, higher rates of disease, injury and suicide, and poorer access to health services (AIHW, 2017).

This urban-rural health divide may be partly due to behavioural risk factors associated with local health culture (Hartley, 2004). For example, rural Australians are more likely to smoke tobacco, get insufficient exercise, and drink more alcohol compared to urban residents (AIHW, 2017). But after accounting for socioeconomic and behavioural risk factors, some diseases occur at higher rates in cities, suggesting the physical environment of cities could act to promote the development of certain ailments and chronic health conditions. The hallmarks of urbanization (land-use change, population growth, and changing social behaviours) have also been identified as drivers of disease emergence (Jones et al., 2008; Weiss and McMichael, 2004; Woolhouse and Gowtage-Sequeria, 2005). And despite significant public heath advances, a quarter of child deaths globally are still due to poor environmental conditions (WHO, 2018a). The urban physical environment is easier to modify through policies and legislation than public behaviour, so understanding how the urban environment impacts health could lead to substantial public health gains.

While there have been several important syntheses exploring the ways cities impact health (Freudenberg et al., 2006; Galea et al., 2005; Galea and Vlahov, 2005; Vlahov et al., 2007; Vlahov and Galea, 2003, 2002), none have explicitly identified "urban associated diseases" (UADs). Presumably this is because of the tremendous variation within and among cities (Fig. 1), making identification of UADs challenging. Over 1000 metropoles have agreed to the goal of becoming "Healthy Cities" (WHO, 2018b). However, such a worthy goal cannot be attained if we do not first identify the ways in which cities degrade health.

In this synthesis we begin the important effort of identifying urban associated diseases (UADs) starting with the most important diseases of our time. We focus on diseases that (a) have risen concurrent with urbanisation, or (b) have been directly associated with cities in some way. We draw on expertise across diverse health fields to examine the evidence for an urban connection for these diseases and the mechanisms driving those connections. We uncover some important characteristics of cities that are associated with disease, including some well-known disease drivers like air pollution and some surprisingly consistent but less known drivers (i.e. altered exposure to environmental microbiomes). We highlight the research gaps and outline options for filling these gaps. In the supplementary material we provide an in-depth overview and description of each disease, including further information/evidence on the urban-rural comparison as well as an outline of potential factors that may confound inference of an urban-association. This literature synthesis is intended to kickstart a rigorous examination of UADs and their drivers to better predict global health burden, inform health system planning and policy, and guide urban design.

2. Urban-associated diseases (UADs): What are they and which diseases were examined

Here we define UADs as: any disease that increases in prevalence or severity due to urban living or urban growth or is expected to increase due to future urbanisation trends. For this synthesis, we examine diseases of immune disfunction (e.g. allergies, asthma and auto-immune diseases), non-communicable lifestyle diseases (e.g. cardiovascular disease, obesity, etc.) and infectious diseases (e.g. respiratory infections) which cumulatively represent most of the global health burden.

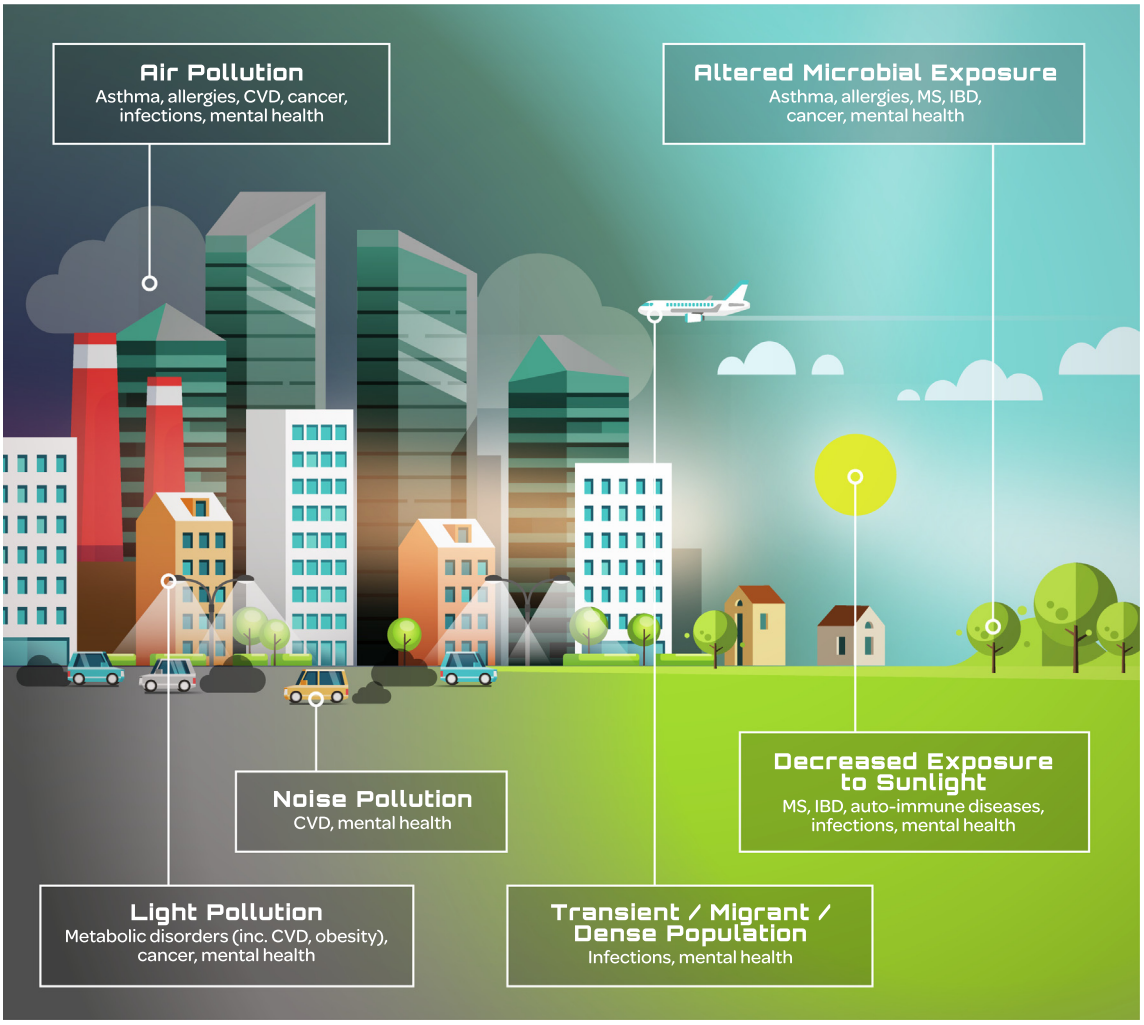

Fig. 2. An infographic of the features of urban environments and the diseases that have been associated with those characteristics of cities. Abbreviations used are as follows: CVD: cardiovascular disease; IBD: Inflammatory bowel disease; MS: multiple sclerosis.

Urban disease associations and risk factors are shown in Fig. 2 and additional details of the disease and discussion of the caveats surrounding urban association is provided in the Supplementary Materials.

2.1. Allergies & asthma

The first conditions linked to cities and the urban aristocracy in the 1870s were allergic asthma and hayfever (Blackley, 1873). This eventually provoked the hygiene hypothesis, suggesting that exposure to early childhood infections could help prevent allergies (Strachan, 1989). Since then, rates of allergic and autoimmune diseases have increased, particularly in developed and heavily urbanized nations (Asher et al., 2006). In the United States for example, a 2005–2006 survey of children found that 45% were sensitized to at least one allergen (Salo et al., 2014).

Allergy rates vary globally and are higher in the most developed, urbanized nations (Aït-Khaled et al., 2009; Deckers et al., 2012). Allergy is connected to a myriad of environmental variables, including current and developmental exposure to allergens (Kim et al., 2002; Platts-Mills et al., 1995; Yemaneberhan et al., 1997), pollution (Miyamoto, 1997), endotoxins (Perzanowski et al., 2006), or a lack of exposure to a diversity of environmental microbes (Haahtela et al., 2013; Heederik and Mutius, 2012). Allergic diseases have often been connected with economic development and urbanisation and three prominent hypotheses (Hygiene hypothesis, Old friend's hypothesis and Biodiversity hypothesis) are built upon this association.

Asthma is a chronic inflammatory disease of the respiratory tract that affects approximately 235 million people annually (WHO, 2017). While asthma "endotypes" likely differ in their underlying aetiology (Holgate et al., 2015), atopy (allergy) is consistently the most significant risk factor for asthma, particularly in developed nations (Weinmayr et al., 2007). So, while asthma has a high level of heritability, the environment can be a critical driver in the expression of asthma symptoms.

After accounting for the potent effect of socio-economic factors in asthma occurrence, there are two key environmental exposures that may explain the urban to rural asthma gradient; air pollution and early life microbial exposure. Air pollution from combustion sources, which are typically at much higher levels in urban environments, is a known risk factor for the development and exacerbation of asthma (Guarnieri and Balmes, 2014). Early-life exposure to diverse microbial communities, such as those in rural farming environments, can protect against asthma (Ege et al., 2011; MacNeill et al., 2013; Stein et al., 2016).

2.2. Autoimmune and inflammatory diseases

The connection between auto-immunity and over-sanitation was first observed in 1966 with an association between multiple sclerosis (MS) and sanitation in cities (Leibowitz et al., 1966). More recently, the biodiversity hypothesis has suggested that the rise of inflammation-

Table 1
Potential urban-associated diseases and the studies that have specifically tested the presence of an urban association. See Table S1 for an expanded table with urban disease association separated by disease and country. Citation index is in Supplementary Materials Appendix 2.

Disease	Countries	Positively associated with	Key citations
Allergies	USA, Saudia Arabia, Finland, Poland	Urban	(*1–5*)
Asthma	Poland, USA, Northern Europe, Poland, India, Saudia Arabia, Ethiopia, Rwanda	Urban	(*2*, *4–10*)
IBD	Canada	No difference	(*11*)
IBD	Global, USA, Northern Europe, Sweden, Canada	Urban	(*7*, *12–15*)
Multiple sclerosis	Canada, England, Poland	No difference	(*16–18*)
Multiple sclerosis	Finland, Sardinia	Rural	(*19*, *20*)
Multiple sclerosis	Isreal, USA, Italy, Czechoslovakia, Romania, Crete	Urban	(*21–26*)
Lupus (Systemic lupus erythematosis)	Greece	Urban	(*27–29*)
Cardiovascular disease	Iran, United Arab Emirates, Saudi Arabia, Occupied Palestinian Territory	Rural	(*30*)
Cardiovascular disease	China, USA, India and Bangladesh	Urban	(*31–36*)
Cancer	South Korea	No difference	(*37*)
Cancer	Iran	Rural	(*38*)
Cancer	Global (review), Iran, Spain, South Korea	Urban	(*37–41*)
COPD	China, Rwanda	No difference	(*10*, *42*)
COPD	United States, Thailand	Rural	(*43*, *44*)
Diabetes	Thailand and Korea	No difference	(*45*)
Diabetes	Australia, USA	Rural	(*46–48*)
Diabetes	Oman, Myanmar, Global, Bangladesh, India, Philippines and Cambodia, China, Global, India	Urban	(*45*, *49–56*)
Obesity	West Africa	No difference	(*57*)
Obesity	Developed countries, Australia, USA, Canada	Rural	(*58–63*)
Obesity	West Africa, Developing countries, India	Urban	(*58*, *64–66*)
Psychiatric disorders (all)	Global, Netherlands, Denmark	Urban	(*67–69*)
Mood disorders	Global, Developed nations, Netherlands, Canada	Urban	(*67*, *68*, *70*, *71*)
Mood disorders	Developing nations, Turkey	Rural	(*70*, *72*, *73*)
Mood disorders	Japan, Ghana	No difference	(*74*, *75*)
Anxiety disorders	Global, Netherlands	Urban	(*67*, *68*)
Anxiety disorders	Turkey	Rural	(*72*)
Psychosis, schizophrenia	Developing nations	No difference	(*76*)
Psychosis, schizophrenia	Global (Review), Isreal, Denmark	Urban	(*77–81*)
Substance-use disorders	Global, Netherlands	No difference	(*67*, *68*)
Suicide	Spain, USA, Australia	Rural	(*82–84*)
Mosquito-borne infections: Dengue	Global, Burkina Faso, China, Taiwan	Urban	(*85–87*)
Mosquito-borne infections: Malaria, Ross River virus	Sub-Saharan Africa, Kenya, Republic of the Congo, Australia, Australia	Rural	(*88–92*)
Respiratory infections/ tuberculosis	India, Viet Nam, China	Rural	(*93–95*)
Respiratory infections/ tuberculosis	India, Pakistan	Urban	(*96–98*)
STIs	Global (Systematic review), USA	No difference	(*99*, *100*)
STIs	Papua New Guinea	Rural	(*101*)
STIs	Global, USA, Niger, Vietnam	Urban	(*102–105*)

Cancer: includes gastric, esophageal, skin, breast, lung, prostate, colorectal, and pancreatic cancer; COPD: Chronic obstructive pulmonary disease; IBD: Inflammatory bowel disease; Anxiety disorders: includes panic disorder, phobias, generalized anxiety disorder and OCD; Mood disorders: includes depression, distress, bipolar disorder; STIs: sexually transmitted infections, including chlamydia, gonorrhoea, human papilloma virus, herpes simplex virus, human immunodeficiency virus.

related diseases (including auto-immune diseases and cancer) is a consequence of early-life exposure to a reduced diversity of microbes (Haahtela et al., 2013). Presumably, this disconnect between humans and diverse environmental microbial communities is greatest in urban areas (Hanski et al., 2012; Ruokolainen et al., 2015; Schnorr et al., 2014). The recent trend of increasing urbanization, auto-immune and inflammatory diseases, particularly in developed nations circumstantially supports this hypothesized connection (Haahtela et al., 2013; Lehtinen et al., 2011). Here we focus on MS, a chronic, auto-immune disease of the central nervous system, and inflammatory bowel disease (IBD), a collection of diseases characterised by inflammation of the digestive tract. Both conditions have important genetic components and strong environmental mediators.

The prominent environmental risk factors for MS appear to be low vitamin D levels (which help explain the observed latitudinal gradient), smoking, and parasite exposure (explaining the early association with sanitation; Koch et al. 2013). Over the past few decades, MS rates have been rising faster in developed, urban nations compared to less urban, developing nations but evidence of associations with cities has been conflicting (Table 1). Recent evidence has identified a key role for the gut microbiome in moderating MS symptoms (Berer et al., 2017; Cekanaviciute et al., 2017; Miyake et al., 2015).

Inflammatory bowel diseases (IBD)—most commonly Crohn's disease (CD) and ulcerative colitis (UC)—occur at higher rates in Western societies (e.g., USA, Australia, Canada, Europe). However, countries with historically low incidence rates, such as India and China, have experienced increasing cases in recent years, underlining the importance of environmental drivers (Rioux et al., 2007). The aetiology of IBD revolves around four interacting, complex factors: genetic predisposition, altered intestinal immune function, dysbiosis (an imbalance) of the gut microbiota, and environmental factors which trigger a cycle of intestinal inflammation (Ananthakrishnan, 2015; Kaplan, 2015; Rosenfeld and Bressler, 2012). Inversely associated with both CD and UC are tap-water consumption, contact with farm animals, and exposure to pets in childhood (Bernstein et al., 2006).

2.3. Lifestyle and chronic diseases

The shift to living in an urban environment comes with many changes to diet, activity levels, and social interactions, among others. Diseases associated with these "lifestyle" changes are diverse and interdependent; they include cardiovascular disease (CVD), obesity, diabetes, chronic obstructive pulmonary disease (COPD), cancer and mental illness. This "lifestyle" group of non-communicable diseases

(NCD) is the largest and most important group of diseases today. Lifestyle diseases were first associated with developed nations but have been rising rapidly in developing nations, particularly in urban areas. There are some underlying risk factors common to many of these diseases, including smoking, hypertension, alcohol consumption, low fruit and vegetable intake, and physical inactivity (Danaei et al., 2005; Joseph et al., 2017; Yusuf et al., 2004). Other urban-associated characteristics that have recently been linked to lifestyle diseases include exposure to air pollutants (Brook et al., 2010; Danaei et al., 2005) artificial lights at night (Garcia-Saenz et al., 2018; Lane et al., 2017), and noise (Münzel et al., 2016). With increased urbanization, an growing proportion of the population will be exposed simultaneously to these environmental risk factors (Münzel et al., 2016).

2.3.1. Cardiovascular disease

In 2015, CVD accounted for a third of all deaths globally (Roth et al., 2017) and was the leading cause of NCD-related deaths, with ischemic heart disease and stroke accounting for 85.1% of this mortality burden (Wang et al., 2016). Most cases of CVD are associated with a few common and modifiable risk factors across regions and population groups: abnormal lipids, smoking, hypertension, diabetes mellitus, abdominal obesity, psychosocial factors, lack of fruit and vegetables in diet, high alcohol consumption, and physical inactivity (Joseph et al., 2017; Yusuf et al., 2004). The relationship between urban and CVD is complex with different patterns and trends apparent for different regions, CVD conditions and population groups. Regardless of this complexity there is evidence of urban-rural disparities in CVD prevalence, mortality and trends with urban areas often having the greater burden, particularly in developing nations (Table 1; Supplementary Materials).

2.3.2. Cancer

Cancer, a decidedly diverse group of diseases, forms the second leading cause of death worldwide (Fitzmaurice et al., 2017). While not extensive, some research has examined cancer rates between urban and rural areas and have found several cancers associated with urban living (Table 1). There are a number of behavioral risk factors for cancer that are also common to other NCDs including smoking, alcohol consumption, low fruit and vegetable intake, and physical inactivity (Danaei et al., 2005). However, environmental factors such as exposure to air pollutants (Brook et al., 2010) artificial lights at night (Lane et al., 2017), and noise (Münzel et al., 2016) may also be contributing to rising cancer rates.

2.3.3. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease, a chronic lung condition characterized by fixed airflow obstruction (Barnes et al., 2015), was the third leading cause of death in 2010 (Lozano et al., 2012). With a few genetic exceptions (e.g. α1-antitrypsin deficiency), the geographic distribution of COPD is determined by the prevalence of exposure to cigarette smoke or indoor biomass burning, which are generally higher in rural areas. When these risk factors are adjusted for, the regional relationship is largely absent (e.g. Pothirat et al., 2015), suggesting no association with cities.

2.3.4. Obesity and diabetes

World-wide, the proportion of overweight and obese people doubled from 1980 to 2008; 52% of the global adult population is now considered to exceed a healthy body mass index (WHO, 2018c). However, the reasons contributing to the energy imbalance and resultant weight gain are complex and multifactorial. Clearly, an increased availability of foods high in fat and sugar, increased serving sizes and sedentary lifestyles have contributed to this but many other factors including changing microbiomes also appear to be important (Vangay et al., 2018). With the increase in obesity comes a concomitant rise in several associated diseases, most prominently diabetes, but also cardiovascular diseases, various cancers, endocrine issues and musculoskeletal disorders (Guh et al., 2009).

Generally, obesity and diabetes are associated with urban areas in developing nations and rural areas in developed nations (Table 1) though these associations are expected to be temporally dynamic. An analysis of type 2 diabetes mellitus prevalence rates with urbanisation indicated that uncontrolled rapid growth of urban areas is linked to the prevalence of diabetes (Gassasse et al., 2017).

2.3.5. Mental health

Depression and anxiety consistently rank in the top 10 causes of global years lived with a disability and prevalence of mental health disorders (including anxiety and depression) has risen over the last decade (Vos et al., 2016). This may be related to urbanization, since psychiatric disorders broadly, and mood, anxiety and schizophrenic disorders specifically, have been associated with urban living (Peen et al., 2010; Purtle et al., 2019). However, this association is strongest for developed nations and may reverse in developing nations (Peen et al., 2010; Purtle et al., 2019). Urban mental health associations are most prominent in impoverished urban areas, which relates to both the "drift" of people with mental disorders to such locations, and to the environment of such areas promoting poor mental health. Urban environmental effects associated with mental health conditions vary by disorder but include: (i) psycho-social stresses of the urban environment, (ii) low quality housing and neighbourhoods (iii) reduced access to green space, and (iv) air and noise pollution (Engemann et al., 2019; Evans, 2003; Gidlöf-Gunnarsson and Öhrström, 2007).

2.4. Infectious diseases

Over the last few decades, medical and sanitation advances have led to decreases in the mortality burden of infectious diseases; however, in 2010, communicable diseases still caused 20% of all deaths worldwide (Lozano et al., 2012). Lower respiratory-tract infections remain in the top five leading causes of death worldwide, and the most globally important category of infectious diseases (Lozano et al., 2012; WHO, 2018d). Other globally important infectious diseases are HIV/AIDS (a sexually-transmitted infection), diarrhoeal diseases, tuberculosis (directly transmitted), and mosquito-borne infections (e.g. malaria).

Due to their higher population density compared to rural areas, cities present the ideal conditions for any directly transmitted human infection (e.g., influenza, measles, and tuberculosis). This increased risk is mediated through greater disease-transmission probability from host to host. This high population density also concentrates human and commercial waste, making reliable sanitation infrastructure critical to the prevention of water-borne diseases; unfortunately, this infrastructure is lacking in many developing countries and rapidly growing cities. In addition, globalization makes cities not only incubators for outbreaks but also gateways for regional or global pandemics (Alirol et al., 2011). Yet, despite the intuitive association between cities and infectious disease, a quantitative analysis of 24 common infectious diseases found a negative relationship between the percent urban of a country and most tested infectious diseases (Wood et al., 2017). In our analysis, we did not find a clear pattern for urban association of respiratory infections, or sexually transmitted diseases. Mosquito-borne infections could be urban- (e.g. dengue) or rural-associated (e.g. malaria) depending on the transmission ecology of the pathogen. Similarly, sexually transmitted infections (e.g. HIV), once strongly associated with cities show a weakening of the urban association due in part to better access to health care in cities (UNAIDS, 2006).

3. Discussion

The association between disease and cities is complex and context-specific. Urban environments offer potential health benefits, such as improved access to health care, employment, education, and infrastructure, as well as potential health risks (Gong et al., 2012; Pou et al.,

Table 2
Potential drivers of urban associated diseases and key citations.

Urban variable	Diseases linked to this characteristic	Key citations
Air pollution	Asthma	Bowatte et al., 2017; Guarnieri and Balmes, 2014
	Allergies	Miyamoto, 1997; Bowatte et al., 2017; Peden, 2018
	CVD	Brook et al., 2010; Li et al., 2017; Pope et al., 2004
	Cancer	Gharibvand et al., 2017; Turner et al., 2017
	Mental health	Szyszkowicz et al., 2016; Kioumourtzoglou et al., 2017; Davies and Smyth, 2018
	Respiratory tract infections	Frampton et al., 2002
Altered human microbiome or microbial exposure	Asthma	Ege et al., 2011; MacNeill et al., 2013; Stein et al., 2016
	Allergies	Haahtela et al., 2013; Heederik and Mutius, 2012
	MS	Berer et al., 2017; Cekanaviciute et al., 2017
	IBD	Manichanh et al., 2006; Ott et al., 2004
	Cancer	Greaves, 2018
	Mental health	Valles-Colomer et al., 2019; Rieder et al., 2017
Vitamin D	MS	Ascherio et al., 2010
	IBD	Jørgensen et al., 2010
	Infectious diseases	Camargo et al., 2012; Bergmann et al., 2012
	Mental health	Spedding, 2014
	Auto-immune diseases	Mora et al., 2008
Transient/migrant/dense population	Infectious diseases	McMichael, 2004; Alirol et al., 2011
	Mental health	Bhugra, 2004
Artificial light at night	Metabolic disorders inc. CVD and obesity	Lunn et al., 2017; Rybnikova et al., 2016; Zubidat and Haim, 2017
	Cancer	Lane et al., 2017; Blask et al., 2014
	Mental health	Fonken et al., 2012; Lunn et al., 2017
Noise pollution	CVD	Münzel et al., 2016
	Mental health	Gidlöf-Gunnarsson and Öhrström, 2007; Lercher et al., 2002; Stansfeld et al., 2000

CVD: cardiovascular disease; IBD: Inflammatory bowel disease; MS: multiple sclerosis.

2017). Many of the important NCDs examined here are interrelated and share the underlying risk factors of sedentary lifestyle, smoking and an unhealthy diet (including under- and over-nutrition and alcohol use); these "behavioral" risk factors have been covered elsewhere and are not a focus of this review (Beaglehole et al., 2011; Ezzati et al., 2002; Forouzanfar et al., 2016; Lim et al., 2012). Here, we identify the diseases which have potential causative links to, or are exacerbated by, people living in urban areas (Table 1) as well as the underlying, environmental risk factors that can be modified by urban design (Fig. 2). This knowledge will be crucial for allocating future health funding appropriately and for developing healthy urban environments.

Several prominent themes emerged from this analysis that help explain urban disease associations and their geographic heterogeneity. Exposure to elevated levels of air pollution in cities was the most common thread. This well-known environmental risk factor may explain urban associations of asthma, MS, CVD, cancer, mental health conditions and respiratory tract infections (Fig. 2, see Table 2 for citations) (WHO, 2016a). However, this review revealed several drivers, known to many urban- or public-health experts but often overlooked in the broader health literature. Exposure to altered microbiomes with reduced biodiversity has been proposed as a urban risk factor for asthma, allergies, MS, IBD, cancer, and mental health, a connection which supports the hygiene/old friends/biodiversity hypotheses (Table 2; Hanski et al. 2012; Liu 2015; Rook, 2013; Strachan, 1989). Vitamin D levels also emerged as a potential driver responsible for some urban associations (e.g. MS, IBD, auto-immune diseases), as did artificial lights at night, ambient noise, transient/migrant populations, and population density (Table 2). These potentially important risk factors (excluding air pollution) are ignored in four prominent risk-factor analyses published in leading medical journal The Lancet (Beaglehole et al., 2011; Ezzati et al., 2002; Forouzanfar et al., 2016; Lim et al., 2012). Below we examine these characteristics of cities to unpack the patterns of disease association.

3.1. Air pollution, cities and disease

Air pollution contributes to one in nine deaths annually and is the greatest environmental risk to human health (WHO, 2016a). Cities are responsible for 78% of carbon emissions globally (O'Meara, 1999) and ambient air-pollution levels are typically higher in urban environments (WHO, 2016a). Diesel exhaust particles, a key component of urban air pollution, can promote an allergic response in the lung (Brandt et al., 2015), cause oxidative stress and inflammation (Ji et al., 2018; Li et al., 2017) and increase susceptibility to infectious agents (Harrod et al., 2003). A large fraction of diesel-exhaust particles are in the nanometer size range and can cross the alveolar-capillary barrier into the circulating blood with systemic effects (Li et al., 2017; Nelin et al., 2012; Nemmar et al., 2003). Other air pollutants, such as increased levels of SO_2, O_3 and NO_2, are linked to early onset IBD (Kaplan et al., 2010), asthma (Bowatte et al., 2017; Guarnieri and Balmes, 2014), allergies (Bowatte et al., 2017; Miyamoto, 1997; Peden, 2018), inflammation (Kish et al., 2013; Li et al., 2017) and increased susceptibility to respiratory viruses (Frampton et al., 2002).

The highest levels of air pollution occur in low- and middle-income countries where much of the global population lives and population growth rates are high; annual mean pollution levels in these cities often exceeds 5–10 times the recommended limits (WHO, 2016b). From 2008 to 2013, air-pollution levels increased by 8% worldwide (WHO, 2016b). Unfortunately, with the continuing reliance on fossil fuels to power combustion processes in cities, it is likely that air pollution will continue to increase with important health consequences.

3.2. Altered microbiome/exposure to environmental micro-organisms

Ideas like the 'hygiene hypothesis' (Bach, 2002; Strachan, 1989), 'old friends hypothesis' (Rook, 2012), and 'biodiversity hypothesis' (von Hertzen et al., 2011) have emerged to explain why allergic, auto-immune and/or inflammatory diseases occur at higher rates in today's urban society. Hygiene *per se* has been dismissed as a driver of allergic

disease (Platts-Mills, 2015) but exposure to specific ('old friends hypothesis') or diverse ('biodiversity hypothesis') microbial agents is still believed to be important for conditioning proper immune responses and preventing allergic, inflammatory and auto-immune diseases (Greaves, 2018; Haahtela et al., 2013; Rook, 2013, 2009).

Early-life exposure to microbial communities has frequently been connected with reductions in hayfever, atopy and eczema (Ege et al., 2011; Hanski et al., 2012; Ruokolainen et al., 2015). These studies have identified both bacterial diversity (Bisgaard et al., 2011; Ege et al., 2011; Hanski et al., 2012; Ruokolainen et al., 2015; Stein et al., 2016), abundance (Gereda et al., 2000b, 2000a; Stein et al., 2016), and specific bacterial taxa (Ege et al., 2011; Fujimura et al., 2016; Hanski et al., 2012; Lynch et al., 2014) to be protective.

These hypotheses have been corroborated by experimental mouse studies which found that exposure to diversity of microbes can protect against allergic responses (Ege et al., 2011; Fujimura et al., 2014; Schuijs et al., 2015). Mice exposed to diverse, farmyard-type dust exhibit altered immune profiles (e.g. levels of immune cytokines interleukin (IL)-4, IL-5, IL-10, IL-13, and interferon gamma) and a shift away from the type 2 immunity that characterizes allergic disease (Gereda et al., 2000b; Hanski et al., 2012; Liu, 2015; Schuijs et al., 2015). Importantly, the 'greenness' and diversity of the surrounding environment can contribute to the diversity of microorganisms to which the body is exposed and provide protection from atopic sensitization (Hanski et al., 2012). The altered microbial exposure of people living in cities can lead to an inability to regulate chronic inflammation, potentially leading to cancer (Rook and Dalgleish, 2011).

Current urbanization trends are likely to shift people away from interactions with natural areas and biodiverse microbial communities. However, there is potential for biodiverse urban green spaces to help (Flies et al., 2018, 2017); green spaces with higher levels of biodiversity can provide greater health benefits (Carrus et al., 2015; Duarte-Tagles et al., 2015; Fuller et al., 2007; Luck et al., 2011), perhaps through exposure to greater microbial diversity. This apparently important environmental-health component has been overlooked in the environmental risk-factor literature (Ezzati et al., 2002; Forouzanfar et al., 2016; Lai et al., n.d.; Lim et al., 2012). See Table 2 and Supplementary Materials for further details, mechanisms and caveats for connecting microbial exposure to allergies, asthma and autoimmune diseases.

3.3. Vitamin D, cities and disease

The importance of sunlight exposure in preventing rickets has been recognized for over a century. More recently, the connections between sunlight exposure and vitamin D (i.e. 25-hydroxyvitamin D (25[OH]D) levels have been explained, along with a better understanding of the important role of vitamin D in skeletal development and immunomodulation (Mora et al., 2008). Through prospective and observational studies, vitamin-D deficiency has now been associated with a wide range of acute and chronic diseases including cardiovascular disease, IBD, infectious diseases, cancers, allergies, asthma, MS, hypertension, mood disorders, autoimmune diseases and all-cause mortality, among others (Ananthakrishnan et al., 2012; Autier et al., 2014; Cantorna and Mahon, 2004; Holick and Chen, 2008; Litonjua et al., 2016). For many diseases (including CVD, stroke, diabetes, cancer, COPD, MS and all-cause mortality), vitamin D supplementation studies show no effect (Autier et al., 2014). Some suggest the intervention trials conflict with epidemiological observations because they were of insufficient length to see positive effects (Giovannucci, 2014) or conducted in inappropriate populations (Rejnmark et al., 2017). Others say that low vitamin D is an indicator of, rather than a cause of many diseases (Autier et al., 2014). However, vitamin-D intervention studies have shown protective effects for IBD (Cantorna et al., 2018), infectious diseases (Bergman et al., 2013, 2012), and mental health (Shaffer et al., 2014; Spedding, 2014). While there is uncertainty in the precise role of vitamin D on specific diseases, it has clear immunomodulatory effects (Mora et al., 2008) that could contribute to observed health associations.

The impact of urban residence on vitamin-D levels is conflicting; some studies have found no overall difference in urban-rural vitamin-D levels, but where there is a difference, the urban population typically shows lower levels (Atiq et al., 1998; Harinarayan et al., 2007; Mithal et al., 2009; Puri et al., 2008; Sari et al., 2017). There can also be a synergistic effect of air pollution on vitamin-D deficiency in urban settings, whereby air pollution acts to block UVB rays and also reduces outdoor activity, leading to supressed levels of vitamin D in the population (Agarwal et al., 2002).

Vitamin D deficiency is a re-emerging global problem (Ginde et al., 2009; Holick and Chen, 2008; Mithal et al., 2009) due in part to rising obesity rates (Wortsman et al., 2000) and anti-skin cancer public health messages among other drivers. Though Vitamin D insufficiency is rising, so too is supplementation in developed nations (Rooney et al., 2017); how these trends will interact with urbanisation to shape long-term vitamin-D deficiency rates is unclear.

3.4. Artificial light at night

In addition to air pollution, urban areas also have more artificial lighting at night, which is considered an environmental pollutant (Davies and Smyth, 2018). While there is insufficient evidence to reliably determine the impact of outdoor lighting on human health (Davies and Smyth, 2018), there is an emerging view that by disrupting behavior, sleep and melatonin (Lunn et al., 2017; Ohayon and Milesi, 2016), artificial light might be a risk factor for metabolic disorders including obesity and cardiovascular disease (Lunn et al., 2017; Rybnikova et al., 2016; Zubidat and Haim, 2017), hormone-dependent cancers (Blask et al., 2014; Garcia-Saenz et al., 2018; James et al., 2017; Kim et al., 2017; Lunn et al., 2017; Rybnikova et al., 2017) and mental health (Fonken et al., 2012; Lunn et al., 2017).

Satellite images show an increase in artificial light, with the global footprint of artificially lit outdoor areas growing by 2.2% per year between 2012 and 2016 (Kyba et al., 2017). Artificial light emission is expected to continue to increase in the future, especially given related trends of increasing population and urbanization. It will be essential to better understand the health implications of artificial light exposure, so as to promote lighting technologies that minimize impacts on human and ecological health, and to develop light-pollution policies that take into account more than just energy efficiency (Hölker et al., 2010).

3.5. Caveats, challenges and solutions

Understanding the impact of urbanization on human health is a critical, yet complex question. We must first acknowledge the inadequacy of the urban-rural distinctions; this crude binary division of the human population cannot hope to capture all the social, cultural, economic and physical differences among geographic areas that are important for health. Some studies use urbanization rates, percent urban or the agglomeration index to search for relationships with disease metrics but none fully capture the complexity of cities and their residents. For instance, poverty is a major driver of health outcomes and while poverty is often associated with rural areas, there is significant poverty in cities. Indeed, income inequality is often heightened within cities, a confounding factor which may mask important environmental health impacts when the urban population is analyzed as a whole. While it can difficult to disentangle the relationship between poverty/economic change and urbanicity, it is important to try to do so with regards to health.

It is equally important to acknowledge the heterogeneity among urban areas. First, urban residents in developed versus developing nations face very different health challenges; any urban health study should separately analyze these categories as the coarsest of spatial disaggregations (Pou et al., 2017). Furthermore, no two cities are alike;

Table 3
Current challenges to identifying urban-associated disease and their drivers, with proposed solutions and examples.

Challenge to identifying urban-associated diseases and drivers	Solutions
Heterogeneity in exposure of the urban residents within a city	Within-city studies that collect individual health data as well as information about the living environment, behaviour, economic and psychosocial factors. Machine learning and path analysis to tease apart dependencies and causal relationships
Heterogeneity among cities and countries in the experiences and exposures of residents and disease definitions and detection efforts	International studies that collect environmental, cultural, socioeconomic and behavioural data in addition to standardized health data
Lack of health, social and environmental data in developing nations and impoverished areas of cities	Build partnerships with community leaders and health clinics in these locations to understand the health and social experiences there. Use satellite imagery and tools (e.g. Google Earth Engine), machine learning or object recognition algorithms to create fine-scale spatial data in less accessible locations
Lack of longitudinal studies to identify how disease trends vary across locations	Create longitudinal studies. Access data from hospitals and published studies across the world to identify trends and the geographic and economic variation in those trends. Engage citizen scientists in providing samples and data
Identifying the mechanisms underlying disease associations	Pair epidemiological studies with animal models to experimentally demonstrate health pathways

Several studies have surmounted these issues in various ways, including the following fine publications: Aït-Khaled et al., 2009; Cohn, 2008; McDonald et al., 2018; Pearce et al., 2007; Stein et al., 2016; Teo et al., 2013; Yusuf et al., 2004.

a global study of the objectively measured built environment found a 38-fold difference in median residential density and an 18-fold difference in median park densities across 15 cities in 11 countries (Adams et al., 2014). It is due to this heterogeneity that we have focused on the environmental mechanisms underlying health associations and consider how those features are likely to change into the future.

Finally, we identified a yawning gap in the literature in this realm: we found no quantitative and systematic studies identifying the diseases associated with cities. We recognize the challenges to answering this question and propose solutions for filling this knowledge gap in Table 3. We also highlight examples of studies that have successfully addressed each challenge as evidence that these roadblocks are not insurmountable.

4. Conclusions

The question of how current urbanisation trends will impact global health is a pressing concern, yet there is surprisingly little effort to synthesize the trends in this area. The global urban population will approximately double (from 3.3 billion to 6.3 billion) between 2007 and 2050 (UNDESA, 2014). Rapid urban development must occur to support those populations and 90% of urban growth by 2050 is expected to occur in developing regions of Africa and Asia (UNDESA, 2014). Those that will be most impacted by unhealthy urban environments are the poorest and most vulnerable citizens. However, cities can be protective of health; by identifying UADs and their drivers, there is tremendous potential to reduce health inequity and the global health burden.

This review highlights potential UADs and several important urban risk factors, some of which have been relatively ignored in the literature (Prüss-üstün et al., 2003). Air pollution is an important and well-known environmental risk factor in urban areas. However, the role of reduced exposure to microbial biodiversity, vitamin D and artificial light at night, and other factors may also have important negative health impacts that beg further investigation. We recommend further research examining the mechanisms underlying urban-rural health disparities, particularly for the potential UADs and urban environmental factors identified herein and have suggested ways to make those studies most effective (Table 3).

Declaration of Competing Interest

The authors declare that they have no competing financial interests.

Acknowledgements

We are very grateful for feedback from Prof. David Vlahov on a draft of this piece; Prof. Vlahov's thoughtful and expert critique strengthened our final manuscript. We would also like to thank Dr. Andy Flies who provided input and support in the development of this manuscript. This work was funded by Australian Research Council grant FL160100101.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105187.

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