Science of the Total Environment 636 (2018) 963–967

Contents lists available at ScienceDirect

Science of the Total Environment

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

Short Communication

The framework of urban exposome: Application of the exposome concept in urban health studies☆

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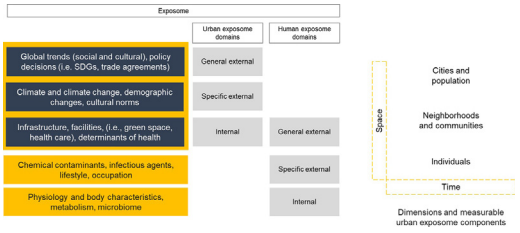
HIGHLIGHTS

- The urban exposome presents a city-oriented study framework based on the exposome approach used in population studies.
- The urban exposome framework focuses on the spatiotemporal monitoring of environmental and health indicators.
- Primary data collection, and routinely collected data combined define the urban exposome of cities.
- Practical aspects of the urban exposome study framework are discussed in a case study conducted in Limassol, Cyprus.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 13 December 2017
Received in revised form 29 March 2018
Accepted 24 April 2018
Available online xxxx

Editor: D. Barcelo

Keywords:
Exposome
Urban health
Environment
Disparities
Climate change
Metabolomics
Cities
Monitoring
Spatiotemporal
Indicators

ABSTRACT

Horizontal challenges, such as climate change or the growing populations, and their manifestations require the development of multidisciplinary research synergies in urban health that could benefit from concepts, such as the human exposome. Cities are composed of interconnected systems which are influenced, by global trends, national policies and local complexities. In this context, the exposome concept could be expanded having the city setting in its core, providing the conceptual framework for the new generation of urban studies. The objectives of this work were to define the urban exposome and outline its utility.

The urban exposome can be defined as the continuous spatiotemporal surveillance/monitoring of quantitative and qualitative indicators associated with the urban external and internal domains that shape up the quality of life and the health of urban populations, using small city areas, i.e. neighborhoods, quarters, or smaller administrative districts, as the point of reference. Research should focus on the urban exposome's measurable units at different levels, i.e. the individuals, small, within-city areas and the populations. The urban exposome framework applied in the city of Limassol, Cyprus combines three elements: (i) a mixed-methods study on stakeholders' opinions about quality of life in the city; (ii) a systematic assessment of secondary data from the cancer and death registries, including city infrastructure data; and (iii) a population health and biomonitoring survey. Continuous assessment of environmental and health indicators that are routinely collected, and the incorporation of primary data from population studies, will allow for the timely identification of within-city health and environmental disparities to inform policy making and public health interventions. The urban exposome could facilitate evidence-based public health response, offering researchers, policy-makers, and citizens effective tools to address the societal needs of large urban centers.

☆ Competing financial interests: None.

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https://doi.org/10.1016/j.scitotenv.2018.04.329
0048-9697/

1. Introduction

More than half of the global population nowadays lives in urban areas calling for increased attention to urban population's dynamics, policies and trends ("WHO|Urban population growth," 2016). The current "urban life context", including urbanicity, urbanization and all issues pertaining to urban life under the scope of sustainable development is not one-dimensional (United Nations Human Settlements Programme et al., 2016; Vlahov and Galea, 2002; World Health Organization and United Nations Human Settlements Programme, 2010). Thus, attempts to define cities by the population size fall short of addressing their complexity. Cities are multidimensional systems of varying hierarchy. They are further perplexed by their spatiotemporally-dependent population characteristics, which, in turn, are influenced by trends and processes operating at local, national or supranational levels. This is clearly reflected in national, international, and global initiatives that address urban issues, such as the Sustainable Development Goals (SDGs) 3 ("Good health and well-being") and 11 ("Sustainable cities and communities"), the World Health Organization's (WHO) Healthy Cities initiative, the actions of the United Nations' Human Settlements Program (UN-Habitat) or the recent Ostrava Declaration of the 6th Ministerial Conference on Environment and Health (EURO/Ostrava2017/7) (*Goal 3: Sustainable Development Knowledge Platform*, 2016, *Goal 11: United Nations Partnerships for SDGs Platform*, 2016, p. 11, "UN-HABITAT.:. Our Mission," 2016, "WHO|Healthy Cities," 2016).

In urban settings, health and environmental issues are pressing and need to be addressed using holistic approaches that are accompanied by multi-, inter- and/or trans-disciplinary, sustainable interventions. This view, however, comes with certain advantages and challenges. The main advantage is that multiple urban issues may be tackled simultaneously through the development of synergies that lead to mutual benefits. Moreover, the translation of technical concepts and ideas from one discipline to another hinders the development of interdisciplinary approaches within the field of urban health. Therefore, new concepts and ideas could unify the efforts of dealing with urban issues.

Within this context, global efforts focusing on urban health issues could perhaps benefit from implementing the relatively new concept of the human exposome, i.e., the totality of exposures throughout lifetime that has recently emerged within the field of environmental health sciences (Wild, 2012). The human exposome captures both the entities of totality and integration. Thus, if applied in the field of urban studies and most specifically in urban health, the "urban exposome" could offer researchers, and decision makers with a unifying and global framework to holistically and comprehensively approach the multidimensionality of global urban issues. The urban exposome framework could serve for the integration of hierarchically important clusters and networks of urban variables that would feed either into disease risk management or improved urban design and planning strategies or other challenges. The main objective of this work is to provide a definition of the urban exposome and outline its application using a case study.

2. Defining the urban exposome

The human exposome is a dynamic entity that is divided into three major domains, i.e., general and specific external, and the internal domain, keeping the individual as the point of reference, as presented by Wild in 2012 (Wild, 2012). Since then, the human exposome concept has been extended and enriched to include (sub)entities such as the indoor exposome (Dai et al., 2017), the eco-exposome (National Research Council, 2012), the systems biology-based adverse outcome pathways exposome (Escher et al., 2016) and the most recent pollutome defined as the totality of all forms of pollution that have the potential to harm human health (Landrigan et al., 2017). The urban exposome could be seen in one view as the sum of exposures that are related to life in the city (Probst-Hensch, 2017). However, this definition does not take into consideration how cities and their environments are shaped (from populations, to infrastructures and services) and how they spatiotemporally evolve. Thus, speaking in exposome terms, and keeping *both a global and local perspective*, cities are the result of the integration of interconnected, "living" systems (i.e. infrastructure systems, governance systems, social networks etc.) and their networks, which operate in a dynamic equilibrium and comprise of independent units that constantly interact with the city residents/dwellers. For example, the infrastructure system includes units ranging from water/wastewater/gas distribution system, to transportation, to green spaces, while, in another case the governance system's units are the different institutions that develop and guide policy within the city. These systems are all shaped and managed at various scales of the urban locality from the level of neighborhood, to that of communities, municipalities, to the whole city level.

Therefore, the concept of the "urban exposome" could provide us with the theoretical framework of visualizing and assessing urban life by combining the following domains (Fig. 1), to be used in parallel with those used for the human exposome (Wild, 2012), i.e.,

- External urban domain: parameters influencing the development and progress of urban settings that cannot be directly modified by the urban setting itself (i.e. by the local population or by local decision making or governance systems).
  - General external urban domain: global trends (social and cultural), policy decisions (e.g., UN sustainable development goals, international trade agreements).
  - Specific external urban domain: climate manifestations (including climate change impact, e.g., droughts, floods, increasing temperature) and its climate mitigation and adaptation efforts, demographic changes (e.g., population ageing, migration), culture/habits (e.g., local traditions).

- Internal urban domain: parameters integral to the urban setting, such as infrastructure (e.g., water/wastewater pipe network, transportation, energy systems), the built environment (indoor air, water and surfaces), facilities (e.g., green space, health care), and major determinants of population health (socioeconomic, psychosocial and others).

Within this context, there is a natural continuum between the urban exposome and the human exposome (Fig. 1). The internal urban domain includes parameters that, although integral to the city, are external to the individuals. Thus, the internal urban domain is in appreciable overlap with the parameters of the general external domain of the human exposome. It follows that the general external domain of the human exposome is accompanied by the specific external domain (i.e. chemical and/or infectious agent exposures, lifestyle/behavior patterns and occupational exposures) as described by Wild (2012). Then, in the individual internal domain of the human exposome, the physiological body attributes and absorption/distribution/metabolism/excretion patterns, may be better characterized by emerging -ome platforms, including the microbiome, metabolome, etc.

Attempts to extend the exposome concept and utility have appeared in the literature. A systems biology-based cellular toxicity emphasis in a recent definition of the exposome further extends the exposome utility and theoretical framework (Escher et al., 2016), while the eco-exposome concept was designed to include broader ecological issues in the human exposome agenda (National Research Council, 2012). Besides the theoretical efforts, funding agencies and research organizations already support exposome research in various ways, In the USA, the cross-fertilisation between two funding organizations, such as the National Institutes of Health (more focus on the internal domain of the exposome) and the National Science Foundation (more focus on the general and specific external domains of the exposome) with activities that lie at the interface of the exposome could pave the way for major scientific advances and breakthroughs. Similarly in Europe

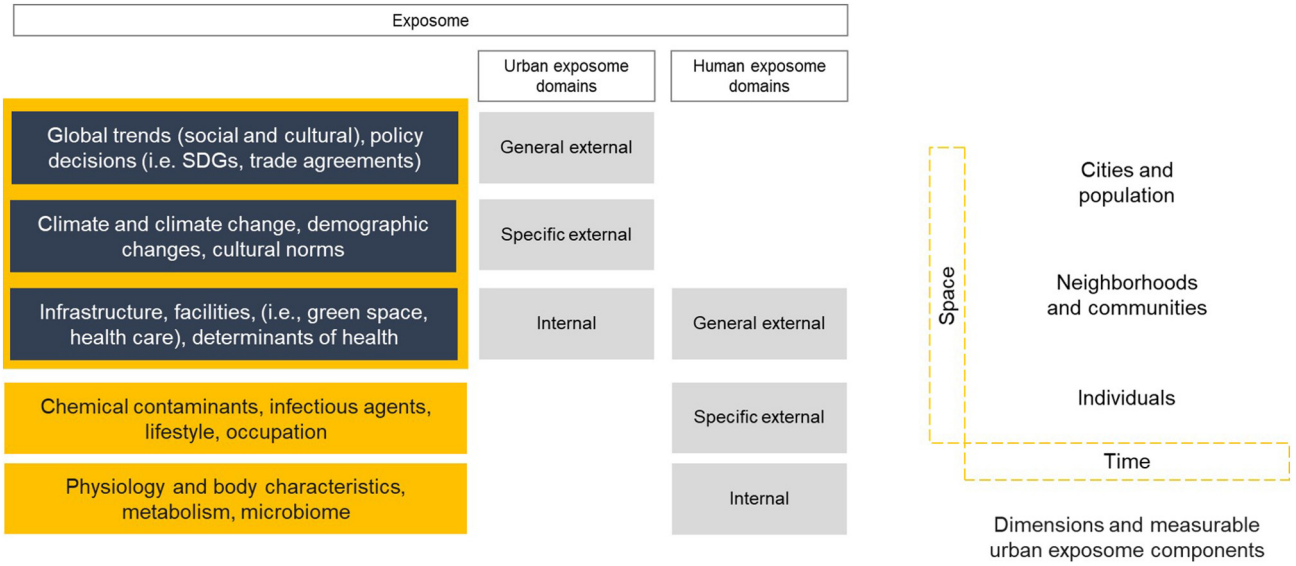

Fig. 1. The continuum of urban exposome - human exposome. Neighborhoods and individuals, cities and populations are the measurable components of the urban-, and human-exposomes, integrating assessments at the local (urban)-, and personal-level.

projects studying the exposome are using integrative approaches which include the urban environments in their study designs and methodologies (i.e. the HEALS project, HELIX or the EXPOsOMICS (Vrijheid et al., 2014; *Project Overview*, 2013; *About EXPOsOMICS|EXPOSOME*, 2016)). In Japan, the exposome concept is integrated in the Japan Environment and Children's study (Ishitsuka et al., 2017; "Japan Environment and Children's Study/Ministry of the Environment Government of Japan," 2018).

The urban exposome framework could be used to connect urban and environmental health if it can be readily applied or, better, if it can be readily described and measured using tools from complementary scientific fields. Thus, the measurement and description of the different urban domains could be done using existing or new specific urban health and environmental indicators that include the dimensions of time and space. The dimension of time is important to allow for the surveillance and monitoring of temporal fluctuations in the urban exposome indicators, while the dimension of space, i.e. measuring the same indicator in multiple within-city small areas, will allow for monitoring of the health outcomes and disparities within the urban setting.

Therefore, *a standalone definition of the urban exposome* could be (Fig. 1): "*the continuous temporal, and spatial surveillance/monitoring of quantitative and qualitative indicators associated with the urban external and internal parameters (belonging to the domains of the urban exposome) that would ultimately shape up the quality of life and the health of the urban population, using small areas of the city, such as neighborhoods, quarters, smaller administrative districts, as the point of reference.*" The indicators that form the building blocks of the urban exposome could be broadly categorized based on the domains described earlier, into the following themes/areas: global trends, policy decisions, demographic changes and cultural norms, the local climate and the manifestations of climate change, infrastructure, and determinants of health (Fig. 1). Thus, one needs to conduct an integrative assessment of qualitative and quantitative indicators to put the urban exposome concept into good practice within the concept of the overall human exposome framework.

The scope of the present viewpoint and the aim of defining the urban exposome as a continuation of the human exposome is to set a study framework of human-city interactions using an integrative rather than a fragmented and reductionist approach. The urban exposome evolves within and between the supranational, national and local settings and legal boundaries that exert their influence on social and economic aspects of the urban community. Thus, its characteristics are defined by the interactions of decision makers, stakeholders, and the general public, as we move from the supranational to the local level. These interactions define how small area differences emerge and how they determine, to an extent, the health status of the city residents.

Cities have to abide, for example, by environmental and/or health policies and regulations of international scope (one example could be the "urban agendas" of the UN or those of the European Union). At the same time, they often have to be harmonized with the objectives and needs of the local governments and those of the citizens, being occasionally, but not always on the same direction. This necessitates the effective communication between stakeholders and citizens. In another example, a new "smart city" intervention might be targeting the quality of life of the citizens, and if resources are limited, their allocation should be optimized through research on how/where the intervention, once implemented will be cost-effective within the urban setting. Then, prospective population studies in specific urban settings could identify targets for interventions aimed to deal with within-city environmental and health disparities. The above-mentioned examples are indicative of the scope of similar settings in which the urban exposome framework could be applied to conceptualize the interactions between different actors and assist knowledge generation and decision making towards addressing health and environmental issues.

3. An urban exposome case study in Limassol, Cyprus

The Republic of Cyprus has a total population of less than one million according to the latest census, and 67.4% reside in urban areas ("Population Census 2011," 2014). The city of Limassol (~200,000 inhabitants in total) is the second largest urban center of Cyprus defined as a medium-sized city (100000–250,000 population) according to the EU/OECD criteria (*Cities in Europe - The New OECD-EC Definition*, 2012; *European Cities – The EU-OECD Functional Urban Area Definition - Statistics Explained*, 2016). The city of Limassol faces all the challenges of modern urban settings such as urban sprawling, excessive residential construction, economic development, increasing populations along with the interrelated issues of within-city health inequalities that are often accompanied by increasing noncommunicable disease incidence rates. To explore the feasibility and highlight the practical implications of the urban exposome concept, a case study in the municipality of Limassol, Cyprus was conducted.

A multidisciplinary approach was used drawing from the fields of social sciences as well as, environmental and public health, using exposure

biomarkers and agnostic omics platforms in an attempt to comprehensively capture all domains of the urban exposome of Limassol (Fig. 2). More specifically, the external urban exposome domain (general and specific) was assessed through a mixed-methods study (quantitative and qualitative analysis) of city stakeholders' perceptions and priorities about the quality of urban life. Citizens, municipality officers and municipal council members were identified as the stakeholders. The specific external and the internal urban exposome domains were assessed through the evaluation of secondary data retrieved from the cancer and the death registries maintained by the Ministry of Health of Cyprus. The internal urban exposome domain was assessed through a population and biomonitoring study within the Municipality of Limassol (approved by the Cyprus National Bioethics Committee). For the population and the biomonitoring study, approximately 130 participants (from 130 visited households) were recruited in the summer of 2017 from all quarters of the municipality following the population distribution. During house visits, tap water samples were collected from the main faucet and free chlorine measurements were obtained in situ. A questionnaire addressing the issues of quality of life in the city, the use of infrastructures, personal habits and the health status was administered (Fig. 2). Specific questions were included to assess habits leading to exposures to environmental chemicals such as disinfection byproducts, metals, plasticizers, pesticides and insecticides. Additionally, participants provided first morning urine samples in two different days for the targeted analysis of biomarkers of exposures related to the exposure activities included in the questionnaires and for untargeted metabolomics analysis. Diaries with the exposure activities the day before the sample collection were also filled in.

From the combination of the results from the secondary data analysis and the population biomonitoring study, a set of indicators will be derived and mapped within the city. The maps will also incorporate existing infrastructures (i.e. green space, health care facilities, water distribution network, etc.) (Table 1). The stakeholders' perceptions will be also incorporated in the qualitative assessment of the secondary and primary data analyses. Overall, the description of the urban exposome for the city of Limassol will incorporate the perceptions of urban stakeholders, the retrospective analysis of secondary data that are routinely collected, and the analysis of primary data obtained for each participant's characteristics. These studies will facilitate the baseline assessment of the urban exposome of Limassol. Follow-up studies will ensure the continuous evaluation of the dynamic nature of the urban exposome.

Table 1
Urban exposome indicators and city infrastructure characteristics used to describe the urban exposome of Limassol, Cyprus.

Indicators	Infrastructure
Secondary data analysis of the cancer and death registries	Proximity to zones of industrial activity
Cancer incidence	Proximity to areas with a lot of traffic
Mortality rates	Green space and leisure parks
Population survey and biomonitoring	Proximity to the sea
Water quality	Health care facilities
Use of green space	Water distribution network
Use of health care facilities	Schools and other education facilities
Education and employment	
Chronic diseases	
Biomarkers of exposures to environmental chemicals (urinary levels of disinfection byproducts, bisphenols, pesticides)	
Metabolomics profiles	
Perception about environmental exposures at the place of residence	

4. Discussion

In the application of the urban exposome, the within-city small areas become a central component, being as important as each individual is in shaping the human exposome. Additionally, in accordance with efforts aggregating individual-level measurements to assess population health, the application of the urban exposome framework within-city areas or small areas with distinct characteristics (e.g., population density, land coverage) will allow for the improved assessment of the variability in exposures and concomitant urban health disparities.

The urban exposome could complement the study of the human exposome in urban health studies around the globe by facilitating the assessment of urban health disparities, urban design and planning challenges and, thus, informing cost-effective public health interventions (Pineo et al., 2017; Rothenberg et al., 2015). For example, exposure-based disparities within cities, and the influence of multi-level stressors (environmental or other, distal or proximal) could be identified by combining secondary data (i.e. from household surveys or the census or urban planning infrastructure databases) about health outcomes with

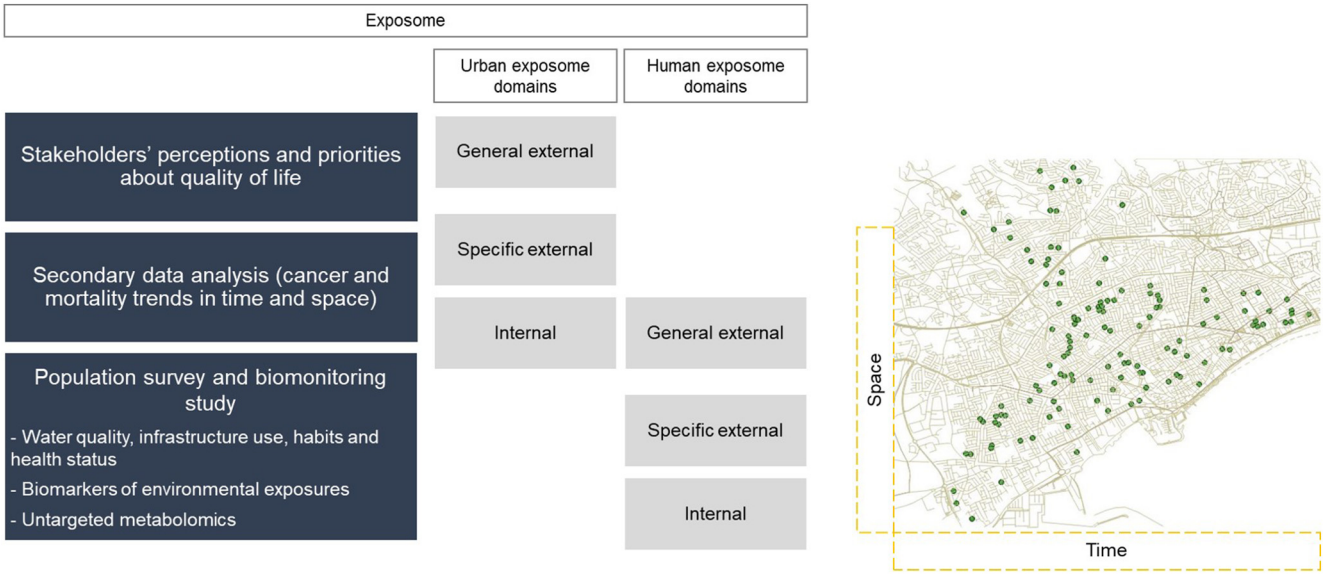

Fig. 2. Schematic depiction of the application of the urban exposome concept for the municipality of Limassol, Cyprus. The map shows the distribution of the houses visited within the limits of the Limassol Municipality for the population survey and the biomonitoring study.

primary data on determinants of health with cross-sectional studies or cohorts that assess environmental/lifestyle/behavior spatiotemporal exposures (i.e. biomonitoring and targeted/untargeted –omics studies) (Andrianou et al., 2014).

Overall, the goal of applying the urban exposome should be to develop a spatiotemporal-based population health surveillance system by: i) integrating available data sources (primary or secondary data); and ii) providing small-area (e.g. neighborhood)-based facts/data to policy for (real-time) evidence-based decision-making. In such a multi-faceted approach, community engagement is also important, as well as promoting the communication channels between citizens, scientists and stakeholders. Thus, the application of the urban exposome refers mostly to an integration of methodologies from social sciences to environmental health, urban planning/design and epidemiology to risk analysis than to a new methodological dogma.

The urban exposome comes as a natural extension, or a conceptual structure to complement the application of the human exposome within a dynamic and perplexed global urban environment of the 21st century. Engaging urban dwellers with their everyday city environment necessitates the adoption of a spatiotemporal continuum between the human exposome and the urban exposome, reflecting upon a locality-based interrelatedness between cities, populations and individuals. Making inferences about cities will aid the assessment of the personal exposomes and the other way around, and similarly, inferences about city population groups will aid the better characterization of the urban exposome (Fig. 1). The importance of the urban environment is acknowledged in the human exposome definition by being part of the general external domain (Wild, 2012), while a few studies have already assessed the human exposome for residents in urban settings (Vineis et al., 2017).

5. Conclusion

Although it may seem as conceptually obvious, an integrative approach that combines the exposome concept with the aspects of urban health and urban planning has not been put forward yet. It is warranted that the application of the urban exposome framework will facilitate the improved organization of health information systems using big data approaches by linking them to targeted prevention and control programs of non-communicable and communicable diseases within the city. Thus, using this paradigm health disparities between small-areas could be timely identified and tailor-made interventions could be developed. Such initiatives will enhance evidence-based public health response and deliver high quality lifestyle interventions for those at high risk and vulnerable groups.

Acknowledgements

We would like to thank Dr. Gary Miller (Emory University) for his valuable input and comments during the preparation of the manuscript. We also thank Chava van der Leek and Solomon Ioannou, as well as the Municipality of Limassol and the Health Monitoring Unit of the Ministry of Health for their contribution to the studies described in the application of the urban exposome.

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