Cyprus University of Technology | Faculty of Health Sciences

Doctoral Dissertation

Definition and application of the urban exposome study framework: from stakeholders' perspectives to non-communicable and communicable diseases epidemiology

Environmental health and urban indicators: an exposome approach

Xanthi D. Andrianou

Limassol, July 2019

CYPRUS UNIVERSITY OF TECHNOLOGY

FACULTY OF HEALTH SCIENCES

CYPRUS INTERNATIONAL INSTITUTE FOR ENVIRONMENTAL AND PUBLIC HEALTH

Doctoral Dissertation

DEFINITION AND APPLICATION OF THE URBAN EXPOSOME STUDY FRAMEWORK: FROM STAKEHOLDERS' PERSPECTIVES TO NON-COMMUNICABLE AND COMMUNICABLE DISEASES EPIDEMIOLOGY

Environmental health and urban indicators: an exposome approach

Xanthi D. Andrianou

Limassol, July 2019

Approval Form

Doctoral Dissertation

DEFINITION AND APPLICATION OF THE URBAN EXPOSOME STUDY FRAMEWORK: FROM STAKEHOLDERS' PERSPECTIVES TO NON-COMMUNICABLE AND COMMUNICABLE DISEASES EPIDEMIOLOGY

Environmental health and urban indicators: an exposome approach

Presented by

Xanthi D. Andrianou

Supervisor: Konstantinos C. Makris, Associate Professor, Cyprus University of Technology

Signature ____

Member of the committee: Contantinos Deltas, Professor, University of Cyprus

Signature ____

Member of the committee: Phaedon Kyriakidis, Professor, Cyprus University of Technology

Signature ____

Cyprus University of Technology

Limassol, July 2019

Acknowledgements

Following the field epi principle of starting with defining the time, place, and person when major events need to be described…this project represents work conducted between 2017 and 2019, from Cyprus and from Italy, with the contribution of researchers from the Cyprus University of Technology, from Maastricht University, and from the Ministry of Health of Cyprus. It has been a challenging task to combine different approaches from qualitative research, to do sample collection and a survey in Limassol during the heatwaves of summer 2017, and to combine routinely collected data from public health surveillance.

Now that, at least, part of this larger project has been completed in the form of this dissertation, I have to thank all those that stood by my side and supported the vague idea of mapping health in Limassol and conducting multi- and inter-disciplinary research.

First, I have to thank the Water and Health Lab, i.e. my supervisor Konstantinos C. Makris, for giving me the freedom to pursue all my research ideas, for being patient, listening and advising, and all lab members with whom I worked since 2013. Pantelis Charisiadis, Corina Konstantinou, and Stephanie Gaengler, thank you for being there in research and as friends during my "lab years", it wouldn't be the same without you. Helena, Luisa, Solona and Manu you are all part of the "extended lab"; thank you for your support and your friendship. I would also like to thank my research committee (Costas Christophi, Herodotos Herodotou, and Stefania Papatheodorou) for their advice and support.

Support received from "outsiders" to my academic bubble has been fundamental for me. Lloyd Akrong, Mei Lee Ling, and Yann Say-Liang-Fat, I am not sure how we managed to keep this "distant friendship" since 2011, but we did it and I am grateful to have you in my life and thank you for being always there for me.

I would have done nothing in this life, neither academically, nor personally, without my parents, my sisters, and my extended family. I don't think I am good enough with words in either Greek or English to express how grateful I am and how important the support of my parents, Dimitris and Eirini, and my sisters, Akrivi and Christina has been in everything I do.

I think my path to research started when my grandmother Xanthi first talked to me about the importance of studying, and through the discussions with my father about travels, history, and life. My father was also the first person that introduced me to the world of Public Health when he explained to me what Laveran's Plasmodium ("το πλασμώδιο του Λαβεράν") is and why he was mentioning all the time to tease my sister, or when he was explaining to us why we should be avoiding exposures to chemicals.😉

This work and everything I do in research is dedicated to my grandmother Xanthi and my father.

Icon made bv Nikita Gobulev from www.flaticon.com

ABSTRACT

The definition of the human exposome provided population studies, exposure assessment and classic epidemiology with new tools to study risk factors and health outcomes. In this study we presented the definition of the urban exposome study framework proposing a holistic approach to tackle urban health issues where cities and smaller, within-city areas are the measurable units creating a continuum with the human exposome. This study framework was applied in a case study in the city of Limassol in Cyprus. In a two-part study that combined qualitative and quantitative elements, stakeholders' perceptions about life in Limassol were described and, we mapped drinking water and quality of life indicators using data collected during a primary cross-sectional study (population survey and water sample collection) in the municipality of Limassol. To complete the application of the urban exposome framework we used routinely collected in cancer incidence (2007-2014), mortality (2007-2015) and tuberculosis (2015-2017) and described their epidemiology using the district of Limassol as a reference and aggregating the data in smaller areas (either postal code areas or municipalities/villages). The study presented the first example of developing the urban exposome of a city from developing the theoretical background to the application.

Keywords: exposome, urban, framework, health, environment, cancer, mortality, infectious diseases

TABLE OF CONTENTS

LIST OF TABLES

Main text

Appendices

LIST OF FIGURES

Main text

Appendices

LIST OF ABBREVIATIONS

Brominated species (brthm
Bromodichloromethane (BDCM)
Bromoform (TBM)
Chloroform (TCM)
Colony forming unit (CFU)
Credible intervals (CI)
Degree of urbanization classification (DEGURBA)
Dibromochloromethane (DBCM)
Environment-wide association study (EWAS)
European Center for Disease Control and Prevention (ECDC)
European Union (EU)
False discovery rate (FDR)
International Agency for Cancer Research (IARC)
Limits of detection (LOD)
Millennium Development Goals (MDGs)
Ministry of Health (MoH)
Ministry of Interior (MoI)
Organisation for Economic Co-operation and Development (OECD)
Partial least squared discriminatory analysis (block PLS-DA)
Relative risk (RR)
Standard deviation (sd)
Sustainable Development Goals (SDGs)
Total viable counts (TVC)
Trihalomethanes (THM)
Tuberculosis (TB)
United Nations (UN)
United Nations' Human Settlements Program (UN-Habitat)
World Bank (WB)
World Health Organization (WHO)

1 Introduction

It has been estimated that more than half of the global population is now living in urban areas giving increasing attention to the study of urban population especially the past ten years (1,2). However, there is no single, harmonized and globally-accepted definition of what constitutes an urban setting, with each country having a specific definition (3). While, the Demographic Yearbook of the United Nations (UN) presents non-aggregated data on urban and rural areas along with demographics on capital cities and cities of 100,000 or more inhabitants (3), the urban (or city) definition developed by the European Union (EU) in collaboration with the Organisation for Economic Co-operation and Development (OECD) is based on the presence of 'urban centres' (4). The World Bank (WB), on the other hand, uses its own population estimates and the urban to total population ratio provided by the UN to derive estimates for the urban population (2). A summary of the EU/OECD definition is presented in Table 1.1.

Urban settings have distinct characteristics compared to rural settings. These include differences in the way of life and the living standards which are generally considered to be higher in the urban settings (3). The size, the density, the diversity and the complexity are factors describing an urban setting, and in this context, urban health becomes a function of the living conditions as they are shaped by the municipal, national and global trends (5). Therefore, urban health is by definition a multidisciplinary field (5,6) in which the study of environmental risk factors and exposures within each urban setting are central. The challenges of addressing urban health issues have been also summarized in the most recent report of the World Health Organization (WHO) in 2016 (7).

Cyprus has a total population of less than one million according to the latest census, and 67.4% reside in urban areas (8). The main urban centers of Cyprus are Nicosia, the capital, and Limassol, with both defined as medium sized cities (100,000-250,000 population) according to the EU/OECD criteria (4,9). Nicosia and Limassol face all the challenges of the modern urban settings such as urban sprawling, increasing populations along with the interrelated issues of within-city health inequalities, increasing noncommunicable disease incidences.

Table 1.1 EU/OECD[1] urban settings definition.

A 4-step definition is used for cities starting from urban centres (4). Urban centers are defined as: *"…a cluster of contiguous grid cells of 1 km² with a density of at least 1500 inhabitants per km² and a minimum population of 50 000"* (10). Municipalities with >50% of their population in the urban center can become part of the city. A functional urban area is then defined by the city and the commuting zone (which is defined by specific criteria on commuting patterns) (4).

1.1 Addressing urban health issues globally and locally

The issues of urbanization have received a lot of attention and have prompted the development of different international initiatives. The UN has set up the agency United Nations Human Settlements Program, called UN-Habitat, to "promote socially and environmentally sustainable towns and cities with the goal of providing adequate shelter for all" (11), whilst the WHO, linking urban life and health, has developed the framework of the Healthy Cities (12). The first joint report between the WHO and the UN focusing on urban health was the "Hidden cities and Global urban report", published in 2010 (13) which was followed by the "Global report on urban health equitable, healthier cities for sustainable development", in 2016 (14).

Cities in the Sustainable Development Goals and the New Urban Agenda

Urban health was not explicitly included in the Millennium Development Goals (MDGs) (15). Nonetheless, in the Hidden Cities report, it was stated that tackling urban health inequalities was a pre-requisite for reaching the MDGs and this statement stemmed from the fact that cities had – and still have – a significant proportion of a country's population (13). Contrary to the MDGs, the sustainable development goals (SDGs) refer explicitly to urban settings. More specifically SDG 11 focuses on sustainable cities and communities (16). Urban health is addressed, overall, in the SDGs by the combination of SDG 11 and

---

[1] The EU-OECD definition includes both a spatial and population density criterion. No administrative criteria are strictly used. Cities might be larger than the what is defined by the local administration (i.e. municipality) or more than one cities might be sharing the same urban center.

SDG 3 that has health as its objective (17). However, as it was also noted in the "Global report on urban health" published in 2016, health and urbanization were not clearly linked in any of the SDGs (14).

More recently, the New Urban Agenda, which was agreed upon during the United Nations Habitat III conference in Quito, Ecuador in October 2016 (11) has set the path for sustainable urban development with specific principles and commitments. The necessity of applying a "health lens" on the decisions taken within the New Urban Agenda has been pointed out clearly by the WHO along with the necessity of multidisciplinary cooperation (12). Besides the initiatives that set the pace of developing and evaluating healthy and sustainable urban environments at the global scale such as the Healthy Cities or the UrbanHEART (13,14), regional initiatives have also been developed, for example, within the EU (15–17) or at national level e.g. in South Africa (18). While not limited to health and the environment, these initiatives place, implicitly or explicitly, urban health in the core of the decision-making for more sustainable development and provide the background for prioritizing the urban issues and the development of indicators to assess the current state of urban health and life, in general.

While neither of the main Cypriot cities (Nicosia or Limassol) nor the municipalities or other smaller areas that are part of their extended urban areas were part of the Healthy Cities network until recently (the network of Healthy Cities for Cyprus was established in 2019 (18)), various urban health studies have been undertaken by local research institutions (19–22). Nicosia, more specifically, was mentioned also in the latest urban health report (2016) as it was shown that there are within-city differences in environmental exposures which may be driven by different infrastructure characteristics such as those of the drinking water pipe network (14,22).

The governmental institutions covering the issues of urban health and environment are mostly within the Ministry of Health (MoH) and the Ministry of Interior (MoI) . They tackle different aspects of urban issues, either focusing on health or sustainable urban development (21,22). The Health Monitoring Unit, for example is one of the MoH units responsible for providing information on public health issues as it routinely collects and records various information on births, mortality, and cancer (23). On the other hand, the Department of Town Planning and Housing of the MoI is responsible, as indicated by its name, for the town planning following the principles of sustainability for the improvement and maintenance of the natural and build environment (25,26)

1.2 Public and environmental health within the city: an exposome approach

It is evident from the current "urban life context", as it is also evident from the multiple global initiatives that urbanicity, urbanization and all issues related to urban life or development are not one dimensional. What adds to it, is that any attempt to define cities only by the population size falls short of addressing the complexities of the urban setting. Cities are complex systems defined by spatial and population characteristics which, in turn, are influenced by trends in local, national and international levels. This observation has given rise to the study of cities using the principles of systems science (27). Within the context of systems science, public and environmental health are intuitively linked with the field of urban health and urban studies. The increasing populations living in cities only strengthen that link. What follows is that urban challenges are unique to different cities, as they are defined by the combination of the specific environments, physical and social, by decision-making processes, resources etc. Thus, health and environmental issues in urban settings require holistic approaches and specific interventions to be tackled.

It is warranted that a closer look in public and environmental health issues from the urban perspective will formulate sustainable health interventions for the urban population. New concepts and ideas can be applied to unify the efforts of dealing with the urban issues, one of these concepts is the concept of the "exposome", which is originally used mostly in the field of exposure assessment and captures the ideas of totality and integration (28,29).

Briefly, the exposome was first introduced by Wild (2005) as the totality of exposures throughout lifetime (28). However, as the exposome started attracting more attention from the research community and more data were collected, exposure assessment methodologies were refined, and more exposome definitions emerged (Table 1.2). All the definitions aimed to capture the meaning of totality, and the other major characteristic of the exposome, i.e. its multi-dimensionality (Table 1.2). The personal exposome, therefore, is a dynamic entity, which has been divided by Wild (2012) in three major domains, i.e., internal, general external, and specific external, where the individual is the point of reference (29). In exposome terms, cities are also dynamic entities, shaped and influenced by various parameters ranging from policy decisions to environmental conditions and at various scales of the urban locality (from the level of the neighborhood, to communities, municipalities, to the city level). Therefore, an exposome which will be applied in the field of urban studies and most specifically urban health, i.e. the "urban exposome", can give researchers, stakeholders, and decision-makers the common ground to discuss and, thus, solve the issues arising in urban settings. The concept of the "urban exposome" could provide the theoretical background of visualizing and assessing urban life as the result of the interaction and combination of three domains which parallel those used in the definition of the human exposome (as described by Wild in 2012, Figure 1.1), i.e.,

- General external: global trends, policy decisions
- Specific external: climate manifestations, demographic change, culture
- Internal: infrastructure (e.g., water/wastewater pipe network, transportation, energy systems), and facilities (e.g., green space, health care), determinants of health (socioeconomic and others)

The main objective of estimating the urban exposome of a specific setting (spatial dimension) is the systematic assessment of the of environmental and health indicators over time (dimension of time). This can be achieved using a multidisciplinary approach, drawing from the fields of public and environmental health, as well as exposure assessment and epidemiology, to develop the methodology for the assessment of the urban exposome through linking environmental and health indicators.

Table 1.2 Exposome definitions

Year	Author	Definition
2005	Wild (28)	The exposome encompasses life-course environmental exposures (including lifestyle factors), from the prenatal period onwards.
2014	Miller and Jones (30)	The cumulative measure of environmental influences and associated biological responses throughout the lifespan including exposures from the environment, diet, behavior, and endogenous processes.
2014	Dictionary of Epidemiology (31)	A potential measure of the effects of life course exposures on health. It comprises the totality of exposures to which an individual is subjected from conception to death, including those resulting from environmental agents, socioeconomic conditions, lifestyle, diet, and endogenous processes. Characterization of the exposome could permit addressing possible associations with health outcomes and their significance, if any, alone or in combination with genomic factors.

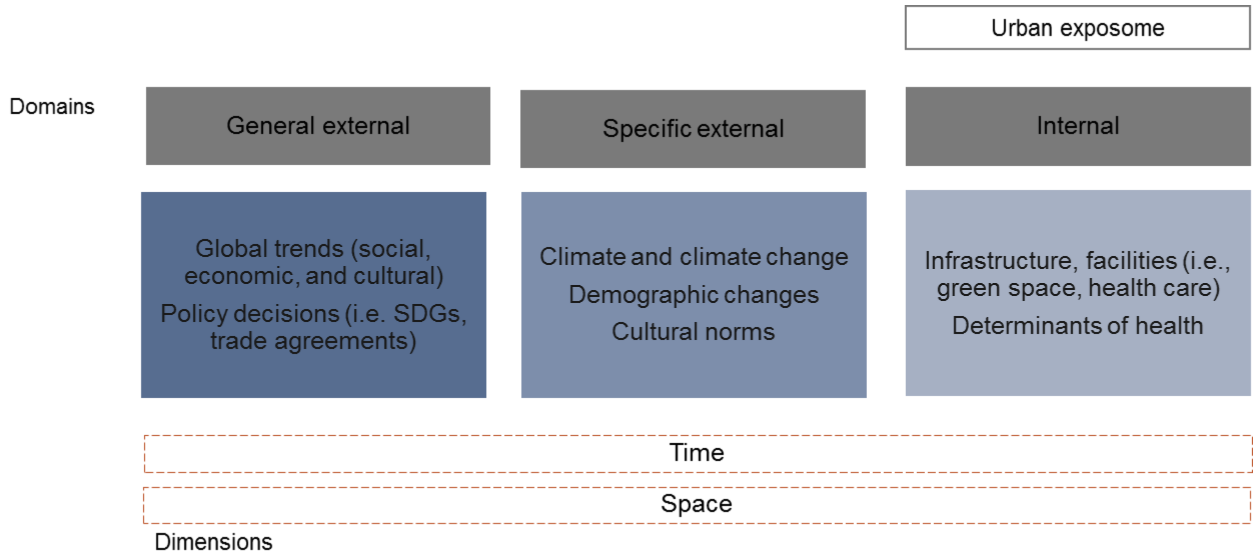


Figure 1.1 Urban exposome: an exposome application for the urban settings.

1.3 Limassol, Cyprus: background, urban health status and progress

Limassol district is located in south-west Cyprus. According to the latest population estimates in 2017 the population of the district was estimated to be 242,000 (32). The district of Limassol has overall 111 municipalities/villages. According to the 2016 EU degree of urbanization classification (DEGURBA) (retrieved from the Cyprus Statistical Services) 14 of the 111 (12.6%) these municipalities/villages are classified as densely populated areas and belong to the urban center of Limassol (city of Limassol), five (4.5%) are classified as intermediate (at least 50% of the population living in urban cluster and less than 50% live in urban center), and 92 (82.9%) as thinly populated (i.e. at least 50% of the population lives in rural grid cells) (33,34). The city of Limassol, specifically, has a population of ~200,000 inhabitants in total and it is the second largest urban center of Cyprus after the capital, Nicosia. Limassol is a medium-sized city (100,000-250,000 population) (4,9) The municipality of Limassol which is the largest municipality of Cyprus is the main urban hub of the city of Limassol (Figure 1.2). The municipalities/villages surrounding the municipality of Limassol, include on one end municipalities of population more than 10,000, i.e. Kato Polemidia, Mesa Geitonia, Agios Athanasios, Germasogeia, and Ypsonas, and, on the other end, small municipalities/villages (Mouttagiaka, Agios Tychonas, Parekklisia, Monagrouli, Moni, Pyrgos Lemesou, and Tserkezoi) with population ranging from more than 3000 to less than 100 (according to the 2011 census) (33).

Limassol, especially the urban center, that is located by the sea, has become an important economic hub. The past few years large construction projects have reshaped the “looks” of the city. Significant contribution to the economy of Limassol comes from the agriculture, agri-food manufacturing (e.g. wine industry, beverages production) as well as from other industrial activities that take place within the district as several pharmaceutical, packaging and metal companies are located there (35) Tourism and other activities within the service sector including but not limited to, shipping, or real estate and information technology play an important role in supporting the local economy (35).

The fast-paced progress that has been observed in Limassol the past few years has not been paralleled with specific research on urban health in the areaand there is a lack of urban health data to guide local public health interventions. Public health research on the urban environment of Limassol is almost nonexistent. Indicative of this is the fact that until 2017 only eight studies were retrieved from PubMed containing the terms “Limassol” or “Lemesos” and “health” [search details: (“Limassol[Text Word] OR Lemesos[Text Word]) AND health[Text Word]”; data of search: 6 June 2019]. Repeating the same search for Nicosia [search details: (“Nicosia[Text Word] OR Lefkosia[Text Word]) AND health[Text Word]”; data of search: 6 June 2019], 31 studies were retrieved (Table S1. 1).

The gap in knowledge about the current health status of Limassol combined with Limassol’s role as an emerging economic hub in Eastern Mediterranean and an urban center that faces the challenges any modern urban setting is facing, e.g. 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, indicates that focusing urban, public health studies in the area of Limassol can have added value for future public health interventions to improve life in the city.

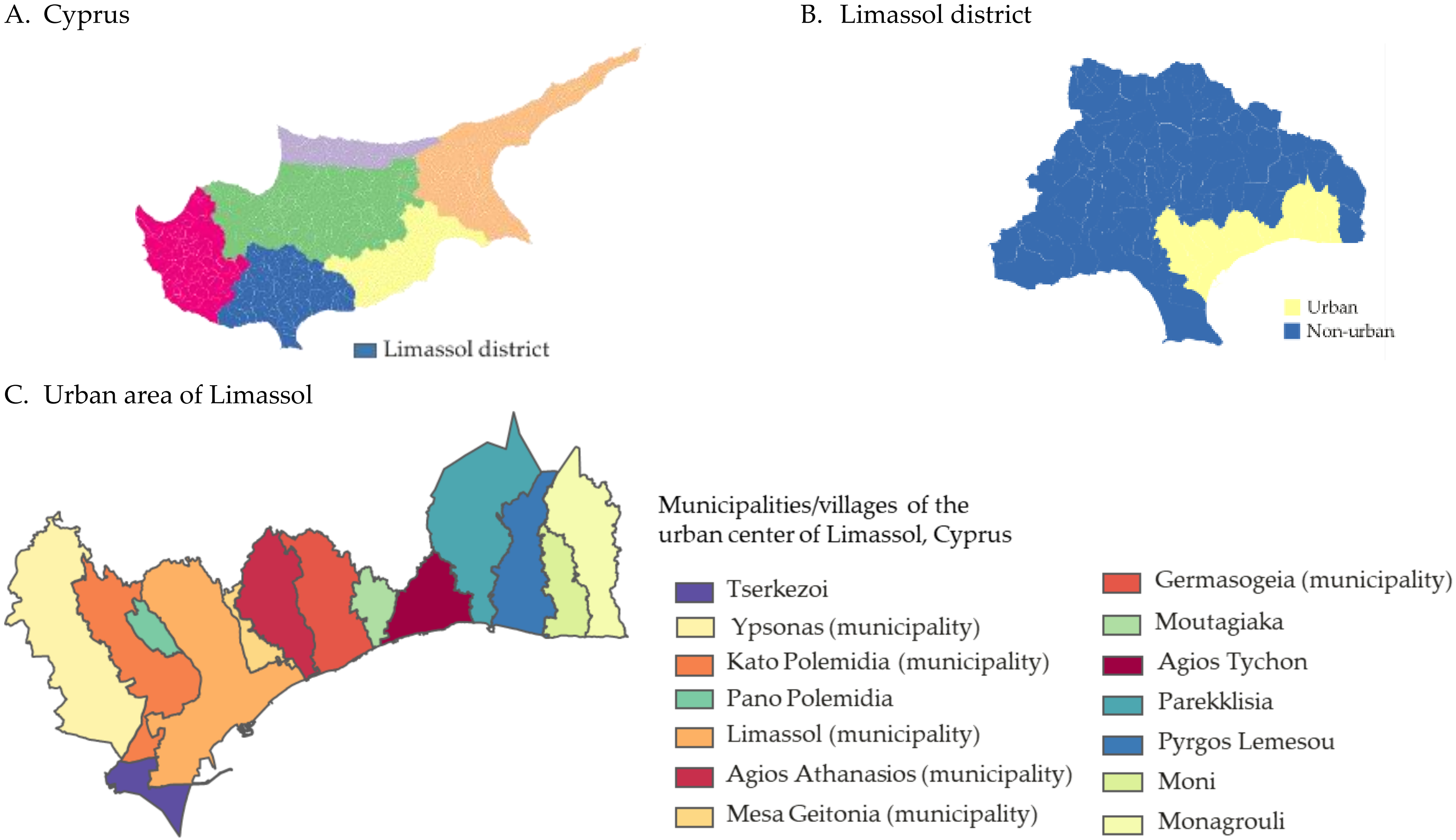


Figure 1.2 Maps of: (A) Cyprus, (B) the district of Limassol, and (C) the urban area of Limassol. The maps were created using shapefiles retrieved from the Open Data portal of the Government of Cyprus (2018).

1.4 Aims and objectives

Having initially defined the urban exposome in a rather simple manner, the aim of the present study was to further refine the definition and combine it with a proof-of-concept study on which focuses on the assessment of the urban exposome of the cities of Cyprus through a multidisciplinary approach. Thus, the specific study objectives were:

- To define the urban exposome, and
- To present the application of the urban exposome study framework using primary and secondary data using the Cypriot city of Limassol as the study setting.

2 The framework of the urban exposome: definition and application of the exposome concept in urban studies

Xanthi D. Andrianou[1], Konstantinos C. Makris[1]

[1] Cyprus International Institute for Environmental and Public Health, Cyprus University of Technology, Limassol, Cyprus

Science of Total Environemnt, 2018; 636:963-967. doi: 10.1016/j.scitotenv.2018.04.329

Abstract

Horizontal challenges, such as climate change, 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 cities 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 applications.

The urban exposome can be defined as the temporal-, and spatial-based continuous 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 population, 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 registry, including city infrastructure data; and (iii) a population survey and biomonitoring study. Continuous assessment of environmental and health indicators which are routinely collected, and the incorporation of primary data from population studies, will allow timely identification of within-city health and environmental disparities which can then, inform policy and public health interventions. The urban exposome could facilitate evidence-based public health response through timely identification of small-area disparities within cities and offer researchers, policy-makers, and citizens with effective tools to address the societal needs of large urban centers.

2.1 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 (1). The current "urban life context", including urbanicity, urbanization and all issues pertaining to urban life under the scope of sustainable development are not one-dimensional (13,14,36). Thus, attempts to define cities by the population size fall short of addressing their complexity. Cities are multi-dimensional 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) (11,12,16,17).

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 exposome, i.e., the totality of exposures throughout lifetime that has recently emerged within the field of environmental health sciences (29). 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 a unifying and global framework to researchers, stakeholders, and decision-makers to holistically and comprehensively approach the multi-dimensionality 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.

2.2 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 (29). Since then, the human exposome concept has been extended and enriched to include (sub)entities such as the indoor exposome (37), the eco-exposome (38), the systems biology-based adverse outcome pathways exposome (39) and the most recent pollutome defined as the totality of all forms of pollution that have the potential to harm human health (40). The urban exposome could be in one view the sum of exposures that are related to life in the city (41). 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 (Figure 2.1), 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).

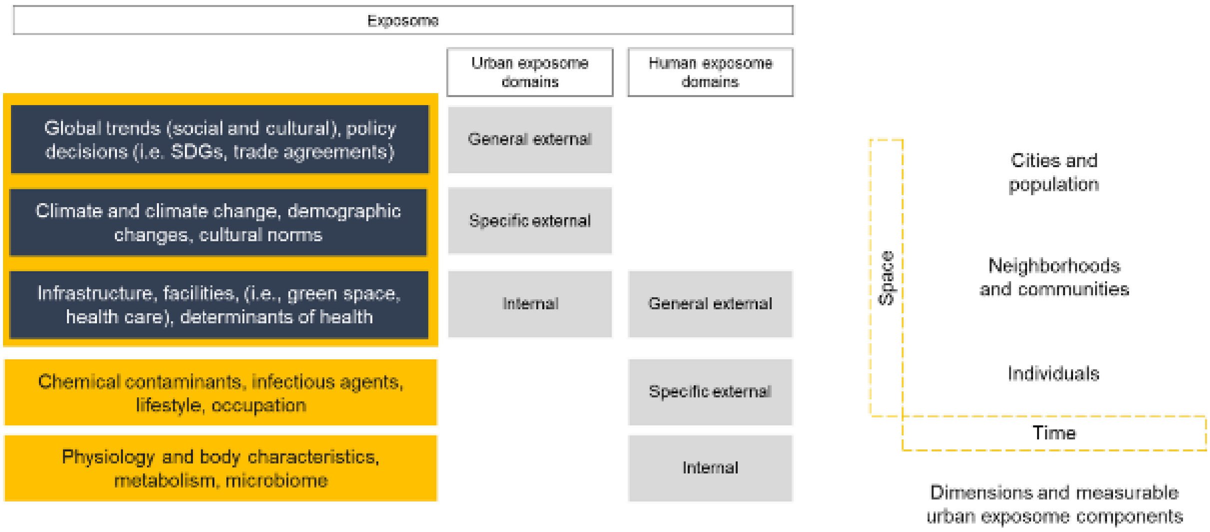


Figure 2.1 The continuum of urban exposome – human exposome. Neighborhoods and individuals, cities and population are the measurable components of the urban-, and human-exposomes, integrating assessments at the local (urban)- and personal-level.

Within this context there is a natural continuum between the urban exposome and the human exposome (Figure 2.1). 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 (39), while the eco-exposome concept was designed to include broader ecological issues in the human exposome agenda (38). 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 in the USA, such as the National Institutes of Health (internal domain of the exposome) and the National Science

Foundation (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 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 (42–44)). In Japan, the exposome concept is integrated in the Japan Environment and Children's study (45,46).

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 (Figure 2.1): "*the temporal, and spatial continuous 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 (Figure 2.1). 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 origin (one example can be the "urban agendas" of the UN or those of the European Union). At the same time, they often have to harmonize 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 the 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 to address health and environmental issues.

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 (8). The city of Limassol (~200000 inhabitants in total) is the second largest urban center of Cyprus defined as a medium-sized city (100000-250000 population) according to the EU/OECD criteria (4,9). 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 (Figure 2.2). More specifically, the external urban exposome domain (general and specific) were 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 survey and biomonitoring study within the Municipality of Limassol. The study was approved by the Cyprus National Bioethics Committee. For the population survey 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 in the different quarters. 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 (Figure 2.2). 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.

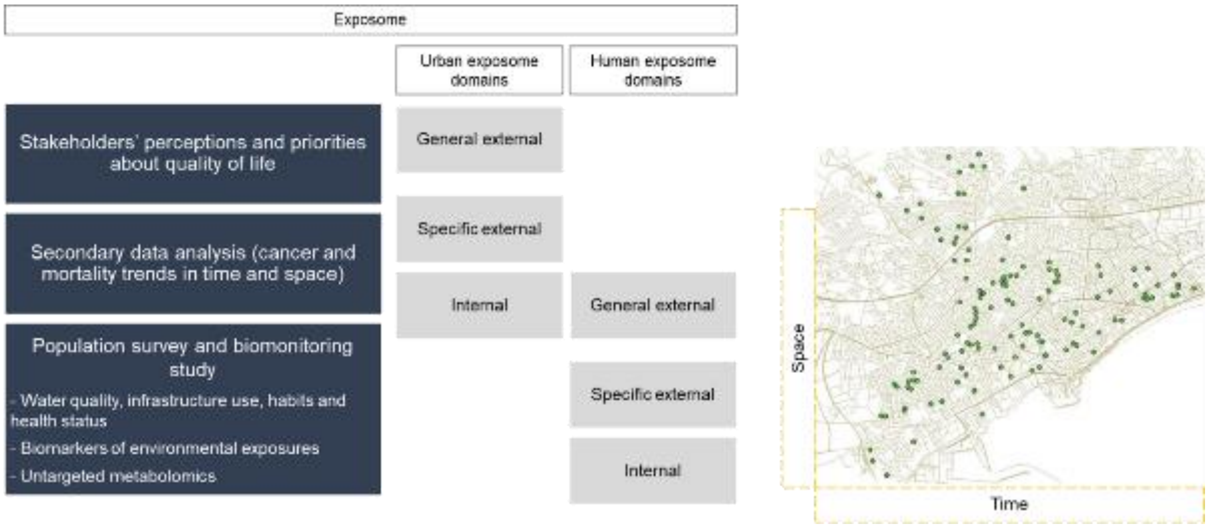


Figure 2.2 Schematic depiction of the application of the urban exposome concept for the municipality of Limassol, Cyprus. The map shows the distribution of the houses visited within the limits of the Limassol Municipality for the population survey and the biomonitoring study.

From the combination of the results from the secondary data analysis, and the population and 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 2.1). The stakeholders' perceptions will be also incorporated in the qualitative assessment of the results 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 be 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 2.1 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	

2.3 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 and urban design and planning challenges and, thus, by informing cost-effective public health interventions (47,48). 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) on health outcomes or determinants of health with cross-sectional studies or cohorts that assess environmental/lifestyle/behavior spatiotemporal exposures (i.e. biomonitoring and targeted/untargeted –omics studies) (22).

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 (Figure 2.1). The importance of the urban environment is acknowledged in the human exposome definition by being part of the general external domain (29), while a few studies have already assessed the human exposome for residents in urban settings (49).

2.4 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 to 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.

3 Application of the urban exposome framework using drinking water and quality of life indicators: a proof-of-concept study in Limassol, Cyprus

Xanthi D. Andrianou[1], Chava van der Lek[1,2], Pantelis Charisiadis[1], Solomon Ioannou[1], Kalliopi N. Fotopoulou[1], Zoe Papapanagiotou[3], George Botsaris[3], Carijn Beumer[2], Konstantinos C. Makris[1]

[1] Cyprus International Institute for Environmental and Public Health, Cyprus University of Technology, Limassol, Cyprus
[2] Department of Health, Ethics and Society, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands
[3] Department of Agricultural Sciences, Biotechnology and Food Sciences, Cyprus University of Technology, Limassol, Cyprus

PeerJ. 2019; 7:e6851. doi: 10.7717/peerj.6851.

Abstract

Cities face rapid changes leading to increasing inequalities and emerging public health issues that require cost-effective interventions. The urban exposome concept refers to the continuous monitoring of urban environmental and health indicators using the city and smaller inter-city areas as measurement units in an interdisciplinary approach that combines qualitative and quantitative methods from social sciences, to epidemiology and exposure assessment.

In this proof of concept study, drinking water and quality of life indicators were described as part of the development of the urban exposome of Limassol (Cyprus) and were combined with agnostic environment-wide association analysis (EWAS). This study was conducted as a two-part project with a qualitative part assessing the perceptions of city stakeholders, and quantitative part using a cross-sectional study design (an urban population study). We mapped the water quality parameters and participants' opinions on city life (i.e. neighborhood life, health care and green space access) using quarters (small administrative areas) as the reference unit of the city. In an exploratory, agnostic, environment-wide association study analysis, we used all variables (questionnaire responses and water quality metrics) to describe correlations between them.

Overall, urban drinking-water quality using conventional indicators of chemical (disinfection byproducts-trihalomethanes) and microbial (coliforms, E. coli, and Enterococci) quality did not raise particular concerns. The general health and chronic health status of the urban participants were significantly (FDR corrected $p\text{-value}<0.1$) associated with different health conditions such as hypertension and asthma, as well as having financial issues in access to dental care. Additionally, correlations between trihalomethanes exposures and participant behavioral characteristics (e.g. household cleaning, drinking water habits) were documented.

This proof-of-concept study showed the potential of using integrative approaches to develop urban exposomic profiles and identifying within-city differences in environmental and health indicators. The characterization of the urban exposome of Limassol will be expanded via the inclusion of biomonitoring tools and untargeted metabolomics.

3.1 Introduction

The definition of the exposome in 2005 by Dr. Wild introduced a paradigm in environmental and population health research, which promotes studies that either encompass simultaneous assessment of multiple exposures of the general population or focus on specific time windows of susceptibility (i.e. pregnancy), to capture the totality of environmental/lifestyle/behavioral exposures (28,50–52). The definition of the exposome along with the advances in methodologies for high throughput analysis in shorter time has also redefined the study paradigm in environmental health (53). Thus, decoding the exposome will not benefit only environmental health, but it will lead to better understanding of disease development and progression and it will allow for comprehensive monitoring of environment-disease associations.

The exposome as a paradigm has fostered innovation in exposure assessment. It allows for intra- and inter-disciplinary approaches in public health to become more widespread than they are now, as it is indicated by the number of "exposomes" that have been defined to address different totalities and with different units of reference (37–39).

Cities are dynamic and complex systems that become the future focus of public health systems, because they currently host more than half of the global population and generate >80% of the global GDP (54,55). Using terminology similar to the one used for the human exposome, the urban exposome extends the utility of the human exposome, and it is defined as the totality of indicators (quantitative or qualitative) that shape the quality of life and health of urban populations (56). Monitoring of these indicators that can be either external or internal city parameters, is not merely the sum of individual human exposures, but places cities and their smaller areas in the center of an urban-oriented study framework, previously defined as the urban exposome framework (56). Following the urban exposome approach, the quality of life in urban centers is concurrently assessed together with other indicators, such as water quality, or prevalence/incidence of communicable and non-communicable diseases using interdisciplinary methodology. This framework expands previous study approaches where the urban exposome is defined as the sum of exposures in cities (41,57), and proposes a more interdisciplinary and holistic approach to assess health determinants of the general population.

To present the first application of the urban exposome framework, we used drinking-water quality metrics and quality of life indicators. As more people nowadays live in cities, providing easy access to safe and affordable water, as well as eliminating possible within-city health and societal disparities becomes more challenging. Besides the technical provisions to maintain water of good quality, the uninterrupted availability of water becomes an issue due to climate change manifestations, especially in areas that are already or expected to be hit harder by extended droughts and other related meteorological phenomena. Europe, overall, is expected to face increases both in the extent of geographical areas affected by droughts and in the duration of such climatic events (58). Especially, cities located in Southeast Europe and the Mediterranean region are predicted to face challenges in maintaining water availability and adequate water quality in the future (58). Therefore, cities and their smaller areas (i.e. neighborhoods, or other small administrative areas) are warranted to address water-related issues, such as water demand, safety, security and quality issues, while tackling societal inequalities and health disparities. In this context, the concept and the study framework of the urban exposome can be introduced to help scientists and policy makers in the systematic spatio-temporal surveillance and monitoring of a city's heterogeneous health profile.

The urban exposome study framework has a hypothesis-generating scope and goes beyond the classical one exposure-one outcome urban studies. Therefore, our aim was to present a proof-of-concept study using the urban exposome framework to monitor urban health dynamics. The study setting was at Limassol, Cyprus. The urban center of Limassol ("city of Limassol") is defined as a medium-sized city (~200,000 inhabitants according to the 2011 Population Census of Cyprus) (8,59) and it consists of the municipality of Limassol and neighboring municipalities. The city of Limassol currently faces rapid economic development with half of the urban population of the city residing within the municipality of Limassol (~110,000 inhabitants).

The specific objective of this analysis was to describe chemical and microbiological parameters of drinking water quality, coupled with quality of life indicators as measured in the Municipality of Limassol, in summer 2017. In this approach we used quarters which are the smallest within-municipality administrative areas, as the unit of reference. To complete the urban exposome of Limassol to the extent possible, additional analysis of routine surveillance data is necessary but it goes beyond the scope of the present analysis.

3.2 Materials and methods

3.2.1 Application of the urban exposome in the municipality of Limassol, Cyprus

We have previously described the urban exposome as all indicators that need to be continuously monitored for the assessment of city health (56). Within the framework of the urban exposome, external to the city parameters that cannot be influenced by the city itself can be either general (e.g. global trends and policy decisions) or more specific (e.g. climate change impacts, demographic changes, culture). It follows that internal parameters are those that are integral to the city, such as infrastructure, built/neighborhood environment and determinants of population health (e.g. socioeconomic factors). Either external or internal to the city parameters described before can influence and be influenced by each other both horizontally (within each domain) and/or vertically (between domains). A study was conducted in the summer of 2017 to describe the water and quality of life aspects of the urban exposome of Limassol, following an integrative and interdisciplinary approach (Figure 3.1). This approach included the following parts:

- A perceptions survey with a mixed-methods approach to evaluate the perceptions of stakeholders (i.e. citizens and municipality officials) about the quality of life and certain environmental risks (e.g. chemical and microbial risks in drinking-water) in the city.

- A cross-sectional urban population study with a short questionnaire and collection of tap water samples from households distributed in the quarters of the municipality of Limassol to evaluate water quality indicators and citizens' attitudes about the environment, quality of life in the city and self-reported health status.

In this analysis, we focus on the general external urban exposome through the perceptions study and the internal urban exposome through the inclusion of drinking water chemical/microbiological indicators, responses on neighborhood's quality of life and participant characteristics (Figure 3.1). Using the human exposome framework as a reference, this study also explored the human exposome domains, i.e., the general external domain (perceptions study), the specific external domain (drinking water and quality of life indicators) and the internal domain (participant characteristics) (Figure 3.1).

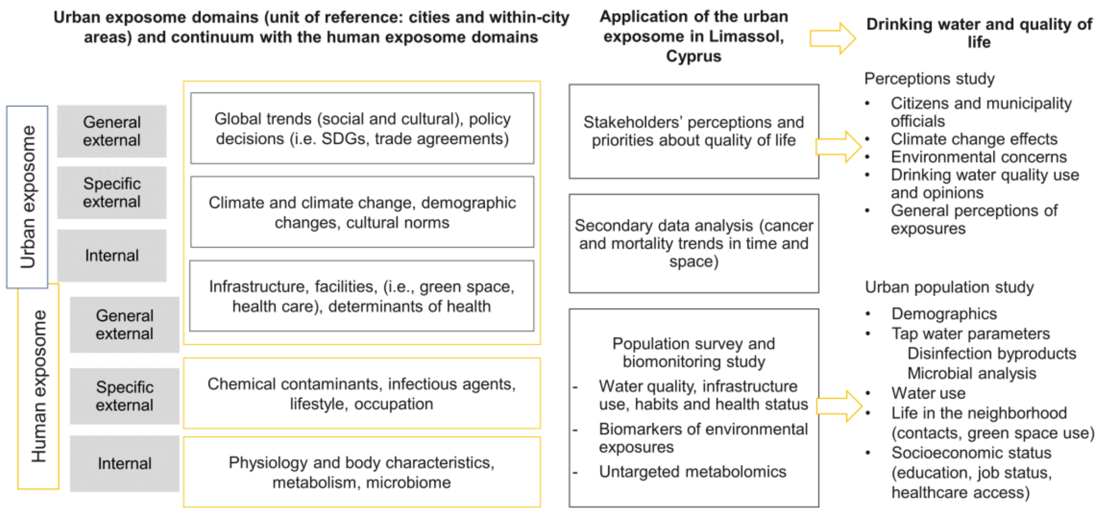


Figure 3.1 Urban exposome-human exposome continuum, and the practical application of the urban exposome framework in the urban setting of Limassol city.

3.2.2 Perceptions study

For the perceptions study, the urban community-based participatory research methodology was applied to actively engage the municipality of Limassol officers and citizens (identified as community stakeholders) about urban health issues (60). The stakeholders' perceptions were assessed using a mixed methods approach. Face-to-face interviews were conducted, and short questionnaires were administered to the municipality officials (i.e. technical officers from the municipality of Limassol and neighboring municipalities). The questions asked during the face-to-face interviews and the questionnaire for the municipality officers focused on the identification of trends shaping the city of Limassol, assessment of the climate change manifestations and their impact, scoring of environmental health concerns, an assessment of what was believed to be the citizens' major health threats with regards to urban life, and perspectives about future opportunities to improve health in the city. For the citizens' perceptions, an online anonymous questionnaire initially distributed via email among staff at the Cyprus University of Technology campus that is in the municipality of Limassol, and then to the general public via mailing lists maintained at the Cyprus International Institute for Environmental and Public Health for the dissemination of newsletters, and social media (Facebook). This online questionnaire included various questions on climate change perceptions, environmental concerns in general, health perceptions and perceptions about drinking-water quality.

3.2.3 Urban population study

A cross-sectional population study was set up in the municipality of Limassol, Cyprus. Participants (n=132) were recruited after being informed about the study through phone calls made in collaboration with the Municipality of Limassol, in the summer of 2017 from all quarters of the municipality, following the 2011 Census population distribution (Table S3. 1). For this study, we also collected urine samples which will be used in the biomonitoring part (measurement of chemical exposures in urine) of the assessment of the urban exposome (not included in this analysis). Thus, sample size estimations were based on the assumption that a total of 120 participants randomly selected from the whole municipality would allow us to evaluate the baseline levels of environmental exposures, as according to previous biomonitoring studies a sample of at least 120 randomly selected participants is adequate to capture the 95th percentile of the population levels (61).

Quarters that are small in area and population, with one participant, were merged with neighboring ones and three quarters located along the beachfront, each having one participant were also merged together (Figure S1). To ensure high spatial coverage only one participant was recruited per street.

Tap water samples were collected from all participating households and *in situ* measurements of free chlorine were taken during house visits. The drinking water indicators that were assessed were trihalomethanes (THM) along with the free chlorine, from the category of the chemical parameters, and total coliforms, *E. coli, Enterococcus* spp., *Pseudomonas aeruginosa*, and total viable counts (TVC) at 22 °C and 37 °C, from the category of the microbial parameters. These indicators (besides free chlorine) are also routinely monitored in the European Union (62) . All participants were asked to complete a questionnaire that included, among others, questions about life in their neighborhoods, self-reported health status and drinking water habits. The questionnaire was adapted by the validated urban health and the European Health Survey questionnaires (63–65). From this questionnaire the quality of life indicators (e.g. access to health care services, life in the neighborhood and use of green spaces) were assessed.

The study was approved by the National Bioethics Committee of Cyprus (decision number: 2017/23). All participants read and signed the informed consent documents before data collection. The STROBE statement is available in the supplementary material (66).

3.2.4 Water sampling and analysis

The main faucet used for satisfying the water needs of the participating household was selected for drinking-water sampling. The tap water faucet was externally cleaned with ethanol prior to sample collection, and the water was then left to flow freely for ~30 seconds. Tap water samples for trihalomethanes (THM) analysis were collected in falcon containers with oxidation preservative mixture, while the tap water samples used in the microbial analysis were collected in sterile polypropylene vials. The THM analysis was conducted according to the previously published methods by Charisiadis et al. (67). All four THM species were measured in the collected tap water samples from the participating households: chloroform (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform (TBM). The limits of detection (LOD) were 0.13μg/L for TCM and DBCM, and 0.11μg/L for BDCM and TBM.

Microbial analysis was conducted after the water was cultured onto selective media for the detection and enumeration of total coliforms, *E. coli*, *Enterococcus* spp., *Pseudomonas aeruginosa*, and total viable counts (TVC) at 22 °C and 37 °C. The methods used for the microbial analysis are presented in Supplementary Methods document.

All water samples were collected from the main faucet of the household used to satisfy their potable needs and it was directly connected to the municipality's water supply.

Residual chlorine was measured with a portable photometer (MaxiDirect, Lovibond, Amesbury, England) in water directly collected from the tap using the DPD (N,N-diethyl-p-phenylenediamine) method.

3.3 Statistical analysis for the urban population study

3.3.1 Descriptive analysis of the questionnaire responses

Descriptive statistics (i.e. means and standard deviation for the continuous variables, and frequencies and percentage by category for the categorical variables) were calculated for the responses to the questionnaire. The descriptives were grouped by category of question (i.e. demographics and other background characteristics, drinking water habits and cleaning activities, lifestyle and behavioral indicators, healthcare services access, health status, life in the neighborhood) for the complete study population (n=132).

3.3.2 Descriptive analysis of the water indicators and water habits

Descriptive statistics for the drinking-water THM and microbial counts were separately presented for the samples collected directly from the tap when no filter was attached (n=119) from those 13 samples that were collected with a filter present. When THM values were below the LOD (n=4 for TCM and n=1 for TBM), they were imputed to LOD/2. The sum of all THM species (total THM) and the sum of the brominated species (BrTHM; i.e.

BDCM, DBCM, and TBM) were calculated. For the statistical analysis of the microbial water quality we considered the presence or absence of colonies for *E. coli* and *Enterococcus spp.* instead of the absolute count number (62). For the coliforms, *Pseudomonas aeruginosa*, and TVC at 22 and 37 °C presence or absence, the percentage of samples with detected colonies were described. Specifically, for TVC at 22 and 37 °C a smaller number of samples was analyzed (n=95) due to external contamination. For the THM concentrations the descriptives included: mean, standard deviation (sd), median and percentiles, i.e. 25^{th}, 95^{th} percentiles, and the range, i.e. min and max, while for the microbial analysis the frequency of samples with at least one colony forming unit (CFU) (and the percentage) was calculated. Water samples collected from households (n=13) having permanently connected point of use filters in the main faucet were excluded from the main statistical analysis.

The results of the THM and microbial analyses were presented separately for the total THM, the *E. coli* and the *Enterococci* spp., as they are considered of higher priority compared to the single THM species and the other microbial indicators (e.g., coliforms).

3.3.3 Mapping of the water and the quality of life indicators

To evaluate how indicators pertaining to the water and quality of life are distributed in different quarters of Limassol, we mapped a selection of urban indicators by quarter. For the water quality indicators, the median levels of total THM, free chlorine, BrTHM per quarter were mapped, as well as, the percentage of samples with detectable levels of coliforms and TVC. From the urban questionnaire data, all indicators were mapped. However, for brevity, we present in the maps and discuss select indicators per category for the following: (i) issues on access to health care services due to delays and financial constraints, (ii) life in the neighborhood, and (iii) two indicators from the category on access to green spaces to illustrate potential differences between quarters.

3.3.4 Exploratory environment-wide association study (EWAS)

We performed an exploratory environment-wide association study (EWAS) to agnostically synthesize knowledge and concurrently investigate possible associations of the measured water quality indicators and questionnaire-based socioeconomic, lifestyle and behavioral factors. This exercise helped us to demonstrate how an EWAS approach can be incorporated in analyses that are based upon the urban exposome framework. The outcomes used in the EWAS analysis were three self-reported health status outcomes: (i) general health status, (ii) diagnosed with any chronic disease, and (iii) diagnosed with any disease in the past year ("any disease the past year", i.e. asthma, diabetes, allergies, hypertension, cardiovascular or respiratory illnesses, depression, cancer, musculoskeletal problems) (68). The EWAS analysis included a correlation matrix between all variables, regression analysis, and a multi-omics-based approach to describe correlations between all the variables measured accounting for specific health outcomes.

The variables included in the EWAS approach were divided in the following "blocks/groups" to reflect different parameters of the human exposome, since the analysis was performed at the individual level:

- Block/group 1 (specific external domain): water THM levels, free chlorine
- Block/group 2 (general external and internal domain): drinking water habits (e.g., number of glasses of water consumed by source)
- Block/group 3 (general external and internal domain): household cleaning activities (e.g. dishwashing, mopping, bathroom cleaning)
- Block/group 4 (general external domain): neighborhood quality of life (variables of "highest consensus": heath care access, life in the neighborhood and green urban spaces)
- Block/group 5 (internal domain): participant characteristics (e.g., age, sex, BMI)
- Block/group 6 (internal domain): self-reported diseases in the past year (e.g. asthma, diabetes, allergies, hypertension, cardiovascular or respiratory illnesses, depression, cancer, or musculoskeletal problems).

In all categorical variables the "I don't know/I don't want to answer" responses were re-coded to "missing". Then, scores were added per category (presented in Table S2) and used in statistical analysis when categorical variables could not be used (e.g. correlations).

In the preliminary correlation analysis, all variables (including the three outcomes) were used as continuous and the Spearman correlation coefficient was calculated without any transformations. The results were visualized with a correlation plot. Then, regression models were fitted. The variable for the general health status was used as continuous in linear regression whereas responses for self-reported chronic disease and any disease the past year were used as binary variables in logistic regression. The regression models were repeated after adjusting for age and sex. The continuous predictors were scaled and centered in all regression models. The p-values of all model parameters that were used for inference (i.e. excluding the intercept for the univariable models and excluding the intercept, age, and sex coefficients from the adjusted models) were summarized and corrected for Benjamini-Hoechberg false discovery rate (FDR). Only parameters with an FDR-corrected p-value <0.10 separately applied to the univariate (n=129 tests) and the adjusted models (n=123 tests) were considered statistically significant.

In the last part of the EWAS analysis, we followed an approach used in multi-omics studies where the variables are grouped and partial least squared discriminatory analysis (block PLS-DA) is conducted to identify possible correlations between the variables of the different blocks accounting for an outcome (69). In this analysis, the predictor variables were used as continuous and all outcomes were used as categorical. The correlations between the predictor variables in blocks were presented in circular plots (circo plots) where positive and negative Pearson pairwise connections are shown in the circle and lines indicate the levels of each variable within each outcome category.

All analyses (regressions and block PLS-DA) were performed for the three outcomes using all the blocks/groups as predictors except for the analysis for the outcome "any disease the past year". This variable was created as the summary of the variables of block/group 6 (self-reported diseases the past year). Thus, in this analysis, the separate diseases of block/group 6 were not included due to their association with the outcome of "any disease the past year".

All analyses were conducted in R 3.5.1 with RStudio 1.1.423 (70,71). Input data, the output, scripts and the questionnaires are available in the supplementary material. The packages used in the analysis are listed in Table S3. 3.

3.4 Results

3.4.1 Perceptions study results

Approximately, 10 municipality technical officers were approached for interviews and to fill in the municipality questionnaire. In total, five interviews were conducted, and six questionnaires were administered. The importance of climate change and its effects was pointed out by all municipality officers during the face-to-face interviews and within the questionnaire responses. In rating the environmental concerns (1 for very low and 5 for very high concern), water quality had the lowest score with increasing order of scoring for soil contamination<waste<general chemical exposures<noise<air pollution.

In total, 181 participants responded to the online questionnaire that was addressed to citizens and 134 (74%) filled in the complete questionnaire. Ninety-one of the respondents reported living in Limassol (35% males and 65% females) with a mean age of 35 years old [range:18-77 years old]. The majority (81%) was born on Cyprus, and 13% were born in another EU country, the rest (6%) were born in a non-EU country. As expected from the distribution of the questionnaire among the staff of the university, most of the respondents (84%) were highly educated holding at least a Bachelor's degree. Approximately half of the respondents were married (46%) with children (47%).

Residents of urban Limassol (n=91) were mostly concerned about being severely exposed to air pollution and noise (Table 3.1). Water quality ranked low while air pollution and noise ranked high in the "severely exposed" category among all environmental exposures. Approximately 30% of the respondents reported that they were not exposed to water pollution or soil contamination, but at the same time an equally high proportion of respondents reported "don't know", suggesting inadequate knowledge about the drinking-water or soil quality in their city. With regards to water quality, 81% reported worrying about chemical exposures, and 41% reported they were exposed to chemicals daily.

Among all urban respondents, only ~30% reported the consumption of tap water, while 32% reported treating the water before consumption (filtering or cooking), and 39% mentioned not drinking the tap water at all. Also, the "highest in importance" concerns of the citizens about tap water quality were those associated with either chemicals (47%), or microbes (37%) and much less concern was expressed about the taste (10%).

Table 3.1 Perceptions about environmental exposures among the respondents from the city of Limassol (n = 91).

	Severely exposed	Somewhat exposed	Not exposed	Don't know
Noise (traffic, airplanes, factories, neighbours, animals, restaurants/bars/clubs)	38 (42%)	48 (53%)	5 (5%)	0 (0%)
Air pollution (fine dust, grime, fume, ozone)	40 (44%)	40 (44%)	10 (11%)	1 (1%)
Bad smells (industry, agriculture, waste)	15 (17%)	35 (38%)	39 (43%)	2 (2%)
Water pollution (microbes/chemicals in drinking water)	8 (9%)	22 (24%)	31 (34%)	30 (33%)
Soil contamination (eg., chemical waste dump)	5 (5%)	15 (17%)	32 (35%)	39 (43%)

3.4.2 Population study results

Background information and opinions

In total, 132 residents of the Limassol municipality answered the questionnaire and agreed to water collection from their households' main tap. The distribution of the study participants by quarter and the population can be found Table S3. 1. The mean age was 45.6 years and the majority were females (62.1%). Most of the participants were born in Cyprus [n=114 (86.4%)] living there for all their lives (Table 3.2, Table S3. 4).

Table 3.2 Background characteristics of for the urban population study conducted in Limassol, Cyprus.

	Overall (n=132)
Age (mean (sd))	45.6 (13.2)
Sex (%)	
Females	82 (62.1)
Males	50 (37.9)
BMI (mean (sd))	26.25 (5.06)
Marital Status (%)	
Cohabitating	8 (6.1)
Divorced	15 (11.4)
Married	82 (62.1)
Single	26 (19.7)
Widowed	1 (0.8)
Education (%)	
Primary school	2 (1.5)
Gymnasium	2 (1.5)
High School/Technical School	28 (21.4)
Non-university tertiary education	16 (12.2)
Post-secondary education	6 (4.6)
Bachelor's degree (BSc/BA)	45 (34.4)
Master's degree or doctorate (MSc/MA, PhD)	32 (24.5)

Most of the study participants reported being in very good or good health condition (46% and 43%, respectively). However, 21% reported having a chronic disease and 57% reported at least one of the following health conditions during the past year: asthma, cardiovascular diseases, hypertension, diabetes, liver conditions, cancer, depression, or musculoskeletal problems (Table 3.3). With regards to access to health care, the main questions were about delays due to lack of transportation or long waiting lists (Table S3. 4). Lack of transportation did not seem to be a major constraint to access health care centers among those that opted to answer; however, long waiting lists were reported by 11%. To the question about financial constraints for health care access, delays in dental care were most frequently mentioned (14%). Most participants (64%) reported living close to green spaces, but a total of 63% also reported that these green spaces were not well-maintained and there was a consensus for not using them. A summary of the responses about health care access, lifestyle, the quality of life in the neighborhood and other urban topics can be found in Table S3. 5.

Table 3.3 Health status indicators assessed through the questionnaire among the 132 participants of the urban population study (Limassol, Cyprus).

		Overall (n=132)
General health assessment (%)	**Very good**	61 (46.2)
	Good	57 (43.2)
	So and so	12 (9.1)
	Bad	1 (0.8)
	Very bad	1 (0.8)
Chronic disease (%)	**Do not know**	5 (3.8)
	I don't want to answer	3 (2.3)
	No	97 (73.5)
	Yes	27 (20.5)
Any disease in the past year (%)	**No**	57 (43.2)
	Yes	75 (56.8)

Water quality indicators assessment of drinking water habits

The main chemical water quality indicators assessed were THM. Only 2% of the households' tap water exceeded the THM parametric value (100μg/L). Results conforming with the parametric values were also obtained for the microbial indicators monitored, i.e. *E.coli* and *Enterococci* spp. All samples were within the parametric values (0 CFU per 100mL), except for one household where Enterococci colonies were detected. Total coliforms were detected in 28 of the 132 households and *Pseudomonas aeruginosa* counts were detected in 5 out of the 132 households (Table 3.4 and Table 3.5).

Table 3.4 Chemical drinking water parameters analyzed in water samples collected in Limassol, Cyprus (2017) for n = 119 samples collected from faucets without point of use filter and for n = 13 samples collected from faucets with a point of use filter that could not be removed.

	n	Mean	Standard deviation	Median	25th percentile	75th percentile	Min	Max
Samples collected from faucets without filter								
Regulated chemical parameters								
Total THMs (μg/L)	119	30.5	32.22	15.2	6.99	50.83	3.17	210.5
Non-regulated chemical parameters								
Free chlorine (mg/L)	119	0.2	0.16	0.2	0.05	0.32	ND	0.7
TCM (μg/L)	119	2.1	2.24	1	0.47	3.16	0.07	13.3
BDCM (μg/L)	119	4.9	5.45	2	0.95	7.32	0.91	30.9
DBCM (μg/L)	119	9.1	11.18	2.4	1.18	15.52	1.07	66.2
TBM (μg/L)	119	14.4	14.63	7.7	3.94	22.6	0.06	100.3
BrTHMs (μg/L)	119	28.4	30.24	13.5	6.22	46.94	3.10	197.3
Samples collected from faucets with filter								
	n	**Mean**	**Standard deviation**	**Median**	**25th percentile**	**75th percentile**	**Min**	**Max**
Regulated chemical parameters								
Total THMs (μg/L)	13	9.6	9.0	5.0	4.0	9.9	3.2	28.4
Non-regulated chemical parameters								
Free chlorine (mg/L)	13	0.1	0.1	0.1	0.0	0.1	ND	0.3
TCM (μg/L)	13	0.9	1.0	0.5	0.5	0.7	0.2	3.8
BDCM (μg/L)	13	1.7	1.7	1.0	0.9	1.1	0.9	5.8
DBCM (μg/L)	13	2.1	2.4	1.2	1.1	1.5	1.0	9.5
TBM (μg/L)	13	4.9	6.7	2.2	1.2	5.2	1.0	25.4
BrTHMs (μg/L)	13	8.7	8.5	4.7	3.5	9.4	2.9	28.0

Table 3.5 Microbial drinking water parameters analyzed in water samples collected in Limassol, Cyprus (2017) for n = 119 samples collected from faucets without point of use filter and for n = 13 samples collected from faucets with a point of use filter that could not be removed.

Samples collected from faucets without filter		
	n	**Samples with at least 1 CFU n (%)**
Regulated microbial parameters		
E. coli **(cfu per 100 mL)**	119	0 (0)
Enterococcus **spp. (cfu per 100 mL)**	119	1 (0.8)
Non-regulated microbial parameters		
Coliforms (per 100mL)	119	27 (22.7)
Pseudomonas aeruginosa **(per 100mL)**	119	5 (4.2)
TVC at 22C (per 1mL)	86	12 (14)
TVC at 37C (per 1mL)	86	30 (34.9)
Samples collected from faucets with filter		
	n	**Samples with at least 1 CFU n (%)**
Regulated microbial parameters		
E. coli **(cfu per 100 mL)**	13	0 (0)
Enterococcus **spp. (cfu per 100 mL)**	13	0 (0)
Non-regulated microbial parameters		
Coliforms (per 100mL)	13	1 (7.7)
Pseudomonas aeruginosa **(per 100mL)**	13	0 (0)
TVC at 22C (per 1mL)	7	1 (14.3)
TVC at 37C (per 1mL)	7	3 (42.9)

The drinking-water consumption habits reported by the urban participants similarly reflected what was already observed in the perceptions study (presented earlier) where only 30% reported consuming tap water and most participants reported a preference for The majority reported using tap water in general, however bottled water use was noted by most respondents. The more frequently reported single drinking water source was bottled water (30%) followed by tap water (22%). A comparable proportion of the participants reported the combined use of tap water and bottled water (Table 3.6). More than half of the study partipants reporting consuming less than one glass of water per day from the tap (median number of glasses consumed from tap was 1 glass/day) (Table 3.6).

Table 3.6 Self-reported choices of water sources by the study participants (n = 132) of the urban population study in Limassol, Cyprus.

Water sources	n (%)
Bottled water	40 (30.5)
Tap water	29 (22.1)
Water from vending machines	4 (3.1)
Spring water	3 (2.3)
Tap water and bottled water	37 (28.2)
Bottled water and spring water	3 (2.3)
Bottled water and water from vending machines	2 (1.5)
Tap water and other	2 (1.5)
Tap water and water from vending machines	2 (1.5)
Tap water and spring water	1 (0.8)
Any three sources (tap water, bottled, water from vending machines, spring water or other)	5 (3.8)

Number of glasses (about 250mL) per day by source	n	Mean	SD	Median
Tap water	130	2.52	3.6	0
Bottled water	130	3.83	4.2	2.2
Water from vending machines	130	0.54	2	0
Spring water	130	0.33	1.3	0
Other source	130	0.51	2.9	0

Mapping of urban indicators of water and quality of life

The measured water quality indicators in each household were aggregated and mapped by quarter. For the chemical water parameters, the mapped median total THM and the brominated species (BrTHM) by quarter showed similar patterns (Figure 3.2). As the BrTHM are a subset of the total THM, their median values by quarter were lower. The highest median THM values were observed in the quarters located between the beachfront and the northern quarter of Agia Fylaxi (near the center of the city). Mapping of free chlorine levels followed an opposite pattern to THM, i.e. higher levels of free chlorine in the seaside quarters and slightly higher in the northern quarter (being closer to the main water treatment plant). The maximum median value of total THM was 63μg/L and it was observed in the center of Limassol (quarter of Agios Georgios). In this quarter, the median free chlorine levels were below detection. The range of the median total THMs by quarter was 6-63μg/L for the small quarters in the beachfront and behind the city port and the quarter of Agios Georgios. The variability of the median free chlorine levels was smaller, ranging from below detection to 0.4mg/L in the quarters of Agia Zoni and Agia Trias (in the center and by the seafront, respectively). A map with the quarter names of municipality of Limassol is available in Supplementary Information (Figure S3. 1).

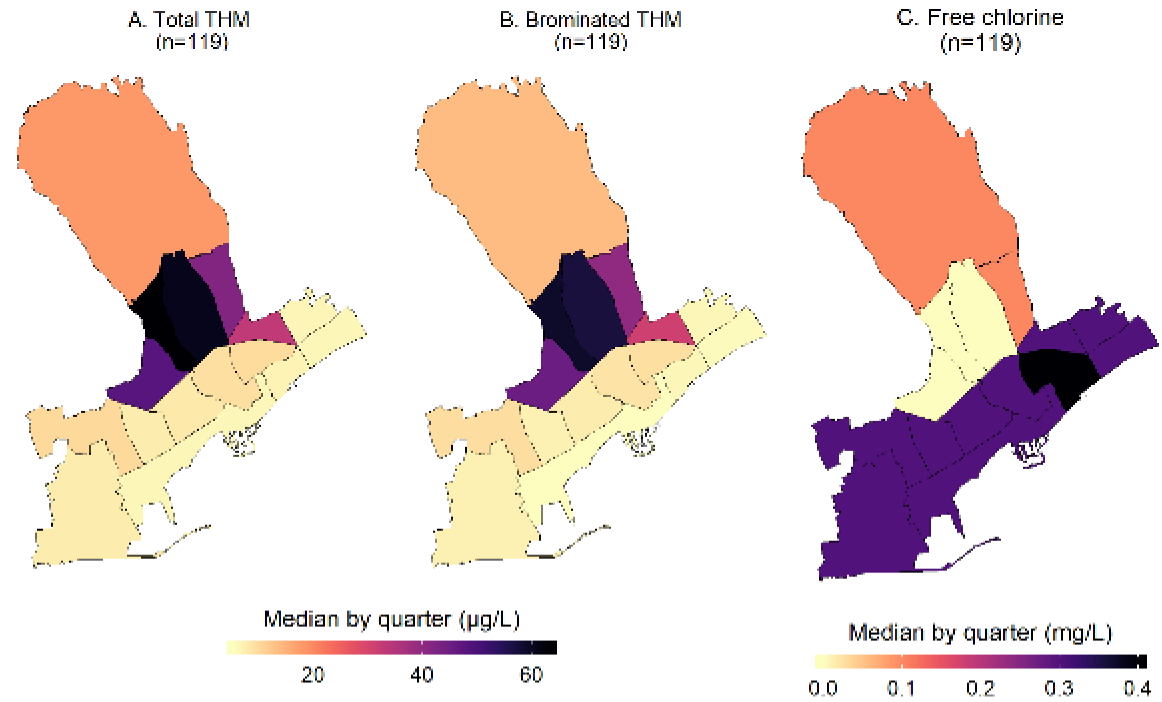


Figure 3.2 Maps of the median water total THM (A), BrTHM (B), and free chlorine (C) levels by quarter within the municipality of Limassol, Cyprus (2017).

With regards to the microbial parameters, as mentioned in the previous section, only one sample had detectable colonies of *Enterococcus spp*. while *E. coli* was not detected at all. Thus, we mapped only the percentage of samples found to be positive for coliforms or had detectable heterotrophic bacteria (TVC at 22 and 37C) (Figure 3.3). In a one quarter, two of the three samples analyzed were positive for coliforms and, therefore, it had the highest percentage of samples with colonies. This quarter was geographically located in the zone with the highest median chlorine levels (0.3 mg/L) (Figure 3.2, Figure 3.3).

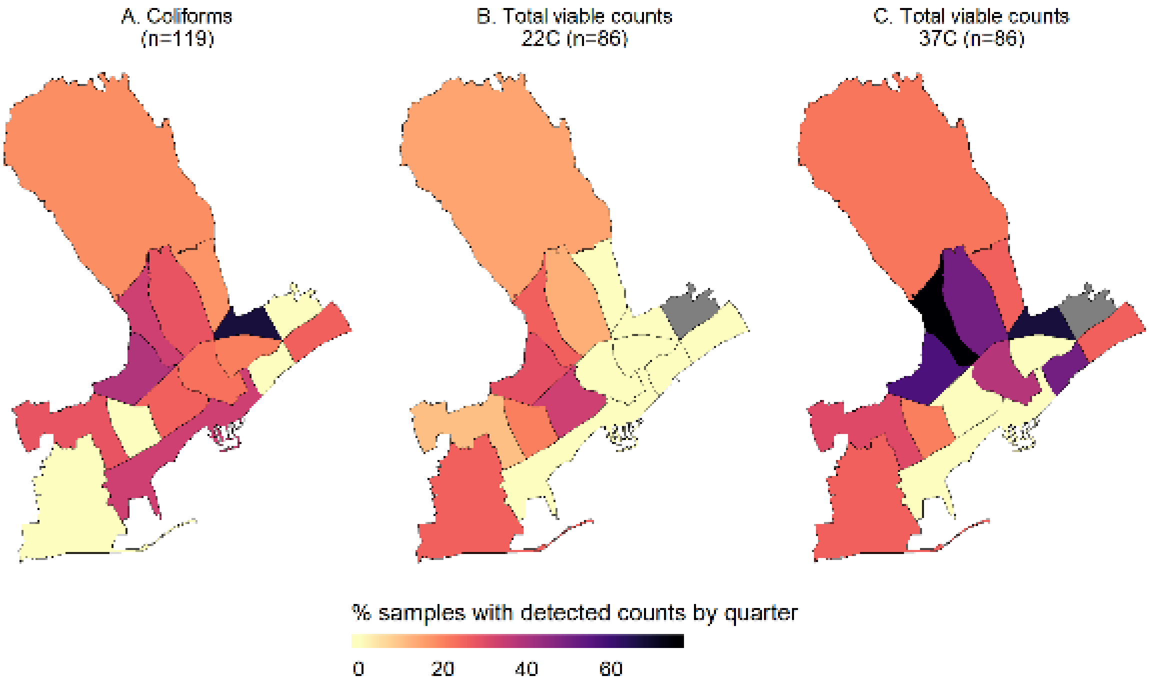


Figure 3.3 Maps of the percentage of samples with detectable counts of the monitored microbial parameters, i.e. Coliforms (A), and total viable counts at 22 (B) and 37C (C), by quarter within the municipality of Limassol, Cyprus (2017).

Description and mapping of access to health care services, life in the neighborhood and use of green spaces

With regards to access to health care, most participants reported having issues with two major parameters, i.e., long waiting lists and financial constraints to access dental care. From the respective maps (Figure 3.4), participants living in the quarters of Katholiki, Agia Trias, Omonoia and Agios Nektarios did not report any issues pertaining to access to health care. Whereas, other quarters such as Agios Ioannis/Arnaoutogeitonia, Agia Zoni and Agios Nikolaos were more consistently in the "mid-range" with 20% participants reporting issues for both indicators. With regards to the question about having someone in the neighborhood to ask for help in emergencies, overall, only 25/132 participants opted for the answers "I don't know" and "I disagree completely or probably" (Figure 3.5). However, responses of strong agreement ("I completely agree" vs all the other options from "I probably agree" to "I completely disagree") varied a lot across the quarters. For example, in Agios Spyridonas only 20% agreed that there is always someone to help them while in Agios Nikolaos 80% (Figure 3.5). With regards to proximity and use of green space, most participants from all quarters reported that they agree living near to green space but they do not use it for activities (Figure 3.6). This is evident in quarters by the seafront and the largest quarter of Agia Fylaxi/Panagia Evangelistria which is peripheral to the city the center and closer to less densely populated areas.

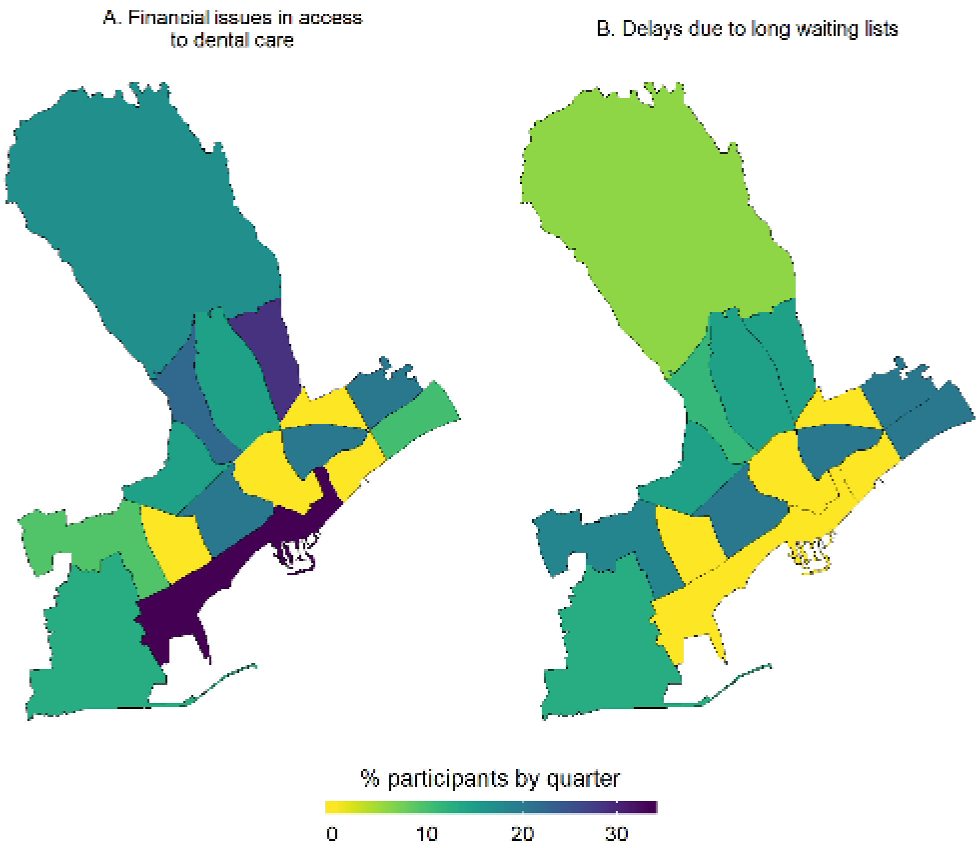


Figure 3.4 Percentage of study participants reporting constraints in access to health care, i.e. financial issue in access to dental care (A) and delays due to long waiting lists (B), by quarter of the Limassol municipality, Cyprus (2017).

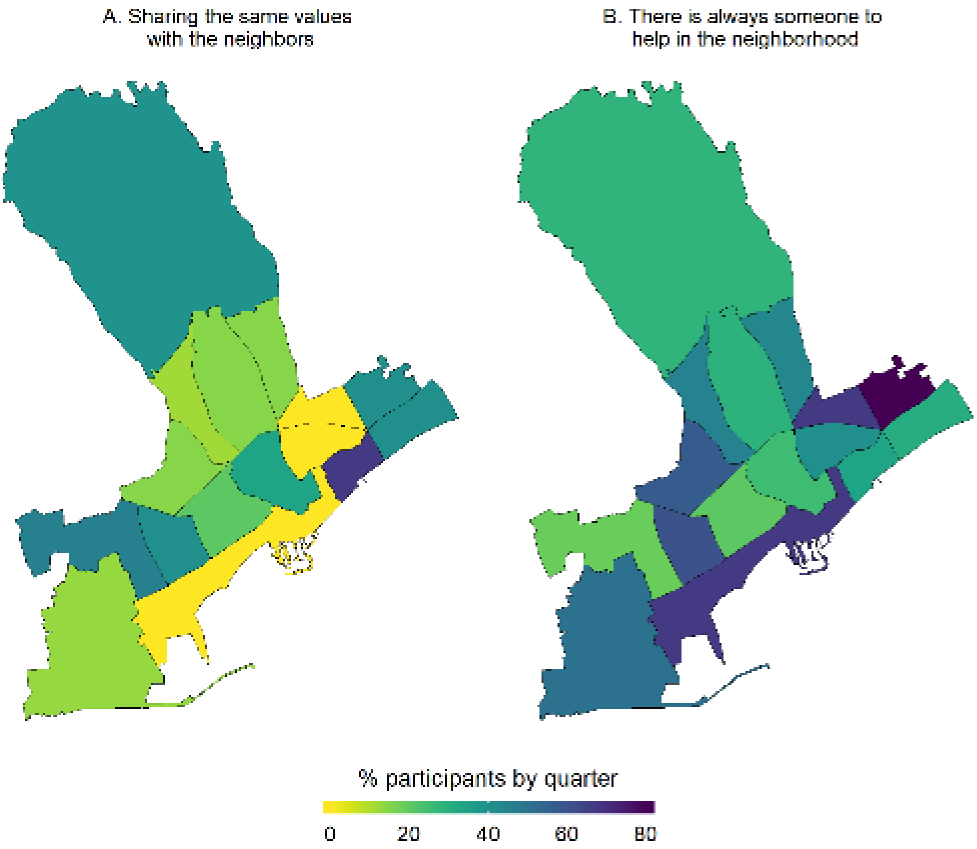


Figure 3.5 Percentage of study participants agreeing with different statements about life in the neighborhood, i.e. on sharing the same values with the neighbors (A), and whether there is someone to help in the neighborhood (B), by quarter of the Limassol municipality, Cyprus, 2017.

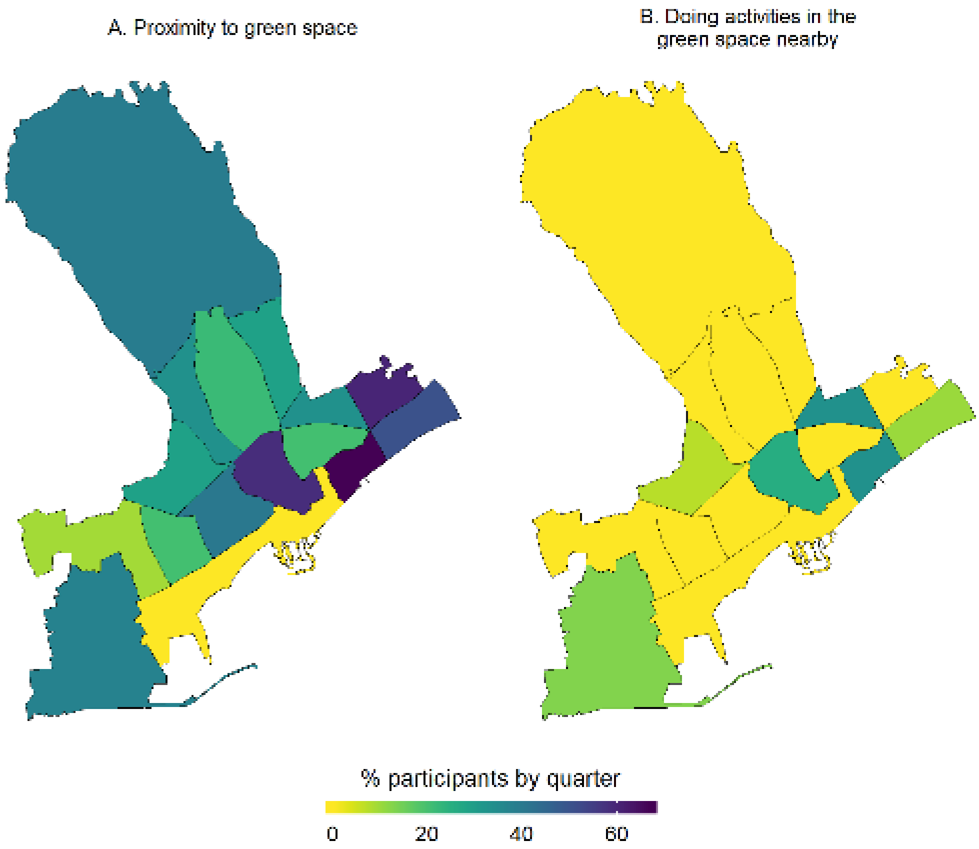


Figure 3.6 Maps by quarter of the percentage of study participants within the quarters of Limassol municipality, Cyprus (2017) agreeing that they live in close proximity to green space (A) and they do activities in the green space nearby (B).

Exploring environment-wide associations within the municipality of Limassol

A correlation plot between all variables used in the EWAS analysis (listed in Table S2) did not show any specific or unexpected patterns of correlation among the urban variables (Figure 3.7). Notable correlations were observed among different variables of the same block/group. All THM compounds in drinking-water correlated well with each other and they were negatively correlated with free chlorine levels. Additionally, strong correlation was observed among the household cleaning variables (mopping, dishwashing and bathroom cleaning). The variables of the "cleaning" block/group (block/group 3) correlated also with certain health conditions, such as musculoskeletal problems (neck problems).

In the regression part of the EWAS analysis, a total of 129 predictors were summarized from the simple models and 123 predictors were used in the models adjusted for age and sex. These predictors include both parameters measured in water, i.e. THM, and questionnaire responses (summarized in Table S2). In the models adjusted for age and sex, four parameters had an FDR-corrected p-value <0.1, i.e., financial issues in access to dental care, depression, hypertension and asthma. Having encountered financial issues in access to dental care [n=18, (14.1%) participants] and depression [n=3, (2.8%) participants) were statistically significant negative predictors for better general health status, while and higher odds of having a chronic disease were associated with hypertension and asthma [n=19, (16.2%) and n=10, (8.5%) participants, respectively]. In the univariate regression, in addition to the parameters that were significant in the adjusted models, musculoskeletal problems (i.e. neck and back problem) were associated with higher odds of having a chronic disease but not with the outcome of general health status. The parameters ranked by the FDR adjusted p-value can be found in Table S3. 6.

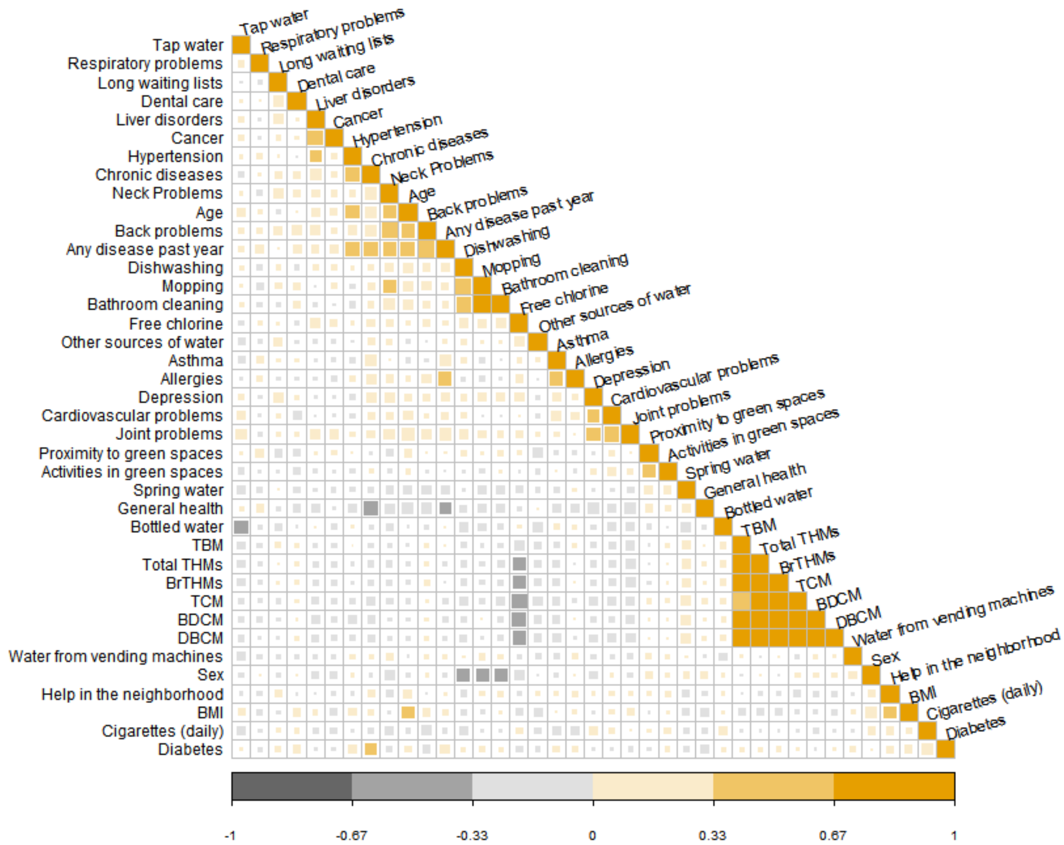


Figure 3.7 Correlation plot (Spearman correlation coefficient) for all the variables used in the environment-wide association exploratory analysis.

The results of the second EWAS analysis and the correlation between the variables used in the PLS-DA models were summarized in the circular plots (circo plots) of Figure 3.8. Again, all three outcomes were used, however, the model for the chronic disease did not converge and thus, the plot is not presented. For the other two outcomes the associations between the variables were not the same, as expected due to the difference in the outcomes between the two models. The THM variables correlated with each other and with the household cleaning activities (i.e. dishwashing, mopping, bathroom cleaning) as it was also shown in the simple correlation plots. The correlations were less in number when the outcome was "any disease the past year" compared to the correlations visualized in the circo plot of the "general health" as an outcome. Additionally, different levels of the predictor variables were noted depending on the outcome, as it can be seen by the lines on the outside perimeter of the circular plot. These lines, however, were not used for interpretation due to the study's exploratory nature to avoid any misleading inferences.

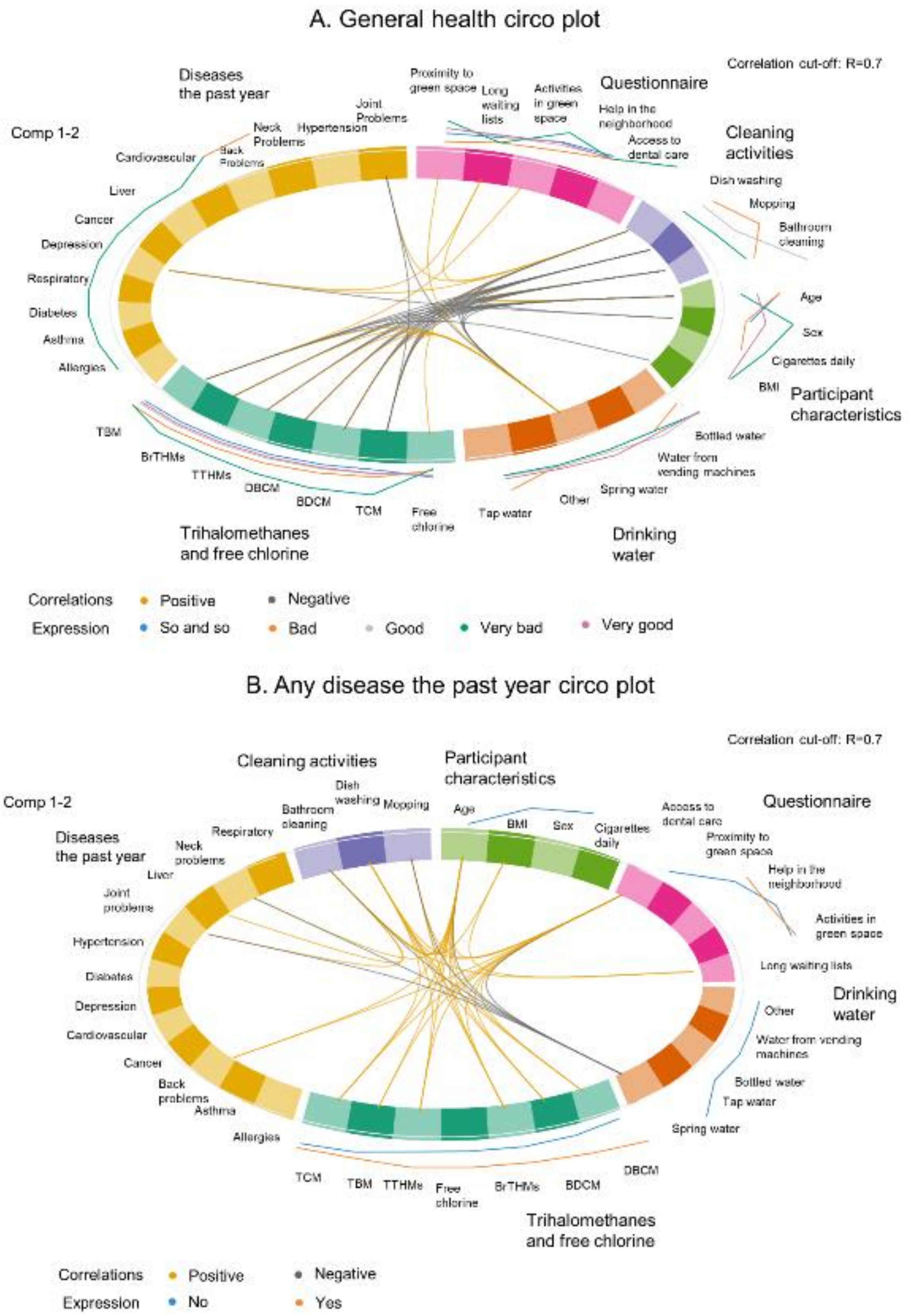


Figure 3.8 Circular plots of the correlations between the variables used in the environmental-wide analysis by block/group of variables accounting for general health (A) and any disease the past year (B).

3.5 Discussion

In this proof of concept study of the urban exposome, we used an interdisciplinary approach to identify trends in perceptions about environmental exposures and how they correlated with the spatially-resolved drinking-water quality trends of chemical and microbial indicators for the municipality of Limassol during the hot season (summer). Quality of life indicators (e.g. access to green spaces, the life in the neighborhood and reasons for delay or financial constraint in access to health care) were mapped at the level of the quarter (smallest administrative unit). No clear disparities at the quarter level were observed for all neighborhood-based queries, but financial constraints, especially for dental care were noted. Additionally, we generated global linkages and correlations between the health status of urban participants and their environmental/lifestyle/behavioral exposures at the individual level. A total of 129 parameters from 36 variables either directly measured in water (water quality) or derived from the survey (quality of life in the city) were integrated using an exploratory, agnostic, exposome-based EWAS approach. The general health and chronic health status of the urban participants were significantly associated in regression analysis with different health outcomes (e.g. hypertension, asthma) and quality of life indicators (e.g. financial issues in access to dental care). Circular correlation plots were derived from 36 urban exposome variables which were divided in six groups and accounted for self-reported health indicators (general health and having any diseases the past year). This study is an application of the urban exposome framework and the first to generate a snapshot of the actual urban exposome of Limassol, Cyprus, with a focus on water and quality of life indicators.

Urbanization, migration and other drivers of societal changes in urban settings are shaping population health and quality of life in cities leading to interventions such as the large scale neighborhood renewal programs that aim to improve living conditions and quality of life in cities (72). The impact of such neighborhood-based programs could be enhanced with the comprehensive assessment of environmental, economic, societal and other health parameters in the city. Within the context of improving urban life, novel paradigms such as the exposome can be adapted to provide a more interdisciplinary approach in tackling urban problems. The urban exposome can be viewed simply as the totality of environmental exposures occurring in cities (41,57). However, this definition is rather centered on individuals and it does not include wider determinants of urban health. For example, a recent study described the human exposome in city-based cohorts and focused on specific exposure-effect associations in one or multiple cohorts being pooled together (57). In this study, we propose a novel approach using the urban exposome as a study framework to describe systematically how broader urban characteristics can be evaluated with an interdisciplinary methodology. Thus, we have placed the city and its smaller areas as the measurable units in the center of this exposome approach. Moreover, we have used the perceptions and the urban population study as two sources of information that can be summarized to provide a snapshot of the urban exposome of Limassol focused on water and quality of life.

The case of water pollution and the provision of safe and clean water to urban dwellers presents one of the most challenging elements to be incorporated within the urban exposome framework. This might be due to the complex systems that drive water quality and water choices given also the aging water infrastructure in urban settings. These challenges are also evident in the literature and in studies of water quality indicators but their links with the exposome are scarce. To our knowledge, the literature in exposome approaches to evaluate water quality is limited and it has not focused on the urban environment or the general population. For example, using an environment-wide association study methodology, the pregnancy exposome study on the INMA-Sabadell Birth Cohort in Spain looked into modeled at the individual level water disinfection byproducts (THM), among a wider set of other exposures ranging from urinary markers of chemical exposures to air pollution and noise (51). They showedthat the three THM "classes" studied (totaland brominated THM, and chloroform) were strongly correlated with each other, but not with the other environmental exposures (51). Albouy-Llaty et al (2016) explored the association between endocrine disruptors (atrazine metabolites and nitrate/atrazine mixture) in drinking water and preterm birth accounting for socioeconomic factors (deprivation index) in the Poitou-Charentes region of France (73).

The exposure to atrazine and the nitrate/atrazine mixture at the individual level was inferred from routine community monitoring of water quality; preterm birth was found to be associated with the deprivation index at the level of the neighborhood but not with the exposure to atrazine metabolites. Exposure to atrazine (measured through the metabolite 2-hydroxyatrazine) was not found to be a significant risk factor for preterm birth when accounting for the socioeconomic status of the area (73).

This is the first application of the urban exposome framework that took place in a medium-sized European city, Limassol, Cyprus. We used an agnostic approach following the urban exposome framework and we described water quality indicators at the level of quarter (the smallest administrative area within a municipality), accounting for urban, general population characteristics and additionally including the opinions/perceptions of residents and municipality technical stakeholders. The analysis included a suite of water quality aspects (chemical and microbial) which belong to the internal domain of the urban exposome and the specific external domain of the human exposome, and stakeholders' opinions about environmental issues (specific external urban exposome and general external human exposome). Moreover, quality of life was assessed through citizens' answers about access to healthcare and green spaces, and it was included along with lifestyle/behavior, and demographics in the EWAS analysis. This analysis is part of developing the urban exposome profile of Limassol and provides a snapshot of the state of the city, which will be combined with analysis of routinely collected.

As mentioned before, our study aimed to provide a methodological approach in a relatively small city. Therefore, the generated associations of different health outcomes and quality of life indicators with general health or with having a chronic disease in the EWAS study should be interpreted with caution due to the lack of adequate statistical power. In our case, the EWAS analysis is limited by the data at hand but, it is more of exploratory nature, as it is a part of this proof of concept study. Previous EWAS-exposome studies have been broader, with larger sample sizes, and, thus, more power (74).

One observation that stood out in the correlation analysis is the negative association of water THM with cleaning activities. Previous studies have shown positive correlations between cleaning activities and urinary THM levels, and not between water THM levels and cleaning activities (75). However, our observation, taking into consideration previous work on the exposure assessment to disinfection byproducts (76), indicates the complexity of exposure assessment using environmental measurements as proxies of exposure, especially in EWAS studies.The inclusion of the perceptions study in developing the urban exposome profile of Limassol, with the use of a qualitative and quantitative approach allowed important community concerns about their urban life to surface. Air pollution was ranked as the most significant concern among the study respondents. Besides the general interest of air pollution and its health effects, Cyprus experiences frequent dust storms (77,78). These events have probably triggered a specific concern among the population making air pollution the most frequently reported environmental concern in our study. Overall, the results presented here, should be interpreted with caution because of limitations in the study design (i.e. the cross-sectional design) and the small sample size or possible sampling bias (especially in the perceptions study).

This proof-of-concept study aimed to showcase the utility of the urban exposome framework in an urban study setting extending the continuum of the human exposome concept, thus, providing the methodological background for future studies. We were able to demonstrate the use of different tools in an integrative and interdisciplinary approach to capture the baseline urban exposome of Limassol municipality in this case. The same approach can be generalized. For example, if applied to other urban dwellings with bigger sample, it will allow us to scale up the application of such integrative and multidisciplinary protocols and will allow for the wider transfer and generalizability of the results. Future studies should also incorporate a more comprehensive assessment of urban quality of life. In this analysis, the indicators of quality of life were limited to life in the neighborhood or the use of green space and the questionnaires were based on indicators previously assessed in larger urban studies which had not included Cypriot cities (64,65). Additional information about social life is available from this study population and it will be incorporated the urban exposome of Limassol. Next steps will incorporate the analysis of routinely collected data of the registries and human biomonitoring analyses in a more complete characterization of the urban exposome in Limassol city. Moreover, given the "stakeholders" assessment of environmental problems, we have moved on with air quality measurements throughout the municipality, which were conducted in the spring of 2018 while we explore how the routinely collected data from the one governmental station for air quality measurements can be also included. This study shows how the goal of developing the urban exposome framework can be achieved by using all the available information in a real-time assessment of urban health and provide a tool for decision-making to stakeholders.

Our analysis did not raise any specific concerns about the quality of tap drinking water at the urban quarter scale of Limassol city using both chemical and microbial indicators. It was shown however, that residents do not trust, in general, the tap water and opt for using bottled water or water from other sources such as the "vending machine" water (groundwater from mountainous wells) which is very common practice in Cyprus. The cost of tap water is lower compared to bottled or "vending machine" water and, thus, it may pose additional burden to household budgets, as it has been shown in other studies (79). Mapping the cost of water by quarter would likely be informative about the existence or not of differences within Limassol in the economic burden of water consumption. Urban green space was particularly noted for being close to participants' households, however, limited use of such green spaces (e.g. parks) was reported. Both aspects of access to health care and the use of green spaces within Limassol, were studied for the first time. Our approach could form the basis for future targeted and more integrative urban studies on these topics.

In general, our first results on the application of the urban exposome are promising and in need for verification and expansion. First and foremost, given the different habits of the citizens, exposome studies need to be more inclusive in the assessment of different water sources. Besides the inclusion of standard water testing parameters, future studies should address participant perceptions which are linked to behaviors, and, thus, exposures. Developing the health profile of a city in urban exposome terms and integrating different approaches comes with several limitations. Spatio-temporal considerations should be accounted for the dynamic nature of urban exposome profiling. Although enough to estimate the background levels of population exposures to chemicals, the relatively small sample size might have not allowed us to capture spatial differences of the indicators measured within the smaller city administrative units. Additionally, the lack of biomonitoring data on water-related exposures (i.e. to disinfection byproducts in urine) have hindered the full deployment of EWAS tool capabilities. However, the availability of urine biospecimen for this survey will allow us to use biomonitoring and untargeted metabolomics tools in a follow-up manuscript.

3.6 Conclusions

Developing sustainable city health profiles with the aid of the urban exposome framework is a novel approach, yet, far from being simple or reductionistic in approach. It demands a comprehensive characterization of relevant indicators ranging from drinking water quality to health perceptions and opinions collected from the general population and technical stakeholders, etc. The urban exposome framework and its application will pave the way for developing the next innovative solutions and public health interventions for the city. This proof of concept case study of the urban exposome in Limassol, Cyprus demonstrates the feasibility of using novel exposome approaches in studying the city and its smaller within-city areas (quarters) as the units of reference. Within this context, the absolute water quality indicators, city residents' and other stakeholders' opinions need to be integrated and expanded along with exposomic profiles, such as metabolomics or other -omics platforms and human biomonitoring protocols.

Thus, we need to develop specific urban exposome studies where city-specific characteristics and within-city interactions and networks, can be used to redefine city health profiles. Evidence-based and city-specific studies will help authorities reach informed decisions about everyday life, about city infrastructure changes and their effects on urban health and personal exposures. This will help the interpretation of inter-city difference and will allow the timely evaluation of within-city challenges.

Acknowledgements

We would like to thank the Municipality of Limassol and all the study participants. Special thanks to Ms. Andriana Till for her contribution to participant recruitment and to Dr. Stephanie Gaengler for the fruitful discussions during data analysis. We would also like to express our gratitude to Drs. Athos Agapiou and Diofantos Hadjimitsis for sharing the map templates for the quarters of Limassol.

4 Routine public health surveillance within the urban exposome framework: a proof-of-concept study in Limassol district, Cyprus

Xanthi D. Andrianou[1], Anna Demetriou[2], Soteroula Soteriou[2], Ioanna Grigoriou[2], Maria Koliou[2], Konstantinos C. Makris[1]

[1]Cyprus International Institute for Environmental and Public Health, Cyprus University of Technology, Limassol, Cyprus
[2]Ministry of Health, Nicosia, Cyprus

Abstract

Background. Routinely collected data of non-communicable or communicable, are one of the pillars supporting public health interventions and prompting response. One of the main components of the urban exposome framework, defined as spatiotemporal surveillance/monitoring of indicators associated quality of life and the health of urban population, where small, within-city areas, is the assessment of routinely collected data. The objective of this study was to analyze the spatiotemporal distribution of cancer cases, mortality, and notified tuberculosis (TB) cases the district of Limassol, Cyprus focusing on Limassol city.

Methods. We analyzed data from the cancer and mortality registry for the periods 2007-2014 and 2007-2015, respectively, and TB cases notified in 2015-2015 in the district of Limassol, Cyprus. Cancer cases were aggregated by postal code area and year, while deaths and TB cases by municipality/village and year. Cancer incidence and mortality rates, as well as TB case notification rates (crude and age-standardadized) were estimated and mapped. Smoothed relative risks for cancer and death were also mapped accounting for spatial correlations.

Results. In total 7055 cancer cases, 13576 deaths and 42 TB cases were analyzed. Cancer and mortality crude rates were highly variable within the study periods and in the different postal code areas and municipalities/villages, respectively. Standardized rates were not as highly variable, and the smoothed RR did not show particular trends for the urban area of Limassol. Overall higher TB case notification rates (crude and standardized) were observed in the urban areas compared to the non-urban areas.

Conclusion. The epidemiology of cancer, deaths and TB in Limassol, Cyprus can be the basis for prospective monitoring of disease trends and for expanding the urban exposome profile of Limassol, Cyprus towards developing public health interventions to address within-city health inequalities.

4.1 Introduction

The study framework of the urban exposome was defined in 2018, in order to present a holistic approach in conducting exposome studies in cities while extending the study of the human exposome and taking into account the differences of smaller within-city areas (56). The need to define the urban exposome as a specific study framework stemmed from the fact that cities nowadays, are estimated to be hosting more than half the global population while they face specific public health challenges, and, to take advantage of the holistic approaches proposed by exposome research in human populations (1,2).

The description of the urban exposome so far has been based on primary studies that addressed mostly questions on specific disease outcomes and for specific populations or overall quality of life in the city (57,80). A part that has not yet been included in the urban exposome studies is routinely collected information on disease epidemiology from surveillance/monitoring data. Disease surveillance is one of the cornerstones of public health as it allows timely monitoring and description of health trends in specific areas, for specific populations, and it can inform public health interventions. The data routinely gathered at national or sub-national levels for the surveillance of communicable and non-communicable diseases can provide a source of information that can be integrated in the urban exposome of any city. Once this city-specific analysis of routinely collected data and the monitoring urban health trends is integrated in the urban exposome it can provide, first, a baseline description of the disease burden in smaller within-city areas and then, it can allow for the continuous monitoring of changes in the city health profile to trigger public health interventions.

As the urban exposome study framework is based on the assessment of both internal and external to the city parameters (or domains, to parallel the human exposome structure) that shape health and quality of life in the city, the assessment of routinely collected data is a part of the specific external and internal urban exposome (56). The routinely collected data can be used within the study framework of the urban exposome as another source of information which allows for timely evaluation of possible changes in disease epidemiology. The use of routine data could be considered more relevant within the urban exposome approach than when studying the human exposome through the assessment of personal exposures given the different objectives the urban exposome and the human exposome have. In the urban exposome approach, where the city and the smaller within-city areas are the units of measurement, disease epidemiology from spatiotemporally collected data can be a tool for the development of public health interventions and for risk response measures. In this context data from communicable and non-communicable diseases are of interest and relevance. Few studies have proposed the simultaneous assessment of these two main categories of diseases with the assessment, for example, of chronic infections and non-communicable diseases to inform exposome studies (81). However, to our knowledge, no study has incorporated routinely collected data in this assessment.

In Cyprus, the Ministry of Health (MoH) and, more specifically, the Health Monitoring Unit, is responsible for maintaining the cancer, the mortality and the birth registries, and the Surveillance and Control of Communicable Diseases Unit is responsible for the surveillance of communicable diseases. Overall, Cyprus, according to the 2017 country health profile has low cancer incidence and low cancer mortality while the most frequently reported cause of death is cardiovascular diseases (82). With regards to infectious diseases, and although, underreporting cannot be excluded, relatively low notification rates of infectious diseases indicate that the burden could be considered relatively small. For example, measles is considered eliminated (between January 1, 2016 and March 31, 2019 only 19 measles cases were reported, nine of which were imported), while mean annual *Campylobacter* incidence between 2008 and 2016 was 3.9 cases per 100,000 (83,84). With regards to tuberculosis (TB), on the other hand, Cyprus is considered a low incidence setting with notification rates ranging from 4.1 per 100,000 in 2013 to 6.2 per 100,000 in 2017 according to the estimates of the European Center for Disease Control and Prevention (ECDC) (85).

In order to complete the description of the baseline urban exposome of Limassol, Cyprus and given that to our knowledge none of the large exposome studies have directly included registry data or an assessment of any infectious diseases epidemiology as part of the studied "exposomes", the aim of the present study was to describe the epidemiology of non-communicable and communicable diseases using routinely collected data and incorporate them in the analysis of the urban exposome. The specific study objectives were to analyze the spatial and temporal distribution of cancer cases, mortality, and notified TB cases within the district of Limassol, Cyprus and within the urban areas of the Limassol city.

4.2 Methods

4.2.1 Extending the application of the urban exposome in Limassol, Cyprus

The urban exposome has been defined as the prospective assessment of urban indicators (56). Following the structure of the urban exposome study framework, in order to complete the assessment of a city's exposome we need to consider: (i) external to the city parameters, i.e. those that cannot be influenced by the city itself and they can be either general (general external urban exposome domain), such as, global trends and policy decisions, or specific (specific external urban exposome domain), such as climate change impacts, demographic changes, culture, as well as (ii) internal to the city parameters e.g. infrastructure, built/neighborhood environment and determinants of population health (e.g. socioeconomic factors) which make up the internal urban exposome domain. The external and internal city parameters interact horizontally and/or vertically, i.e. within each domain and between domains, respectively. Within this framework routinely collected public health data such as those from registries (e.g. cancer registry, birth registry) and from infectious diseases surveillance (e.g. tuberculosis, food-borne diseases incidence) allow for the spatiotemporal description of disease incidence patterns (Figure 4.1). Following the description of drinking water and quality of life indicators in a proof-of-concept study (80), in this study we analyzed data from the cancer and mortality registry, as well as TB notified cases maintained by the Health Monitoring Unit and the Surveillance and Control of Communicable Diseases Unit of the Cyprus . This part extends and completes the baseline characterization of the urban exposome of Limassol with the description of additional parameters of the internal urban exposome.

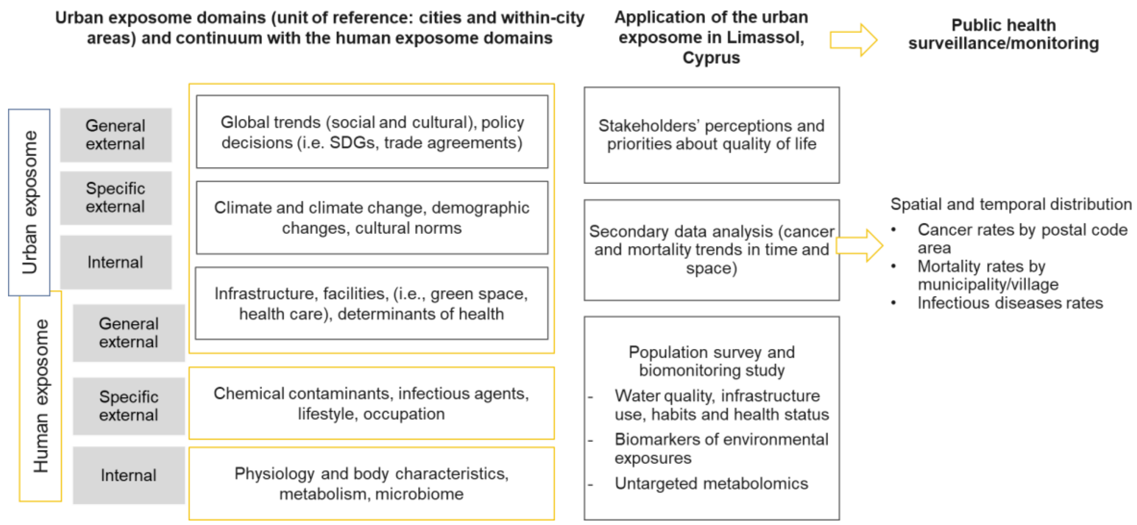


Figure 4.1 Routine public health surveillance within the practical application of the urban exposome framework in Limassol, Cyprus, as part of the urban exposome-human exposome continuum.

4.2.2 Data sources

As mentioned earlier, the Health Monitoring Unit of the Cypriot MoH maintains the cancer and death registries and the Unit for Surveillance and Control of Communicable Diseases is responsible for the surveillance of all notifiable infectious diseases in Cyprus. All non-confidential data were released after acquiring proper approvals by the Ministry of Health (approval numbers: 5.6.01.4.3 (5) and Ι.Υ 5.21.005.10).

Cancer registry data were available for 2007-2014, mortality data were available for 2007-2015, and TB data for 2015-2017. For the cancer cases information on the postal code of residence were available while the municipality/village of residence information were available for the tuberculosis cases and for the deaths. Therefore, cancer cases were aggregated at postal code level, and the TB cases and deaths were aggregated at municipality/village level. Details on the datasets used in this analysis can be found in Table 4.1.

End- and mid-year district population estimates were retrieved from the most recent demographic report (2017) (32) and they were used to estimate the population of smaller areas (either postal code areas or municipalities/villages) using as reference the 2011 census data (8). Details can be found in the Supplementary Material (Section: Estimation of the population at risk per year by postal code and municipality/village and Table S4. 1).

Municipalities/villages of the Limassol district were categorized as urban or non-urban based on the 2016 EU degree of urbanization classification (DEGURBA) (retrieved from the Cyprus Statistical Services) (33). Urban municipalities/villages were considered only those classified as densely populated areas (i.e 50% of the population living in the urban center), and non-urban municipalities/villages were considered all other municipalities/villages that had been classified as intermediate or thinly populated (i.e. at least 50% of the population living in urban cluster and less than 50% in urban centers, or at least 50% of the population lives in rural grid cells, respectively) (33,34).

Map shapefiles were downloaded from the open data portal of the Government of Cyprus (86,87).

Table 4.1 Details of the three datasets used in the analysis of routinely collected data from the Health Monitoring Unit and the Surveillance and Control of Communicable Diseases Unit of the MoH of Cyprus.

Data	Background information	Study period	Spatial level of aggregation
Cancer registry	Age at first diagnosis, sex, primary site (based on the IARC classification)	2007-2014	Postal code area
Mortality registry	Age, sex, cause of death	2007-2015	Municipality/village
Tuberculosis notifications	Age, sex, site (pulmonary/extrapulmonary), birthplace	2015-2017	

4.2.3 Data analysis

Cancer registry data analysis

Descriptive analysis of the cancer registry by age group, sex, and by primary site was conducted for the district of Limassol and by urbanization level (urban vs. non urban).

Cases were aggregated at postal code level. Data were summarized based on the age group at the time of cancer diagnosis, and all cancer incidence rates were calculated using the end-year population.

In total 200 cases (2.8% of the 7055 cases) had missing information in the postal code. Missing information ranged from completely missing postal code, to missing information in the last three, two or one digit of the (4-digit) postal code. Postal codes were imputed using the hot deck method, i.e. the missing postal codes were randomly assigned a value based on the existing postal codes (88). Postal codes with missing information were grouped in nine categories (based on the missing digits) and a separate dataset was created including all cases with a matching (for the category) complete postal code (e.g. for the missing category "----" all cases were selected, or for the "400-" all cases with a postal code with 400 as the first three digits were selected). Then, the missing postal codes were imputed using the complete postal codes of the cases previously subset.

Standardized incidence ratios (SIR; i.e. the ratio of the observed number of cancer cases/expected number of cancer cases) were estimated by postal code area using the district as reference and excluding 15 cases of unknown age (<0.01% of the 7055 cancer cases analyzed) and nine cases in postal code areas that were not enumerated in the 2011 census (one of the nice cases was imputed to the specific postal code not among the ones in the census). The number of observed and expected cases as well as the SIRs were mapped for the whole district and for the urban part of the district of Limassol.

The analysis was repeated using only the cancer cases with primary site in the trachea, bronchus or lungs, coded as C33-C34 by the International Agency for Cancer Research (IARC).

Mortality registry data analysis

Descriptive analysis of the deaths by age group, sex, and category of death was performed for the Limassol district (overall) and by urbanization category (urban vs. non-urban). Data were aggregated by age group at the time of death, and all mortality rates were calculated using the mid-year population. Four-digit codes (municipality/village geo codes) were used to link the different datasets (i.e. mid-year population estimates and aggregated mortality registry data). Eleven records (n=11, 0.1%) of the 13567 had missing information in the variable for residence. Missing information refers to cases for which the place of residence was defined as the district only (geo code 5---) without specification on the municipality/village. The missing geocodes were imputed using hot deck imputation, i.e. they were randomly assigned a value of the ones in the existing geo codes (88).

Crude mortality rates were estimated for the district and by municipality/village including and excluding all reported deaths of unknown age.

Standardized mortality ratios (SMR; observed number of deaths/expected number of deaths) were estimated by municipality/village using the district as reference and excluding two deaths (<0.01% of the 13 567 deaths analyzed) at unknown age.

Tuberculosis notifications data analysis

TB cases were summarized by age group and year of notification, and notification rates were calculated using the end-year population. A descriptive analysis of the TB cases was conducted for the district and the urban vs. non-urban municipalities/villages.

Standardized case notification ratios (SCNR; i.e. the ratio of the observed number of notified TB cases/expected number of notified TB cases) were estimated by municipality/village using the district as reference. The number of observed and expected TB cases as well as the SCNRs were mapped for the whole district and for the municipality of Limassol.

Standardization, mapping at the district level and at the urban areas

Crude district estimates, i.e. cancer incidence, mortality rate, and TB notification rates, were calculated for the whole population and they were not standardized, as a comparison with the national or EU reference populations was beyond the scope of the study. The standardized rations for cancer incidence (SIR), mortality (SMR) and TB case notification (SCNR) were estimated using the district as a reference, in order to provide more specific to the smaller area estimates, as the exposome focus was the within-district, urban setting and overall spatial and temporal changes in epidemiology of cancer, deaths, and TB.

Given that the cancer SIR and SMR rates were estimated for small areas, they might not be reflecting adequately the real risk. To account for possible spatial correlation between the smaller areas within the district as they are defined by the postal codes or municipalities/villages, in an exploratory part of the analysis, the cancer smoothed relative risk (RR) by postal code area (all cancer types and, separately, for cancers in the trachea, the bronchus or the lungs) and smoothed RR for death by municipality/village were calculated using the Besag-York-Mollié model (89–91). This model accounts for the neighborhood structure of the area under study (neighbors are the areas sharing common borders). The 95% credible intervals (CI) for the smoothed RR were estimated from the models. Due to the fact that TB cases were notified in only ten of the 111 municipalities/villages of the district of Limassol, the TB SCNR was smoothing was not conducted.

The observed and expected number of cancer cases, deaths, and notified TB cases as well as the relevant ratios (SIR, SMR, and SCNR), RR (and 95% CI) were mapped and described at the postal code area (cancer) or at the municipality/village level (deaths and TB cases). The maps were created for the whole district of Limassol and then for the urban areas.

The RECORD statement is available in the supplementary material (92). All the analyses were conducted in R (v. 3.6.0) using Rstudio (v. 1.2.1335) (70,93). A complete list of the packages used in available in Table S4. 2.

4.3 Results

4.3.1 Cancer incidence by postal code area at the Limassol district, 2007-2014

In total 7,055 cancer cases were recorded in the district of Limassol between 2007 and 2014. The number by year ranged from 772 in 2007 to 1,003 in 2014 (10.9% and 14.2% of the 7055 cases included in this analysis) (Table S4. 4). Only in urban areas, in 2007 were 685 cases reported (79.4% of the total cases of the district). In urban areas, the cases increased from 2007 to 2008, decreased again in 2009, and since 2009 the number of all cancer cases remained above 700 accounting for 80% approximately of all district cases each year (Table S4. 4).

Mean age at diagnosis during the study period, in the district, was 64 years and the median age was 66. The mean age was lower for the cases in the urban areas compared to the non-urban areas (63 vs 67 years for urban and non-urban areas, respectively). Most cases were reported in males (n=3,624; 51.4%) and n=3,431 (48.6%) in females with similar patterns in urban and non-urban areas (Table 4.2).

The majority of cases were reported in urban areas of the district while the most common types of cancer (according to the IARC grouping for the primary site) were the same for in urban and non-urban settings (Table 4.2). Breast was the most frequently reported overall (1094 cases (15.5%)) in 2007-2014 and for urban and non-urban areas. The second most frequently reported primary site was prostate, followed by colorectal, cancers in the trachea, bronchus, or lungs, and thyroid cancer. The same patterns with regards to the frequency of the most common cancer types were observed in urban and non-urban areas of Limassol.

Table 4.2 Age, sex descriptives and most common types of cancer reported by year in the district of Limassol, Cyprus (overall), and in urban/non-urban areas, 2007-2014.

	2007 (n=772)	2008 (n=839)	2009 (n=826)	2010 (n=888)	2011 (n=907)	2012 (n=926)	2013 (n=894)	2014 (n=1,003)	Total (n=7,055)
Overall									
Age (mean)	64	64	63	64	64	63	64	63	64
Sex									
Female	367 (47.5%)	416 (49.6%)	397 (48.1%)	415 (46.7%)	454 (50.1%)	437 (47.2%)	438 (49.0%)	507 (50.5%)	3,431 (48.6%)
Male	405 (52.5%)	423 (50.4%)	429 (51.9%)	473 (53.3%)	453 (49.9%)	489 (52.8%)	456 (51.0%)	496 (49.5%)	3,624 (51.4%)
Primary site (IARC grouping)									
C50 Breast	131 (17.0%)	130 (15.5%)	121 (14.6%)	131 (14.8%)	149 (16.4%)	126 (13.6%)	147 (16.4%)	159 (15.9%)	1,094 (15.5%)
C61 Prostate	107 (13.9%)	120 (14.3%)	110 (13.3%)	110 (12.4%)	106 (11.7%)	147 (15.9%)	106 (11.9%)	106 (10.6%)	912 (12.9%)
C18-C20 Colorectal	91 (11.8%)	90 (10.7%)	87 (10.5%)	95 (10.7%)	95 (10.5%)	97 (10.5%)	87 (9.7%)	109 (10.9%)	751 (10.6%)
C33-C34 Tr., Br., Lung	62 (8.0%)	67 (8.0%)	68 (8.2%)	86 (9.7%)	89 (9.8%)	81 (8.7%)	100 (11.2%)	95 (9.5%)	648 (9.2%)
C73 Thyroid	33 (4.3%)	46 (5.5%)	41 (5.0%)	61 (6.9%)	62 (6.8%)	72 (7.8%)	53 (5.9%)	89 (8.9%)	457 (6.5%)
Urban (n=5,496)									
Age (mean)	63	64	62	63	63	63	63	63	63
Sex									
Female	298 (49.8%)	342 (50.7%)	304 (46.8%)	317 (47.1%)	357 (50.6%)	341 (48.0%)	349 (49.2%)	398 (51.3%)	2,706 (49.2%)
Male	300 (50.2%)	333 (49.3%)	345 (53.2%)	356 (52.9%)	348 (49.4%)	370 (52.0%)	360 (50.8%)	378 (48.7%)	2,790 (50.8%)
Primary site (IARC grouping)									
C50 Breast	111 (18.6%)	111 (16.4%)	98 (15.1%)	104 (15.5%)	121 (17.2%)	102 (14.3%)	118 (16.6%)	125 (16.1%)	890 (16.2%)
C61 Prostate	73 (12.2%)	89 (13.2%)	82 (12.6%)	79 (11.7%)	79 (11.2%)	105 (14.8%)	73 (10.3%)	79 (10.2%)	659 (12.0%)
C18-C20 Colorectal	74 (12.4%)	71 (10.5%)	63 (9.7%)	75 (11.1%)	74 (10.5%)	73 (10.3%)	69 (9.7%)	87 (11.2%)	586 (10.7%)
C33-C34 Tr., Br., Lung	47 (7.9%)	60 (8.9%)	56 (8.6%)	67 (10.0%)	68 (9.6%)	63 (8.9%)	76 (10.7%)	78 (10.1%)	515 (9.4%)
C73 Thyroid	25 (4.2%)	38 (5.6%)	35 (5.4%)	53 (7.9%)	51 (7.2%)	60 (8.4%)	42 (5.9%)	70 (9.0%)	374 (6.8%)
Non-urban (n=1,359)									
Age (mean)	67	66	67	67	67	66	67	65	67

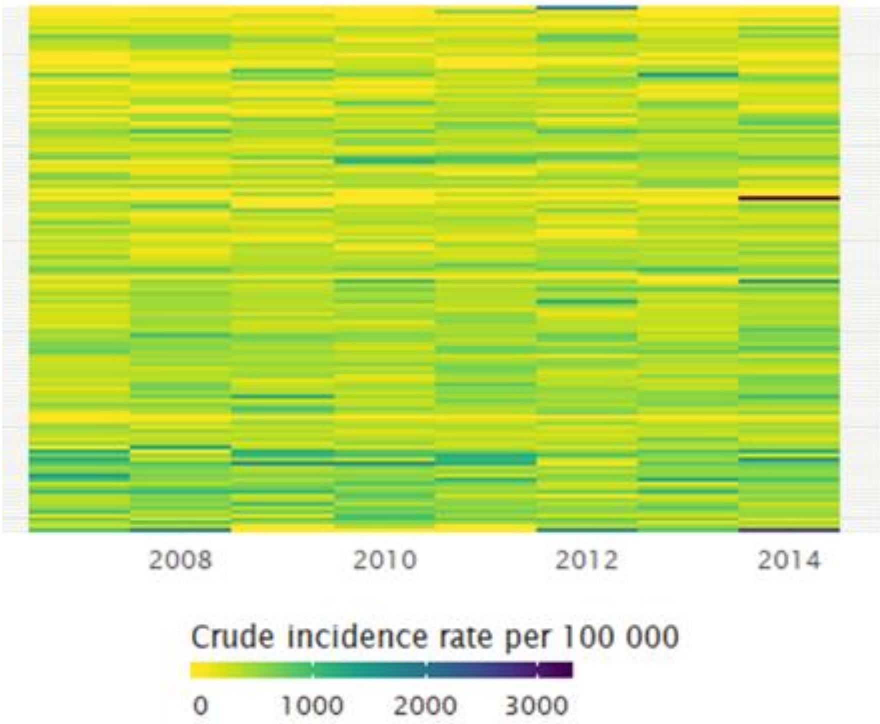
Sex									
Female	60 (38.7%)	61 (42.4%)	82 (51.2%)	82 (46.3%)	82 (48.2%)	81 (43.3%)	83 (50.0%)	94 (47.0%)	625 (46.0%)
Male	95 (61.3%)	83 (57.6%)	78 (48.8%)	95 (53.7%)	88 (51.8%)	106 (56.7%)	83 (50.0%)	106 (53.0%)	734 (54.0%)
Primary site (IARC grouping)									
C50 Breast	18 (11.6%)	17 (11.8%)	18 (11.2%)	25 (14.1%)	23 (13.5%)	22 (11.8%)	27 (16.3%)	29 (14.5%)	179 (13.2%)
C61 Prostate	29 (18.7%)	29 (20.1%)	25 (15.6%)	21 (11.9%)	22 (12.9%)	38 (20.3%)	25 (15.1%)	24 (12.0%)	213 (15.7%)
C18-C20 Colorectal	16 (10.3%)	17 (11.8%)	22 (13.8%)	18 (10.2%)	16 (9.4%)	21 (11.2%)	16 (9.6%)	19 (9.5%)	145 (10.7%)
C33-C34 Tr., Br., Lung	12 (7.7%)	6 (4.2%)	12 (7.5%)	14 (7.9%)	18 (10.6%)	16 (8.6%)	23 (13.9%)	15 (7.5%)	116 (8.5%)
C73 Thyroid	8 (5.2%)	8 (5.6%)	6 (3.8%)	6 (3.4%)	9 (5.3%)	10 (5.3%)	11 (6.6%)	18 (9.0%)	76 (5.6%)

Overall the crude cancer rates (per 100,000) in the district for 2007-2014 ranged from 352.5 (in 2010) to 423.9 (in 2014) (Table S4. 5). Overall median crude incidence and median SIR was higher in the urban areas compared to the non-urban areas within the study period (Table 4.3). Median crude incidence was higher in 2008 compared to 2007. It remained above 330 cases per 100,000 since 2008 and until 2014 when it was the highest of the study period (387.1 cases per 100,000). However, the median SIR did not show many fluctuations ranging from 0.9 to 1.0 between 2007 to 2014 (Table 4.3). In Figure 4.2, the crude incidence rates for the urban and non-urban postal code areas have been visualized by year. Overall the maximum crude incidence for the study period was observed in non-urban postal code areas. However, no clear pattern of higher overall incidence in non-urban areas can be seen.

Table 4.3 Summary of the crude incidence rates for cancer, and SIR, by urban/non-urban areas, in the district of Limassol and by year (2007-2014).

	Crude incidence rate per 100,000					SIR				
	Min	**p25**	**Median**	**p75**	**Max**	**Min**	**p25**	**Median**	**p75**	**Max**
Urban										
2007	0	149.7	300.3	477.6	1,362.4	0	0.6	0.9	1.3	3.2
2008	0	153.1	358.9	504.1	1,869.2	0	0.6	1.0	1.4	3.7
2009	0	160.8	336.9	464.3	1,673.6	0	0.5	0.9	1.4	4.7
2010	0	210.2	335.9	480.5	1,639.3	0	0.6	1.0	1.4	7.9
2011	0	202.6	363.2	505.1	1,217.7	0	0.6	1.0	1.4	5.1
2012	0	203.0	342.1	536.2	1,960.8	0	0.5	1.0	1.4	4.5
2013	0	219.4	338.5	516.9	1,483.1	0	0.7	1.0	1.4	6.4
2014	0	229.5	387.1	572.4	3,225.8	0	0.6	1.0	1.3	14.9
Non-urban										
2007	0	0	223.7	552.0	4347.8	0	0	0.6	1.2	4.5
2008	0	0	254.5	625.4	3571.4	0	0	0.5	1.1	5.3
2009	0	0	256.4	676.9	4166.7	0	0	0.6	1.1	4.5
2010	0	0	296.5	734.1	3703.7	0	0	0.6	1.3	3.8
2011	0	0	321.6	805.8	2222.2	0	0	0.7	1.3	3.5
2012	0	0	316.8	708.4	2589.0	0	0	0.7	1.2	3.6
2013	0	0	304.7	669.7	5000.0	0	0	0.7	1.2	3.9
2014	0	0	428.0	747.0	2857.1	0	0	0.7	1.2	4.8

Urban areas



Non-urban areas

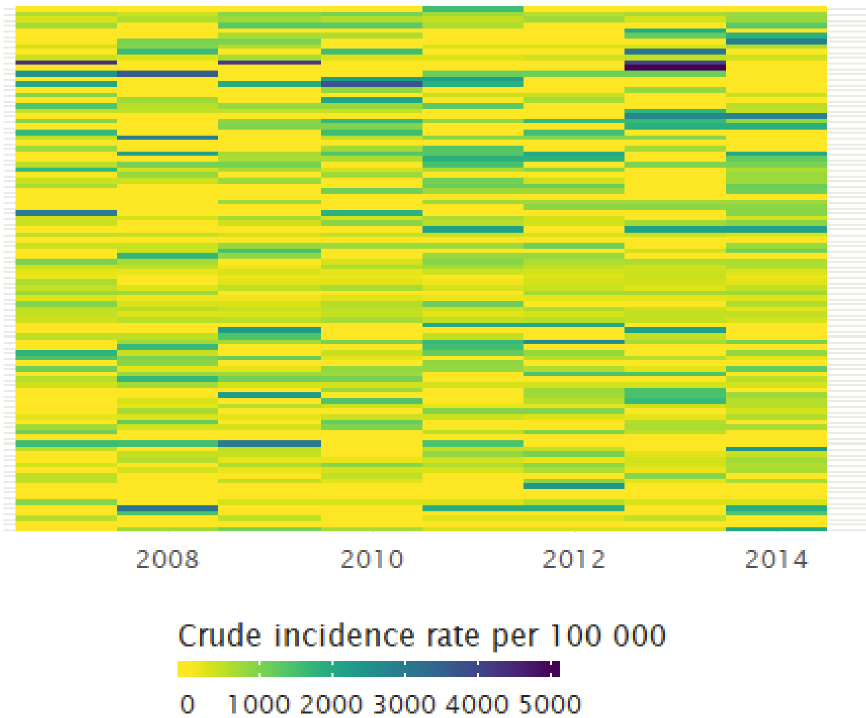


Figure 4.2 Crude cancer incidence rate in the different postal code areas of the Limassol district between 2007 and 2014, by year.

The high rates observed in some of the postal code areas (either urban or non-urban) might not represent the actual cancer burden as the population is very small. Once smoothed to account for the spatial correlation and the random noise the RR of cancer appears to be more homogenous within the district (Figure S4. 1). The between-area variability in the number of observed, or expected cases, and the SIR, as well as the effect of smoothing are more visible when visualized specifically for the urban areas the district. Maps of the observed, and expected number of cases by postal code area and by year for 2007-2014, as well as the maps of the SIR and the smoothed RR maps are available in the supplementary material (Figure S4. 1, and Figure S4. 2).

Trachea, bronchus and lung cancer by municipality/village at the Limassol district, 2007-2015

In total 648 cases of cancer in the trachea, bronchus and lung (as primary site) were reported between 2007 and 2014. Most of the cases within the study period were reported in 2013 (n=100, 15.4%). Within the study period, 2007-2014, the majority of the cases were reported in urban areas, among males (>70%) and in older age groups (median age >65 years-old). Crude incidence in the district of Limassol ranged from 28.3 per 100,000 in 2007 to 41.7 in 2013 (Table S4. 5).

Similar to what was observed for the all-cancer incidence, there was significant variability in the incidence of trachea, bronchus and lung cancer incidence in the different postal code areas of the district of Limassol. Median crude incidence, as well as the SIR was zero each year between 2007 and 2014 (Table 4.5). However, extremes were observed (e.g. max crude incidence rates higher than 280 cases per 100,000 or SIR higher than 6.8 that was observed in 2009) in the urban postal code areas (Table 4.5). As expected, given than trachea, bronchus and lung cancer cases are a subset of all cancer types, the estimates by municipality/village are more sensitive, and the CI of the smoothed RR are wider, indicating the higher variability in incidence between the neighboring postal code areas, as it can be seen in the maps of the supplementary material (Figure S4. 3 and Figure S4. 4).

Table 4.4 Age, sex descriptives of the trachea, bronchus and lung cancer cases reported by year in the district of Limassol, Cyprus (overall), and in urban/non-urban areas, 2007-2014.

	2007 (n=62)	2008 (n=67)	2009 (n=68)	2010 (n=86)	2011 (n=89)	2012 (n=81)	2013 (n=100)	2014 (n=95)	Total (n=648)
Overall									
Age (mean)	68	68	70	68	67	66	68	67	68
Sex									
Female	14 (22.6%)	16 (23.9%)	11 (16.2%)	21 (24.4%)	17 (19.1%)	10 (12.3%)	18 (18.0%)	21 (22.1%)	128 (19.8%)
Male	48 (77.4%)	51 (76.1%)	57 (83.8%)	65 (75.6%)	72 (80.9%)	71 (87.7%)	82 (82.0%)	74 (77.9%)	520 (80.2%)
Urban (n=515)									
Age (mean)	68	68	69	67	66	67	68	67	68
Sex									
Female	3 (25.0%)	0 (0.0%)	2 (16.7%)	2 (14.3%)	6 (33.3%)	4 (25.0%)	3 (13.0%)	5 (33.3%)	25 (21.6%)
Male	9 (75.0%)	6 (100.0%)	10 (83.3%)	12 (85.7%)	12 (66.7%)	12 (75.0%)	20 (87.0%)	10 (66.7%)	91 (78.4%)
Non-urban (n=116)									
Age (mean)	68	70	71	67	73	63	68	67	68
Sex									
Female	9 (19.1%)	16 (26.7%)	9 (16.1%)	16 (23.9%)	10 (14.7%)	6 (9.5%)	15 (19.7%)	15 (19.2%)	96 (18.6%)
Male	38 (80.9%)	44 (73.3%)	47 (83.9%)	51 (76.1%)	58 (85.3%)	57 (90.5%)	61 (80.3%)	63 (80.8%)	419 (81.4%)

Table 4.5 Summary of the crude incidence rates for cancers in trachea, bronchus, and lungs, SIR, and smoothed RR, by urban/non-urban areas, in the district of Limassol and by year (2007-2014).

	Crude incidence rate per 100,000					SIR				
	Min	**p25**	**Median**	**p75**	**Max**	**Min**	**p25**	**Median**	**p75**	**Max**
Urban										
2007	0	0	0	50.8	484.3	0	0	0	1.7	13.0
2008	0	0	0	54.7	337.3	0	0	0	2.2	34.2
2009	0	0	0	47.5	281.7	0	0	0	1.6	6.8
2010	0	0	0	58.5	409.8	0	0	0	1.6	12.2
2011	0	0	0	46.1	542.5	0	0	0	1.2	11.3
2012	0	0	0	47.8	423.7	0	0	0	1.6	21.8
2013	0	0	0	64.8	546.4	0	0	0	1.6	25.0
2014	0	0	0	65.3	448.4	0	0	0	1.6	13.6
Non urban										
2007	0	0	0	0	1,666.7	0	0	0	0	42.2
2008	0	0	0	0	1,190.5	0	0	0	0	15.6
2009	0	0	0	0	1,470.6	0	0	0	0	23.9
2010	0	0	0	0	2,272.7	0	0	0	0	14.1
2011	0	0	0	0	2,127.7	0	0	0	0	33.0
2012	0	0	0	0	1,960.8	0	0	0	0	45.6
2013	0	0	0	0	2,173.9	0	0	0	0	33.7
2014	0	0	0	0	2,173.9	0	0	0	0	30.8

4.3.2 Mortality rates by municipality/village at the Limassol district, 2007-2015

In total 13,567 deaths were included in the mortality registry for the period 2007-2015. The number of deaths by year ranged from 1397 in 2010 to 1,690 in 2015 (10.3% and 12.5% of the 13,567 deaths analyzed) (Table S4. 4). Most deaths overall (n=6,481, 47.8% of deaths in 2007-2015) and each year were reported by the municipality of Limassol that is also the largest municipality of the urban center of the district. Mean age at death over the years ranged from 76 to 77 years (median from 79 to 81 years), while overall 6,489 (47.8%) deaths were reported in females and 7,078 (52.2%) in males (Table 4.6).

With regards to the causes, most deaths were reported as due to diseases of the circulatory system (5,223, 38.5% of all deaths in 2007-2015). Deaths due to circulatory diseases were 40.9% of the 2007 deaths and 35.2% of the 2015 deaths, fluctuating the years between to a high of 41.6% in 2011 to a low of 35.2% in 2013. In absolute numbers, most deaths due to circulatory diseases were recorded in 2007 (n=626) and the lowest number was recorded in 2013 (n=508). The second most commonly reported cause of death was neoplasms (22.6% in 2007-2015), ranging from 20.8% (n=305) in 2008 to 26.4% (n=442) in 2014. Deaths due to infectious and parasitic diseases were 1.5% of the overall reported indicating a low burden, however, an increase from 0.9% and 14 cases only in 2007 to 2.0% and 34 cases in 2015.

Table 4.6 Age, sex descriptives and most common causes of death reported by year in the district of Limassol, Cyprus (overall), and in urban/non-urban areas, 2007-2015.

	2007 (n=1,532)	2008 (n=1,466)	2009 (n=1,421)	2010 (n=1,397)	2011 (n=1,448)	2012 (n=1,569)	2013 (n=1,445)	2014 (n=1,599)	2015 (n=1,690)	Total (n=13,567)
Overall										
Age (mean)	76	76	76	76	77	77	77	77	77	77
Sex										
Females	747 (48.8%)	703 (48.0%)	650 (45.7%)	659 (47.2%)	710 (49.0%)	789 (50.3%)	642 (44.4%)	770 (48.2%)	819 (48.5%)	6,489 (47.8%)
Males	785 (51.2%)	763 (52.0%)	771 (54.3%)	738 (52.8%)	738 (51.0%)	780 (49.7%)	803 (55.6%)	829 (51.8%)	871 (51.5%)	7,078 (52.2%)
Cause of death										
Diseases of the circulatory system	626 (40.9%)	608 (41.5%)	554 (39.0%)	543 (38.9%)	602 (41.6%)	624 (39.8%)	508 (35.2%)	563 (35.2%)	595 (35.2%)	5,223 (38.5%)
Neoplasms	323 (21.1%)	305 (20.8%)	332 (23.4%)	311 (22.3%)	319 (22.0%)	330 (21.0%)	370 (25.6%)	422 (26.4%)	400 (23.7%)	3,112 (22.9%)
Endocrine, nutritional and metabolic diseases	102 (6.7%)	104 (7.1%)	98 (6.9%)	106 (7.6%)	100 (6.9%)	137 (8.7%)	138 (9.6%)	163 (10.2%)	136 (8.0%)	1,084 (8.0%)
Diseases of the respiratory system	107 (7.0%)	89 (6.1%)	99 (7.0%)	108 (7.7%)	94 (6.5%)	113 (7.2%)	95 (6.6%)	95 (5.9%)	148 (8.8%)	948 (7.0%)
External causes of morbidity and mortality	65 (4.2%)	74 (5.0%)	87 (6.1%)	77 (5.5%)	67 (4.6%)	84 (5.4%)	75 (5.2%)	80 (5.0%)	74 (4.4%)	683 (5.0%)
Urban										
Age (mean)	76	76	75	76	76	77	76	76	77	76
Sex										
Females	556 (48.3%)	548 (48.2%)	501 (45.6%)	493 (47.2%)	523 (48.5%)	600 (50.6%)	483 (44.4%)	577 (48.2%)	634 (49.3%)	4,915 (47.9%)
Males	594 (51.7%)	588 (51.8%)	597 (54.4%)	552 (52.8%)	556 (51.5%)	586 (49.4%)	604 (55.6%)	620 (51.8%)	652 (50.7%)	5,349 (52.1%)
Cause of death										
Diseases of the circulatory system	468 (40.7%)	466 (41.0%)	426 (38.8%)	396 (37.9%)	444 (41.1%)	474 (40.0%)	382 (35.1%)	413 (34.5%)	432 (33.6%)	3,901 (38.0%)
Neoplasms	248 (21.6%)	247 (21.7%)	268 (24.4%)	241 (23.1%)	242 (22.4%)	250 (21.1%)	284 (26.1%)	331 (27.7%)	330 (25.7%)	2,441 (23.8%)

Endocrine, nutritional and metabolic diseases	73 (6.3%)	68 (6.0%)	64 (5.8%)	76 (7.3%)	75 (7.0%)	100 (8.4%)	104 (9.6%)	123 (10.3%)	103 (8.0%)	786 (7.7%)
Diseases of the respiratory system	81 (7.0%)	73 (6.4%)	76 (6.9%)	82 (7.8%)	67 (6.2%)	85 (7.2%)	68 (6.3%)	70 (5.8%)	115 (8.9%)	717 (7.0%)
External causes of morbidity and mortality	50 (4.3%)	51 (4.5%)	65 (5.9%)	62 (5.9%)	52 (4.8%)	64 (5.4%)	55 (5.1%)	63 (5.3%)	53 (4.1%)	515 (5.0%)
Non-urban										
Age (mean)	77	77	78	77	79	78	78	79	79	
Sex										
Females	191 (50.0%)	155 (47.0%)	149 (46.1%)	166 (47.2%)	187 (50.7%)	189 (49.3%)	159 (44.4%)	193 (48.0%)	185 (45.8%)	1574 (47.7%)
Males	191 (50.0%)	175 (53.0%)	174 (53.9%)	186 (52.8%)	182 (49.3%)	194 (50.7%)	199 (55.6%)	209 (52.0%)	219 (54.2%)	1729 (52.3%)
Cause of death										
Diseases of the circulatory system	158 (41.4%)	142 (43.0%)	128 (39.6%)	147 (41.8%)	158 (42.8%)	150 (39.2%)	126 (35.2%)	150 (37.3%)	163 (40.3%)	1322 (40.0%)
Neoplasms	75 (19.6%)	58 (17.6%)	64 (19.8%)	70 (19.9%)	77 (20.9%)	80 (20.9%)	86 (24.0%)	91 (22.6%)	70 (17.3%)	671 (20.3%)
Endocrine, nutritional and metabolic diseases	29 (7.6%)	36 (10.9%)	34 (10.5%)	30 (8.5%)	25 (6.8%)	37 (9.7%)	34 (9.5%)	40 (10.0%)	33 (8.2%)	298 (9.0%)
Diseases of the respiratory system	26 (6.8%)	16 (4.8%)	23 (7.1%)	26 (7.4%)	27 (7.3%)	28 (7.3%)	27 (7.5%)	25 (6.2%)	33 (8.2%)	231 (7.0%)
External causes of morbidity and mortality	15 (3.9%)	23 (7.0%)	22 (6.8%)	15 (4.3%)	15 (4.1%)	20 (5.2%)	20 (5.6%)	17 (4.2%)	21 (5.2%)	168 (5.1%)

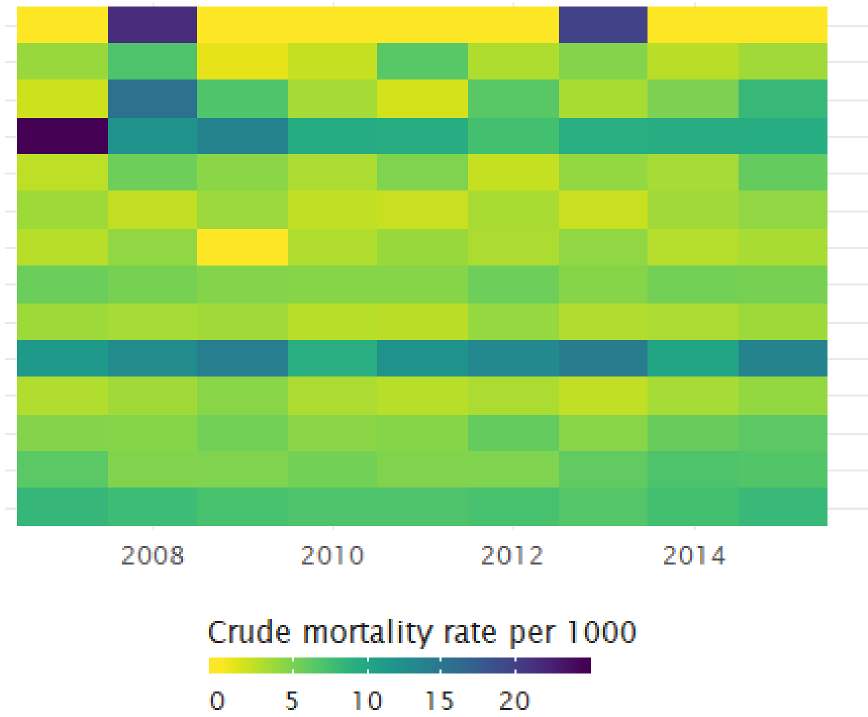
Overall the crude mortality rates (per 1,000) in the district for 2007-2015 ranged from 6 (in 2010 and 2013) to 7.2 (in 2015) (Table S4. 5). In urban areas, within the study period (2007-2015), the median crude mortality rate ranged from 3.2 deaths per 1,000 in 2010 (range: 0-9.5) to 5.4 in 2015 (range: 0-7.6) while median SMR for the study period ranged between 0.8 (2007) and 1.1 (2008) (Table 4.7). Compared to the non-urban areas, the urban median mortality rates were lower. Year-to-year changes in the SMR of the urban areas were not higher than 0.3 which was observed from 2007 to 2008 (from 0.8 to 1.1).

Similar to what was observed in the cancer risk at the level of postal code areas, the mortality rates were also highly variable in the different municipalities/villages (Figure 4.3). Indicative of the high variability in the rates and the sensitivity of the estimates is the fact that the range of crude mortality rates in the urban areas was lower than the range of crude mortality rates observed in the non-urban areas that reached maxima of above 100 deaths per 1,000.

Table 4.7 Summary of the crude mortality rates, and SMR for urban and non-urban areas, in the district of Limassol and by year, 2007-2015.

	Crude mortality rate per 1000					SMR				
	Min	**p25**	**Median**	**p75**	**Max**	**Min**	**p25**	**Median**	**p75**	**Max**
Urban										
2007	0.0	2.7	3.6	6.0	24.4	0.0	0.7	0.8	1.0	2.6
2008	2.2	4.1	5.2	10.9	21.3	0.5	0.9	1.1	1.4	2.6
2009	0.0	3.5	4.4	6.3	14.1	0.0	0.8	1.0	1.1	1.7
2010	0.0	2.7	3.2	5.0	9.5	0.0	0.6	0.9	1.0	1.2
2011	0.0	2.5	4.4	5.9	12.0	0.0	0.8	0.9	1.2	1.6
2012	0.0	3.0	4.3	6.2	12.9	0.0	0.7	0.9	1.1	1.2
2013	2.0	3.3	4.4	6.4	19.6	0.5	0.8	1.0	1.2	2.5
2014	0.0	3.1	4.1	6.5	10.0	0.0	0.8	0.9	1.0	1.2
2015	0.0	3.6	5.4	7.6	13.5	0.0	0.9	1.0	1.1	1.3
Non-urban										
2007	0.0	4.5	10.1	20.0	100.0	0.0	0.4	0.9	1.5	5.8
2008	0.0	1.9	9.3	17.2	65.6	0.0	0.3	0.8	1.4	4.3
2009	0.0	0.0	8.6	16.7	200.0	0.0	0.1	0.8	1.3	57.6
2010	0.0	2.8	8.0	15.9	80.0	0.0	0.3	1.0	1.3	2.8
2011	0.0	2.4	9.4	17.2	68.2	0.0	0.4	0.9	1.2	5.9
2012	0.0	2.1	8.3	17.5	600.0	0.0	0.3	0.9	1.3	160.1
2013	0.0	0.0	7.9	15.0	142.9	0.0	0.0	0.9	1.3	3.6
2014	0.0	5.7	10.5	19.6	80.0	0.0	0.6	0.9	1.2	5.0
2015	0.0	4.2	9.3	16.3	55.6	0.0	0.4	0.7	1.1	3.8

Urban areas



Non-urban areas

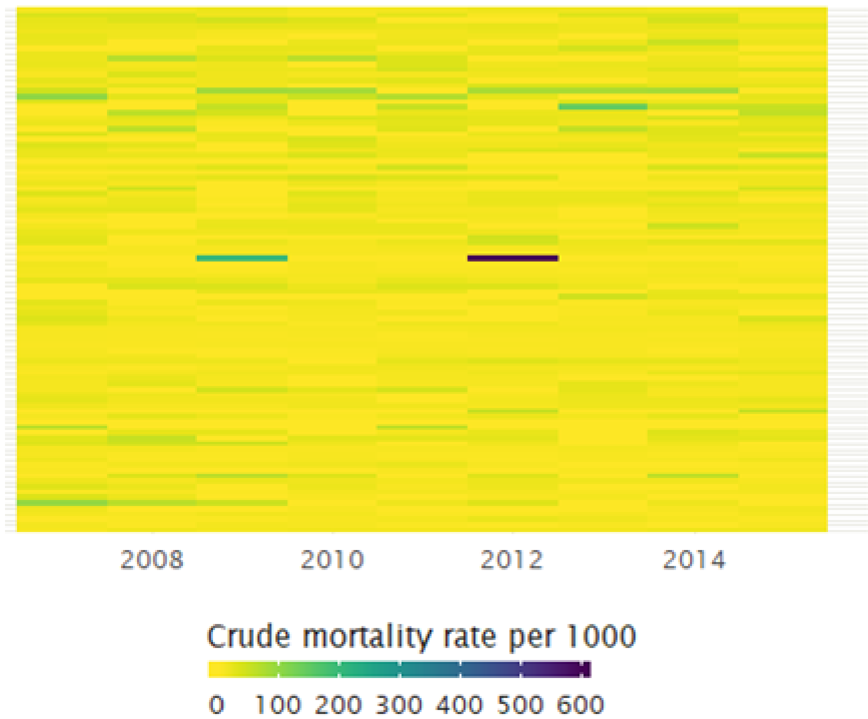


Figure 4.3 Crude mortality rate in the different municipalities/villages of the Limassol district between 2007 and 2015, by year.

The high mortality rates observed might not be accurately representing the actual mortality burden as the population in some areas is very small. Maps of the expected and observed deaths as well as the SMR and the RR (including the 95% CI) estimates for the complete study period (2007-2015) are available in Figure S4. 5. The municipality of Limassol stands out in all the maps as it had the highest number of deaths, as expected given that it is the largest municipality in the district (Figure S4. 5). However, year to year mortality rates and the RR seem to be relatively stable for the whole district but also in the urban area (Figure S4. 5 and Figure S4. 6).

4.3.3 Tuberculosis notification by municipality/village at the district of Limassol, 2015-2017

In total 42 cases of TB were notified in the district of Limassol between 2015 and 2017, in ten (of the 111) municipalities/villages. The majority of the cases (n=26, 61.9%, overall) were notified in the municipality of Limassol (8/17 in 2015, 9/13 in 2016, and 9/13 in 2017) and only six cases were reported in non-urban areas (Table 4.8). Mean age for the study period was 42 years of age (median: 35; range: 4-77 years). The majority of the cases were reported in females overall (n=25, 59.5%) and in each of the three years studied.

Table 4.8 Descriptives of the notified tuberculosis cases in the district of Limassol, Cyprus, 2015-2017.

	2015			2016			2017		
	Overall (n=17)	**Urban (n=13)**	**Non-urban (n=4)**	**Overall (n=12)**	**Urban (n=11)**	**Non-urban (n=1)**	**Overall (n=13)**	**Urban (n=12)**	**Non-urban (n=1)**
Age									
Mean	46	43	56	36	36	35	38	27	**35**
Sex									
Female	10 (58.8%)	8 (61.5%)	2 (50.0%)	7 (58.3%)	7 (63.6%)	-	8 (61.5%)	7 (58.3%)	1 (100%)
Male	7 (41.2%)	5 (38.5%)	2 (50.0%)	5 (41.7%)	4 (36.4%)	1 (100%)	5 (38.5%)	5 (41.7%)	-
Birthplace									
Native	5 (29.4%)	4 (30.8%)	1 (25.0%)	1 (8.3%)	1 (9.1%)	-	3 (23.1%)	3 (25.0%)	-
Foreign-born	12 (70.6%)	9 (69.2%)	3 (75.0%)	11 (91.7%)	10 (90.9%)	1 (100%)	10 (76.9%)	9 (75.0%)	1 (100%)
Site									
Extrapulmonary	4 (23.5%)	4 (30.8%)	-	3 (25.0%)	3 (27.3%)	-	1 (7.7%)	1 (8.3%)	-
Pulmonary	13 (76.5%)	9 (69.2%)	4 (100%)	9 (75.0%)	8 (72.7%)	1 (100%)	12 (92.3%)	11 (91.7%)	1 (100%)

The crude notification rate in the district was 7.2 per 100,000 in 2015, and 5.0, and 5.4 per 100,000 in 2016 and 2017, respectively. In Figure 4.4, the expected and observed number of TB cases in the district of Limassol as well as the SCNR have been mapped. As in the analysis of the cancer and mortality registry data, the municipality of Limassol is shown to be bearing the highest burden compared to the other areas of the district. However, sporadic TB cases were also notified in municipalities/villages neighboring to the municipality of Limassol and within the extended urban center of Limassol, as it can be observed in the maps of the urban area of Limassol (Figure 4.4 and Figure 4.5). There seems to be a spatial trend within the study period, 2015-2017 (Figure 4.5), of TB cases notified from areas in closer proximity to the municipality of Limassol compared to more distant areas (e.g. on the eastern end of the urban center).

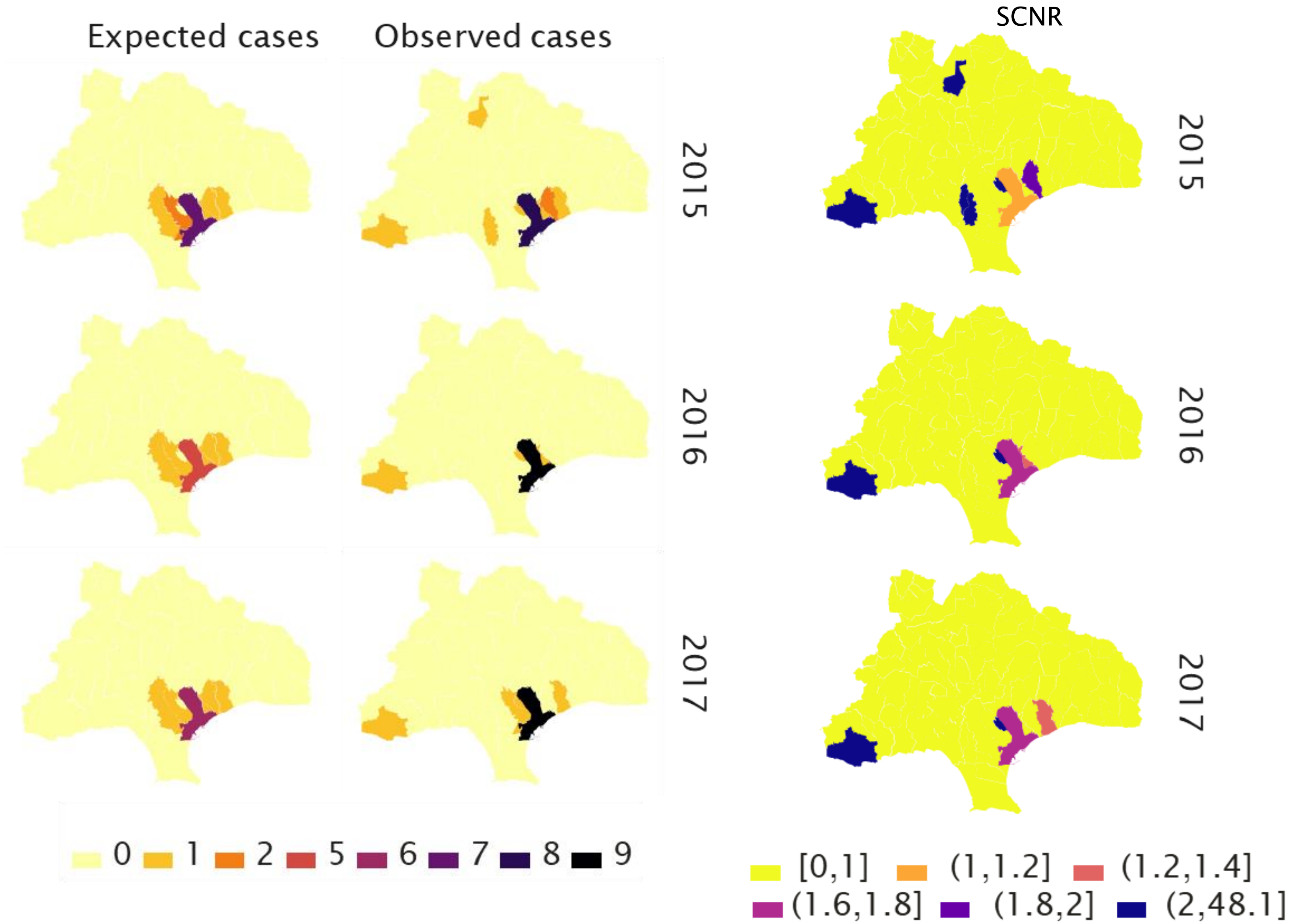


Figure 4.4 Expected and observed number of notified TB cases and SCNR in the district of Limassol, 2015-2017.

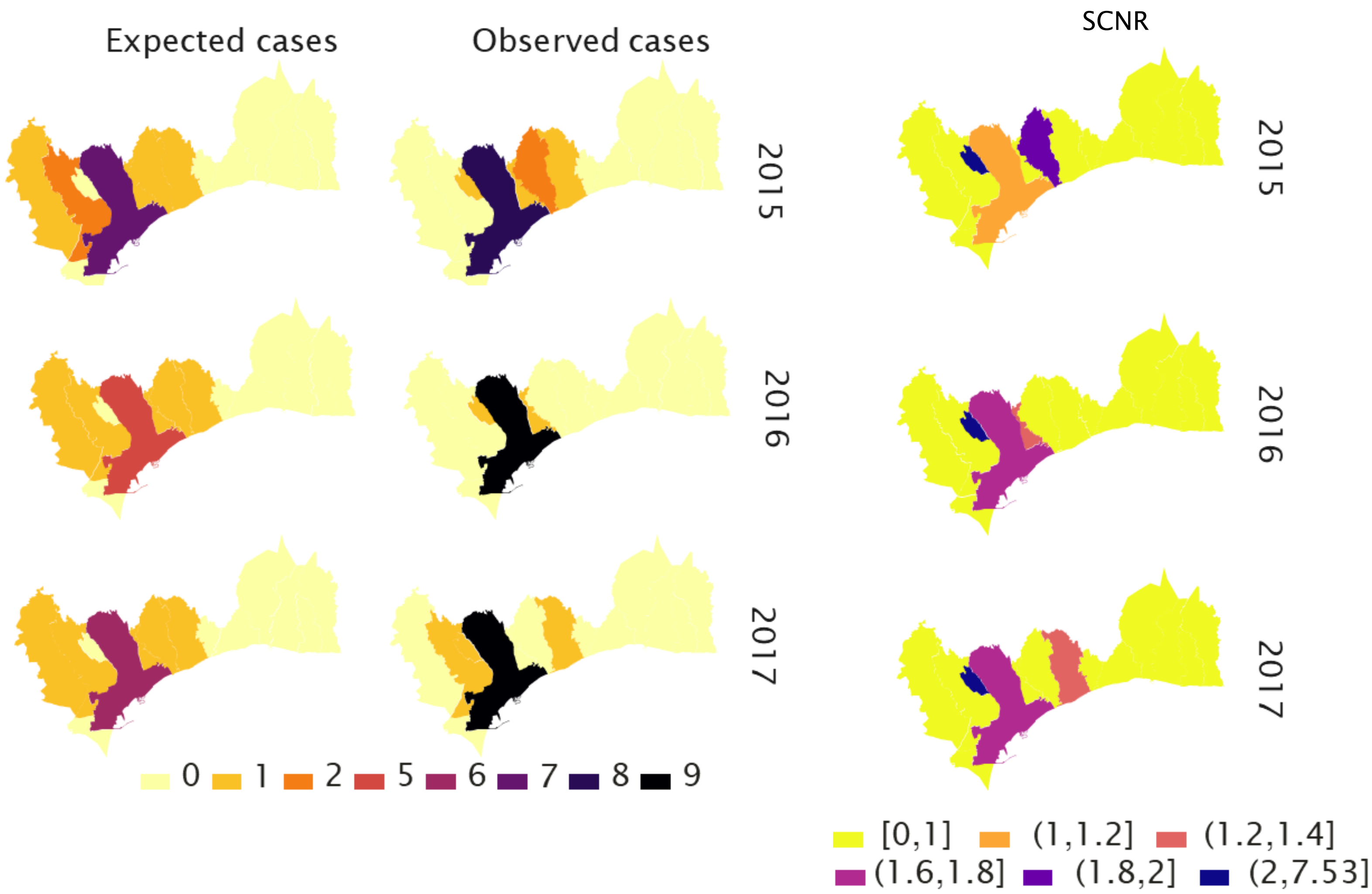


Figure 4.5 Expected and observed number of notified TB cases and SCNR in the urban part of the district of Limassol, 2015-2017.

4.4 Discussion

This is the first urban exposome study focusing on the epidemiology of cancer, mortality, and infectious diseases (using TB as an example) and describing the variability of these diseases/outcomes using small within-city areas as the units of reference. Previous studies have used exposome approaches to describe exposures in cities using rather generic definitions of the urban exposome as the sum of the exposure in the city (57,94). These studies have mostly focused on how exposures might be linked with specific health outcomes and for specific populations (57,94). Viewing the city as the measurable unit of the urban exposome, we used routinely collected data from the cancer registry, the death registry and TB notifications to assess changes in the rates of cancer, deaths, and TB notification in the district of Limassol, Cyprus, and more specifically within the urban center of Limassol.

As expected, due to the population distribution, more cancer cases, more deaths and more TB cases were notified from the municipality of Limassol, that is also the main urban hub of the city of Limassol. Crude cancer rates were higher in the urban areas compared to the non-urban areas during the study period (2007-2014) with more "extreme" maximum values in non-urban postal code areas. The most frequently reported cancers were breast cancer, prostate cancer, colorectal cancer, and trachea, bronchus and lung cancer, as well as thyroid cancers. In the analysis of trachea, bronchus, and lung cancers, the urban areas were found to have higher variability in the crude incidence rates as well in SIR compared to the non-urban areas of Limassol district. With regards to mortality rates, in the urban areas, the maximum values observed were lower compared to the non-urban ones. The largest difference from one year to the next, was observed from 2007 to 2008 when the median crude mortality increased from 3.6 per 1,000 to 5.2 per 1,000. Crude mortality rates per 1,000 in the district of Limassol, were lower or comparable to the national rates every year within the study period (95). Additionally, the mean age at death was lower than the life expectancy at birth for the same years (2007-2015) possibly reflecting the diffences in the time periods, improvement in quality of life and differences in calculating the two indications (i.e. mean age at death and life expectancy at birth) (96,97).TB notification rates for the district declined between 2015 and 2016, and in the study period (2015-2017) there seemed to be higher burden in the municipality of Limassol and its neighboring municipalities.

The aim of this study was to present a baseline assessment of the epidemiology, including the spatial and temporal distribution, of cancer, mortality, and TB notifications in the different areas of Limassol with focus on the urban areas. To this end, the focus was a descriptive analysis to provide methodological tools for the assessment of urban health in Limassol under the framework of the urban exposome. Further statistical analysis and descriptions in terms of statistical significance of the changes in the observed trends was not sought given the exploratory and "proof-of-concept" nature of the study.

Limassol is a city that faces rapid economic development the past few years and it has emerged as one of the most important development hubs in Eastern Mediterranean. However, Limassol itself, compared to the capital of Cyprus, Nicosia, has been studied less in terms of urban and public health. The analysis provided herein, is the first that maps routinely collected data, taking advantage of existing information to build upon them for the development of the urban exposome of Limassol, in combination with the mapping of urban indicators previously analyzed from a population study conducted in 2017 (80).

This analysis is of exploratory nature. Therefore, inferences need to be made with caution and take into consideration the multiplicity of factors that might be influencing the observed changes in the cancer, death, and TB notification rates between the years. This analysis aimed to provide a baseline assessment of the "health status" of Limassol, as it is reflected in the routinely collected data, and a series of limitations need to be considered. Firstly, the calculation of the population at risk in the small areas (either postal code areas, or municipalities/villages) was based on the assumption that the small area populations maintained the same age structure as in 2011 (census year) and that within study periods they accounted for the same proportion of the total district population thatwas enumerated in the most recent census. Small population changes in these small areas might have changed significantly the overall population at risk, however, in this analysis, this could not be considered. Secondly, given the specific characteristics of each data source and data availability, different aggregation levels were used for spatial inference. For example, in the cancer registry postal code areas were used, while for the mortality data and the TB notifications the municipalities/villages were used as reference. The boundaries of the postal code areas or the municipalities/villages might not adequately represent the within-city differences. Future studies could incorporate the development of specific criteria for a more meaningful definition of the small within-city areas, e.g. using infrastrures or land use to allow for uniform data aggregation and better interpretation of the observed variability. Furthermore, data were not available for the same time periods for all the three analyses done. Cancer and mortality data were available for a longer period, i.e. eight years (2007-2014), and nine years (2007-2015), respectively, while the TB notifications data were available for three years (2015-2017).

Using this analysis, and by combining/extending the prospective description of the urban exposome with more primary studies on population health and the assessment of environmental risk factors prospectively, stakeholders can more readily assess the need for interventions to improve public health within Limassol while taking advantage of the most recent scientific evidence. The urban exposome of any city, and of Limassol specifically, is a continuously evolving entity and its prospective assessment can be instrumental for developing targeted/local urban public health interventions.

Different studies and in various settings have used small-area estimates to assess the impact of specific factors in health. For example, recently, in a study in France, the effect of heat waves in mortality was assessed for the city of Paris, or in another study in London, exposures to air pollution and mortality were evaluated (98,99). Various other studies have also used cancer incidence as the outcome, mapping the burden and identifying areas of higher and lower risk (100). What is commonly coming up in the literature, is the one exposure-one outcome approach and the focus on large cities. In the case of the urban exposome of Limassol we opted to build upon the previous literature and studies that describe spatiotemporal distribution of diseases but, also, to move on and combine also infectious diseases' routinely collected data to support the development of the urban exposome profile of a city.

TB was selected as an example of infectious diseases that bears a high burden both for individuals and societies. Cyprus is a country of low TB incidence but the cost of treatment is still high estimated at more than 10,000 euro per patient in 2009 (101,102). From the analysis and the mapping of the cases, there seems to be a trend of TB notifications to be spatially clustered based on the residence of the patients within the municipality of Limassol and in neighboring municipalities/villages. While a more detailed study of possible epidemiologic links between the individual cases was beyond the scope of the present analysis and inferences should be made with caution, the data from this analysis indicate that to achieve elimination, also in Cyprus, special attention should be paid in urban centers.

The aim of the present study was to complete the description of the urban exposome of Limassol, Cyprus by focusing on the urban area and to meet that end, a baseline assessment of routinely collected data with the description of the epidemiology of non-communicable and communicable diseases in the district was conducted. The spatial and temporal distribution of cancer cases, mortality, and notified TB cases within the district of Limassol, Cyprus were mapped for the different study periods for which data were available and they can be used as the baseline to prospectively assess changes in cancer, mortality, and TB case notification burden within the urban areas of Limassol. The information generated from this analysis and the methodological approach presented using the application of the urban exposome study framework in Limassol can be the basis on which future assessments of urban health in Limassol will be conducted and a basis for public health interventions to be developed to tackle within-city health inequalities.

Disclaimer

The data used in this study was collected by the Health Monitoring Unit and the Surveillance and Control of Communicable Diseases Unit of the Ministry of Health of

Cyprus. The ideas and opinions expressed herein are those of the authors. Endorsement of these ideas and opinions by the Ministry of Health of Cyprus is not intended nor should it be inferred.

Acknowledgements

The authors would like to sincerely thank everyone involved in reporting cases, involved in the everyday data collection and the maintenance of the registries and the routine surveillance of infectious diseases in Cyprus.

5 Synthesis

5.1 Urban exposome from definition to application

The definition of the exposome and the advances in omics technologies have widened the scope of population health studies and have provided classic epidemiology with new tools to explore the emergence and distribution of diseases. At the same time, societal progress and changes in the global distribution of human populations that are nowadays mostly living in cities reshapes the way urban health could be studied. The definition of the urban exposome study framework (Chapter 1) proposed a holistic approach in targeting urban health issues by viewing cities and their smaller areas as standalone entities with their own exposome. This "new" exposome, i.e. the urban exposome, encompasses the human exposome and it is an extension of of the human exposome continuum. The study framework described, in detail, in Chapter 2, outlined the different domains of the urban exposome (external and internal) and its associations with the respective domains of the human exposome. Additionally, an application of the urban exposome framework was described for the city of Limassol in Cyprus.

The application of the urban exposome study framework in Limassol, Cyprus was conducted in two different parts. In the first part, detailed in Chapter 3, elements of the external and internal urban exposome of the city of Limassol were studied in the municipality of Limassol. This two-part study was conducted combining qualitative and quantitative elements. First, the perceptions of different stakeholders (i.e. municipality officers and citizens) were described and, then, a primary cross-sectional study was conducted to map drinking water and quality of life indicators using a population survey and water sample collection. The assessment of drinking water chemical (disinfection byproducts-trihalomethanes) and microbial (coliforms, *E. coli*, and *Enterococci*) quality indicators did not raise particular concerns. However, study participants' (i.e. residents of Limassol municipality) general health and chronic health status we found to be linked with chronic health conditions, e.g. hypertension and asthma, and with broader determinants of health such as having financial issues in access to dental care. In the same study, correlations of chemical exposures (as measured in tap water samples from the participants households) and participant behavioral characteristics (e.g. household cleaning, drinking water habits) were documented.

This first proof-of-concept study demonstrated the feasibility of using integrative and holistic approaches to develop urban exposomic profiles to describe within-city differences in environmental and health indicators. To complete the study of the urban exposome of Limassol, in Chapter 4, the study setting was extended to the urban area of Limassol district which, besides the municipality of Limassol, includes five municipalities of population more than 10,000, i.e. Kato Polemidia, Mesa Geitonia, Agios Athanasios, Germasogeia, and Ypsonas, as well as five smaller municipalities (Mouttagiaka, Agios Tychon, Parekklisia, Monagrouli, Moni, Pyrgos Lemesou, and Tserkezoi) with population ranging from more than 3,000 to less than 100 (according to the 2011 census). This analysis was restricted to data routinely collected by the Ministry of Health. Cancer incidence for 2007-2014, and mortality for the period 2007-2015 were mapped in postal code areas and by municipality/village, respectively. Additionally, TB notifications between 2015 and 2017 were also analyzed and the TB burden in the urban area of Limassol was assessed.

As mentioned, in the introduction, there are not many studies addressing public health and urban issues in Limassol. However, notable research efforts have been made and need to be unified to answer the demand to inform and address urban health issues in Cyprus. For example, in a recent study Alverti et al. (2018) mapped routinely collected data to identify links between what was described as "human smart characteristics", socio-demographic and urban indicators (103). This study although not having strictly a health-focused approach assesses broader determinants of health in the urban environment of Limassol. Also recently, social deprivation indices were developed using census data and their possible associations with mortality (104), while heat-related mortality was assessed comparing the urban and rural environment in Nicosia (105) or, in another more descriptive study, breast cancer data were presented however, without taking into account spatial differences (106). All these studies, along with currently run (or under design) studies to describe health in the cities of Cyprus can inform future urban exposome studies not only in Limassol but also in Nicosia. Then, in combination with the study described here, they can inform the continuous surveillance and monitoring of the urban exposomes of Cypriot cities and provide policymakers and stakeholders with the evidence to identify and respond to public health issues.

Any effort to describe the urban exposome, and to prospectively monitor city health, comes with specific challenges which have to do with the feasibility of conducting primary epidemiologic studies in regular intervals or setting up cohort studies with adequate follow-ups, and with the availability of timely secondary data and at levels of aggregation that allow easy data harmonization and comparisons. When conducting an urban exposome study, stakeholder engagement should be prioritized and communication of any results should be conducted in a timely manner.

The three main components of this study were: (i) the development of the theoretical study framework, (ii) a population study with qualitative and quantitative elements, and (iii) an analysis of routinely collected data. All three components are the cornerstones of the continuum between the urban exposome, defined as the continuous monitoring of indicators pertaining to life in the city, and the human exposome (Figure 5.1). To our knowledge, this is the first study that uses a more holistic application of the urban exposome. At the same time, it is the first study in Limassol, Cyprus that has a specific public, and environmental health orientation assessing also disease epidemiology in the city. These results can be of help towards assessing further challenges thatLimassol s facing, and also, it can help towards applying the urban exposome study framework in other, larger cities.

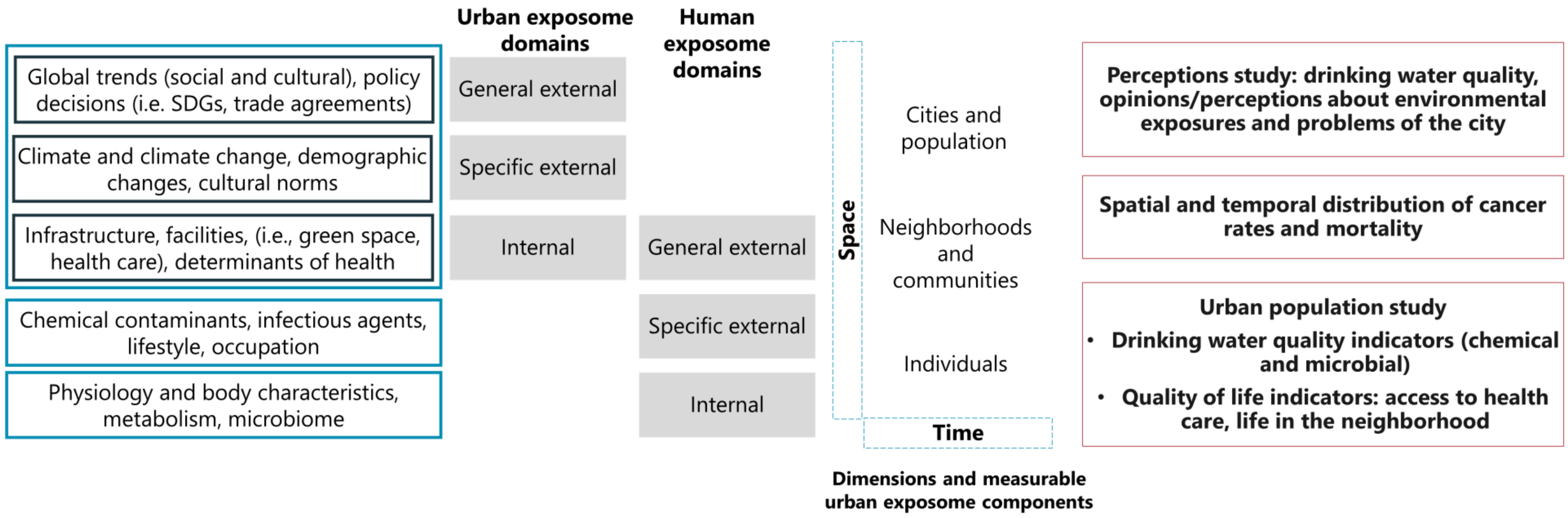


Figure 5.1 Continuum between the urban exposome and the human exposome, and its application in Limassol, Cyprus.

5.2 The position of the urban exposome within the exposome paradigm

The term "urban exposome" has so far very limited use in the literature. Two main studies of "urban exposomes" focus on early life and on how different exposures affect either pregnancy or low birth weight (57,94). Since Dr Wild presented the first definition of the exposome and how its subdivision in three domains i.e., general and specific external, and the internal domain can be used to analyze the life course of exposures, various other "exposomes" have also been used and defined (28,29). For example, the indoor exposome (37), the eco-exposome (38), or the systems biology-based adverse outcome pathways exposome (39) and the pollutome (40) are some of these exposomes. Viewing the urban exposome as the sum of exposures that are related to life in the city (41) it can be considered as a subdivision of the human exposome (i.e. the totality of exposures) which is specific to the time individuals spend in the city.

However, cities are evolving environments, changing and progressing along with the population living in them, along with the infrastructure and along with wider global changes. Therefore, in order to move on from a human-centric exposome while keeping humans, and their exposures in the core, the urban exposome was defined a study framework that allows us to describe how the cities are changing and what is their impact on populations and population health.

So far, various research initiatives have targeted different aspects of the human exposome while as it has been acknowledged by the scientific community more holistic approaches are necessary to combine the different "sub-fields" of public health, epidemiology, infectious diseases and environmental risk factors studies. Unifying approaches are reflected both in scientific opinions and wider public health initiatives (107,108). However, large exposome studies are still mostly focused on assessing "traditional" environmental risk factors but in larger scale (e.g. in multiple cohorts) and with the use of various, more advanced, tools for personal exposure assessment (42–44).

The approaches do not come at odds with the definition of the urban exposome, as it was presented here and as it was applied for the case of the city of Limassol. They present excellent technological approaches and advanced assessment of personal exposures using modern technologies such as geographic information systems and multiple omics. However, they do not address systemic determinants of health which for the case of the cities are largely associated with the city residents behavior and habits, with governance either at national or global level and of course, with changes that go beyond what is "human-controlled" such as those changes that will be the result of climate change and/or the result of the responses to climate change.

Therefore, we need to combine approaches from multiple scientific fields, to use cutting edge technological advances but most importantly, to communicate within the scientific community and address the global changes, and their effects on cities in a way that is at the same time inclusive, cross- and trans-disciplinary, and uniform. The urban exposome study framework, at the first part presented the theoretical background that is necessary to achieve a unified approach for studying the health profile in a city. Whereas, in the second part, presented an inclusive, cross- and trans-disciplinary approach to map health in the city of Limassol, Cyprus.

6 Public health significance and recommendations – extending the urban exposome study framework to application

This study aimed to provide a holistic assessment of urban health issues and incorporate the relatively new concept of the exposome in urban health. Assessment of the exposome is in relatively early stages, worldwide, and while various studies have attempted to capture the totality of exposures, the efforts are hindered by inherent limitations that start from defining the totality of exposures. The approach proposed and implemented here aimed to benefit from the routinely collected data, harmonize them to achieve integration and assessment of correlations among the indicators while conducting a primary population study. This approach aimed to evaluate the totality of urban characteristics and combine them with environmental parameters and health outcomes in order to provide the foundation for the development and application of precise, and effective public health interventions within the urban exposome. Achieving the project goals required the smooth collaboration with the governmental agencies and the assessment of different data sources.

The project was developed to provide the framework of data integration from different sources to inform future public health interventions and decision-making at the local level while following the urban exposome study framework that was defined before the primary data collection and the analysis of the secondary data. Urban settings have unique characteristics and face unique challenges which need to be timely addressed. Thus, a framework for timely public health data integration at the city level can provide policy making advantages to the local authorities that face the urban issues routinely. This can have implications for wider policy making efforts which are targeting also social determinants of health and the alleviation of health inequalities within cities. At the same time, the incorporation of environmental indicators (i.e. air pollution, water quality) and personal measurements (i.e. through biomonitoring) can help refine exposure assessment while addressing wider environmental issues and sustainable development which are implicitly related to health and quality of life.

More specifically, the project provided the methodological foundation for mapping of the environmental health and urban indicators for Limassol, Cyprus which can be extended also to larger cities with higher within-city variability in health determinants, environmental and health indicators. Various studies in Cyprus have been conducted in urban settings but they were mostly using Nicosia as the study site. Moreover, previous studies have been dealing with single outcomes, such as air pollution, water quality or chronic diseases. In this study an innovative approach of combining multiple study designs to investigate a suite of environmental and health parameters was defined and developed to take advantage of the routinely collected knowledge and of setting up a primary study in a study site (i.e. Limassol, Cyprus) that had not been studied before. Understanding how the environmental health and urban indicators are distributed within the city of Limassol will allow the local authorities to identify the needs of the city and better address environmental and health issues.

The health status of the city of Limassol was assessed using an interdisciplinary approach that used routinely collected data, a perceptions study and population study. The study results are readily available to policy makers, the local authorities and can be used to develop public health interventions for the city, as well as to provide baseline information about Limassol. At the same time the study can inform future urban and public health studies for Cyprus that can be conducted also in other cities.

CONCLUSIONS

The exposome, being a relatively newly defined term, has gained recognition as a study framework of human exposures and of the impact of environmental parameters in human health. The scope of the exposome is such that allows the incorporation of various parameters to be used simultaneously within the scope of more traditional population, environmental health studies. The advantages of using exposome approaches are numerous ranging from providing frameworks for interdisciplinary cooperation between fields to allowing description of specific exposures in large population and paving the way for discovery of new disease risk factors. However, in order for the exposome to be integrated in public health interventions, it needs to be more targeted with regards to the study settings and more inclusive of smaller-area parameters that affect health in specific settings. The study framework of the urban exposome was developed as a response to the need of specifying the use of exposome approaches in urban settings while placing the cities and their smaller (within-city) areas in the core as the measurable units. In this context, first we defined the urban exposome and developed a study framework that outlines how the urban exposome can be assessed, including methodological details from the different disciplines that need to be brought together and the data needs. Following the definition of the urban exposome and the development of the study framework, a study, the application of the urban exposome framework in Limassol, Cyprus took place using a combination of quantitative and quantitative approaches. Perceptions of city residents about urban aspects were assessed and a primary population study was conducted in summer 2017. Drinking water parameters and quality of life were assessed in this first part for the application of the urban exposome. Different approaches were used to demonstrate how the urban exposome can be applied to map citizens' perceptions and other indicators for drinking water quality and quality of life. In the second part, surveillance/monitoring data were used to describe spatially and temporally indicators such as cancer incidence and mortality rates. The analysis of all aforementioned parameters, from the perception study, the primary data collection as well as from the routinely collected (secondary) data demonstrates information about the city that can be incorporated to provide policy makers and other stakeholders, including the citizens themselves, with information about the health status and quality of life of the city. The generated information from different sources can further be a “toolkit” that can be timely used to indicate how the urban exposome of Limassol, Cyprus, in this case, and any city, evolves and how it can be assessed, or how the human exposome can be used as an integral part and in continuation to the urban exposome (i.e. the exposome of the city and within-city areas) to address questions about the progress of a city towards a healthier status.

REFERENCES

1. WHO | Urban population growth [Internet]. WHO. 2016 [cited 2016 Sep 15]. Available from: http://www.who.int/gho/urban_health/situation_trends/urban_population_growth_text/en/

2. Urban population (% of total) | Data [Internet]. [cited 2016 Sep 15]. Available from: http://data.worldbank.org/indicator/SP.URB.TOTL.IN.ZS

3. United Nations Statistics Division - Demographic and Social Statistics [Internet]. [cited 2016 Jul 14]. Available from: http://unstats.un.org/unsd/demographic/sconcerns/densurb/densurbmethods.htm

4. European cities – the EU-OECD functional urban area definition - Statistics Explained [Internet]. 2016 [cited 2016 Sep 14]. Available from: http://ec.europa.eu/eurostat/statistics-explained/index.php?title=Archive:European_cities_%E2%80%93_the_EU-OECD_functional_urban_area_definition

5. Galea S, Freudenberg N, Vlahov D. Cities and population health. Soc Sci Med. 2005 Mar;60(5):1017–33.

6. Vlahov D, Galea S. Urban health: a new discipline. The Lancet. 2003 Oct 4;362(9390):1091–2.

7. WHO | Health as the pulse of the new urban agenda [Internet]. WHO. [cited 2016 Oct 21]. Available from: http://www.who.int/phe/publications/urban-health/en/

8. Population Census 2011 [Internet]. Statistical Service, Republic of Cyprus. 2014 [cited 2014 Sep 9]. Available from: http://www.mof.gov.cy/mof/cystat/statistics.nsf/census-2011_cystat_en/census-2011_cystat_en?OpenDocument

9. Cities in Europe - The new OECD-EC definition [Internet]. 2012 [cited 2017 Feb 13]. Available from: http://ec.europa.eu/regional_policy/en/information/publications/regional-focus/2012/cities-in-europe-the-new-oecd-ec-definition

10. Glossary:Urban centre - Statistics Explained [Internet]. [cited 2016 Oct 16]. Available from: http://ec.europa.eu/eurostat/statistics-explained/index.php/Glossary:Urban_centre

11. UN-HABITAT.:. Our Mission [Internet]. [cited 2016 Oct 7]. Available from: http://mirror.unhabitat.org/categories.asp?catid=10

12. WHO | Healthy Cities [Internet]. WHO. 2016 [cited 2016 Dec 10]. Available from: http://www.euro.who.int/en/health-topics/environment-and-health/urban-health/activities/healthy-cities

13. World Health Organization, United Nations Human Settlements Programme, editors. Hidden cities: unmasking and overcoming health inequities in urban settings. Kobe, Japan: World Health Organization; UN-HABITAT; 2010. 126 p.

14. United Nations Human Settlements Programme, World Health Organization, Kobe Centre. Global report on urban health equitable, healthier cities for sustainable development. [Internet]. Kobe, Japan: WHO Kobe Centre; 2016 [cited 2016 Aug 12]. Available from: http://apps.who.int/iris/bitstream/10665/204715/1/9789241565271_eng.pdf

15. WHO | Millennium Development Goals (MDGs) [Internet]. WHO. [cited 2016 Oct 7]. Available from: http://www.who.int/topics/millennium_development_goals/en/

16. Goal 11: United Nations Partnerships for SDGs platform [Internet]. 2016 [cited 2016 Aug 12]. Available from: https://sustainabledevelopment.un.org/partnerships/goal11/

17. Goal 3: Sustainable Development Knowledge Platform [Internet]. 2016 [cited 2016 Aug 12]. Available from: https://sustainabledevelopment.un.org/sdg3

18. Healthy Cities Cyprus News [Υγιείς Πόλεις: Συμμετοχή του πολίτη στην αποτύπωση της ταυτότητας υγείας της πόλης] [Internet]. Cyprus Univeristy of Technology. 2019 [cited 2019 Jul 7]. Available from: https://www.cut.ac.cy/news/article/?contentId=171230

19. Middleton N, Yiallouros P, Kleanthous S, Kolokotroni O, Schwartz J, Dockery DW, et al. A 10-year time-series analysis of respiratory and cardiovascular morbidity in Nicosia, Cyprus: the effect of short-term changes in air pollution and dust storms. Environ Health. 2008 Jul 22;7(1):39.

20. Kolokotroni O, Papadopoulou A, Middleton N, Kouta C, Raftopoulos V, Nicolaidou P, et al. Vitamin D levels and status amongst asthmatic and non-asthmatic adolescents in Cyprus: a comparative cross-sectional study. BMC Public Health. 2015;15:48.

21. Tsangari X, Andrianou XD, Agapiou A, Mochalski P, Makris KC. Spatial characteristics of urinary BTEX concentrations in the general population. Chemosphere. 2017 Apr;173:261–6.

22. Andrianou XD, Charisiadis P, Andra SS, Makris KC. Spatial and seasonal variability of urinary trihalomethanes concentrations in urban settings. Environ Res. 2014 Nov;135:289–95.

23. Ministry of Health (Cyprus) [Internet]. [cited 2017 Feb 14]. Available from: http://www.moh.gov.cy/moh/moh.nsf/index_en/index_en?OpenDocument

24. Ministry of Interior (Cyprus) [Internet]. [cited 2017 Feb 14]. Available from: http://www.moi.gov.cy/moi/moi.nsf/index_en/index_en?OpenDocument

25. Τμήμα Πολεοδομίας και Οικήσεως - Υπουργείο Εσωτερικών [Internet]. [cited 2017 Feb 14]. Available from: http://www.moi.gov.cy/moi/tph/tph.nsf/index_gr/index_gr?OpenDocument

26. Τμήμα Πολεοδομίας και Οικήσεως - Ανακοινώσεις [Internet]. [cited 2017 Feb 14]. Available from: http://www.moi.gov.cy/moi/tph/tph.nsf/All/FC99BF0648CD2A27C22580C100476248?OpenDocument

27. Batty M. The new science of cities. Cambridge, Massachusetts: MIT Press; 2013. 496 p.

28. Wild CP. Complementing the Genome with an "Exposome": The Outstanding Challenge of Environmental Exposure Measurement in Molecular Epidemiology. Cancer Epidemiol Biomarkers Prev. 2005 Aug 1;14(8):1847–50.

29. Wild CP. The exposome: from concept to utility. Int J Epidemiol. 2012 Feb 1;41(1):24–32.

30. Miller G. The Exposome: Purpose, Definition, and Scope. In: Exposome: a primer. Elsevier; 2014. p. 1–12.

31. Porta MS, Greenland S, Hernán M, Silva I dos S, Last JM, International Epidemiological Association, editors. A dictionary of epidemiology. Six edition. Oxford: Oxford University Press; 2014. 343 p.

32. Demographic Report, 2017 [Internet]. Cyprus Statistical Service - Population and Social Conditions - Population. [cited 2019 Jul 3]. Available from: https://www.mof.gov.cy/mof/cystat/statistics.nsf/All/77A0741D88AEB4B7C225834E003F69F2?OpenDocument&sub=1&sel=1&e=&print

33. Classification for the Degree of Urbanisation in Cyprus [Internet]. Cyprus Statistical Service. [cited 2019 Jul 4]. Available from: https://www.mof.gov.cy/mof/cystat/statistics.nsf/classifications_en/classifications_en?OpenForm&print

34. Degree of urbanization classification: methodology - Eurostat [Internet]. [cited 2019 Jul 5]. Available from: https://ec.europa.eu/eurostat/web/degree-of-urbanisation/methodology

35. Benner M, Hirth J, Kraatz F, Ludwig K, Schrade J. Regional development in the context of economic reform: The case of Limassol [Internet]. 2017 [cited 2019 Jul 7]. Available from: https://mpra.ub.uni-muenchen.de/76834/

36. Vlahov D, Galea S. Urbanization, urbanicity, and health. J Urban Health. 2002;79(1):S1–12.

37. Dai D, Prussin AJ, Marr LC, Vikesland PJ, Edwards MA, Pruden A. Factors Shaping the Human Exposome in the Built Environment: Opportunities for Engineering Control. Environ Sci Technol. 2017 Jul 18;51(14):7759–74.

38. National Research Council. Exposure Science in the 21st Century: A Vision and a Strategy [Internet]. 2012 [cited 2017 Nov 2]. Available from: https://www.nap.edu/catalog/13507/exposure-science-in-the-21st-century-a-vision-and-a

39. Escher BI, Hackermüller J, Polte T, Scholz S, Aigner A, Altenburger R, et al. From the exposome to mechanistic understanding of chemical-induced adverse effects. Environ Int [Internet]. 2016 [cited 2016 Dec 12]; Available from: http://www.sciencedirect.com/science/article/pii/S0160412016309187

40. Landrigan PJ, Fuller R, Acosta NJR, Adeyi O, Arnold R, Basu N (Nil), et al. The Lancet Commission on pollution and health. The Lancet [Internet]. 2017 Oct 19 [cited 2017 Nov 2];0(0). Available from: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)32345-0/abstract

41. Probst-Hensch N. Happiness and its molecular fingerprints. Int Rev Econ. 2017 Jun 1;64(2):197–211.

42. Project Overview [Internet]. HEALS. 2013 [cited 2016 Aug 4]. Available from: http://www.heals-eu.eu/index.php/project/

43. Vrijheid M, Slama R, Robinson O, Chatzi L, Coen M, van den Hazel P, et al. The human early-life exposome (HELIX): project rationale and design. Environ Health Perspect. 2014 Jun;122(6):535–44.

44. About EXPOsOMICS | EXPOSOME [Internet]. 2016 [cited 2016 Aug 3]. Available from: http://www.exposomicsproject.eu/

45. Ishitsuka K, Nakayama SF, Kishi R, Mori C, Yamagata Z, Ohya Y, et al. Japan Environment and Children's Study: backgrounds, activities, and future directions in global perspectives. Environ Health Prev Med. 2017 Dec 1;22(1):61.

46. Japan Environment and Children's Study / Ministry of the Environment Government of Japan [Internet]. 2018 [cited 2018 Mar 26]. Available from: http://www.env.go.jp/chemi/ceh/en/

47. Pineo H, Glonti K, Rutter H, Zimmermann N, Wilkinson P, Davies M. Characteristics and use of urban health indicator tools by municipal built environment policy and decision-makers: a systematic review protocol. Syst Rev. 2017;6:2.

48. Rothenberg R, Stauber C, Weaver S, Dai D, Prasad A, Kano M. Urban health indicators and indices—current status. BMC Public Health. 2015;15:494.

49. Vineis P, Chadeau-Hyam M, Gmuender H, Gulliver J, Herceg Z, Kleinjans J, et al. The exposome in practice: Design of the EXPOsOMICS project. Int J Hyg Environ Health [Internet]. 2017 [cited 2016 Sep 2]; Available from: http://www.sciencedirect.com/science/article/pii/S1438463916301304

50. Andra SS, Austin C, Wright RO, Arora M. Reconstructing pre-natal and early childhood exposure to multi-class organic chemicals using teeth: Towards a retrospective temporal exposome. Environ Int. 2015 Oct;83:137–45.

51. Robinson O, Basagaña X, Agier L, de Castro M, Hernandez-Ferrer C, Gonzalez JR, et al. The Pregnancy Exposome: Multiple Environmental Exposures in the INMA-Sabadell Birth Cohort. Environ Sci Technol. 2015 Sep 1;49(17):10632–41.

52. Cui Y, Balshaw DM, Kwok RK, Thompson CL, Collman GW, Birnbaum LS. The Exposome: Embracing the Complexity for Discovery in Environmental Health. Environ Health Perspect. 2016 Aug;124(8):A137–40.

53. Buck Louis GM, Smarr MM, Patel CJ. The Exposome Research Paradigm: An Opportunity to Understand the Environmental Basis for Human Health and Disease. Curr Environ Health Rep. 2017 Mar;4(1):89–98.

54. Urban Development Overview [Internet]. [cited 2018 Jul 9]. Available from: http://www.worldbank.org/en/topic/urbandevelopment/overview#3

55. Zhang XQ. The economic role of cities. Nairobi: United Nations Human Settlements Programme; 2011.

56. Andrianou XD, Makris KC. The framework of urban exposome: Application of the exposome concept in urban health studies. Sci Total Environ. 2018 Sep 15;636:963–7.

57. Robinson O, Tamayo I, de Castro M, Valentin A, Giorgis-Allemand L, Hjertager Krog N, et al. The Urban Exposome during Pregnancy and Its Socioeconomic Determinants. Environ Health Perspect. 2018;126(7):077005.

58. Samaniego L, Thober S, Kumar R, Wanders N, Rakovec O, Pan M, et al. Anthropogenic warming exacerbates European soil moisture droughts. Nat Clim Change. 2018 May;8(5):421–6.

59. Statistics on European cities - Statistics Explained [Internet]. [cited 2017 Feb 3]. Available from: http://ec.europa.eu/eurostat/statistics-explained/index.php/Statistics_on_European_cities

60. Rojas P, Neutra R. Stakeholder and participant involvement. In: Environmental Epidemiology. 1st ed. New York: Oxford University Press; 2008. p. 296–9.

61. Becker K, Seiwert M, Casteleyn L, Joas R, Joas A, Biot P, et al. A systematic approach for designing a HBM Pilot Study for Europe. Int J Hyg Environ Health [Internet]. 2013 [cited 2013 Dec 4]; Available from: http://www.sciencedirect.com/science/article/pii/S1438463913000989

62. EU Council. Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption. [Internet]. European Union Council; 1998 [cited 2014 Apr 29]. Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:01998L0083-20031120&qid=1398774065521&from=EN

63. Statistical Service - Population and Social Conditions - Health - Announcements - Survey Results: European Health Interview Survey, 2014 [Internet]. [cited 2018 Jul 14]. Available from: http://www.mof.gov.cy/mof/cystat/statistics.nsf/All/4DE6CF465BC4DDCAC225806800372D29?OpenDocument&sub=3&sel=1&e=&print

64. EURO-URHIS2 [Internet]. [cited 2018 Jun 30]. Available from: http://results.urhis.eu/Default.aspx

65. Pope D, Puzzolo E, Birt C, Guha J, Higgerson J, Patterson L, et al. Collecting standardised urban health indicator data at an individual level for adults living in urban areas: methodology from EURO-URHIS 2. Eur J Public Health. 2016 Jan 7;

66. Elm E von, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. The Lancet. 2007 Oct 20;370(9596):1453–7.

67. Charisiadis P, Andra SS, Makris KC, Christophi CA, Skarlatos D, Vamvakousis V, et al. Spatial and seasonal variability of tap water disinfection by-products within distribution pipe networks. Sci Total Environ. 2015 Feb 15;506–507:26–35.

68. Patel CJ, Bhattacharya J, Butte AJ. An Environment-Wide Association Study (EWAS) on Type 2 Diabetes Mellitus. PLoS ONE. 2010 May 20;5(5):e10746.

69. Rohart F, Gautier B, Singh A, Lê Cao K-A. mixOmics: An R package for ’omics feature selection and multiple data integration. PLoS Comput Biol. 2017 Nov;13(11):e1005752.

70. RStudio Team. RStudio: Integrated Development Environment for R [Internet]. 2019. Available from: http://www.rstudio.com/

71. R Core Team. R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2017. Available from: http://www.r-project.org/

72. Kramer D, Lakerveld J, Stronks K, Kunst AE. Uncovering How Urban Regeneration Programs May Stimulate Leisure-time Walking Among Adults in Deprived Areas: A Realist Review. Int J Health Serv. 2017 Oct;47(4):703–24.

73. Albouy-Llaty M, Limousi F, Carles C, Dupuis A, Rabouan S, Migeot V. Association between Exposure to Endocrine Disruptors in Drinking Water and Preterm Birth, Taking Neighborhood Deprivation into Account: A Historic Cohort Study. Int J Environ Res Public Health. 2016 Aug 9;13(8):796.

74. Patel CJ, Manrai AK. Development of exposome correlation globes to map out environment-wide associations. In: Biocomputing 2015 [Internet]. Kohala Coast, Hawaii, USA: WORLD SCIENTIFIC; 2014 [cited 2018 Nov 1]. p. 231–42. Available from: http://www.worldscientific.com/doi/abs/10.1142/9789814644730_0023

75. Charisiadis P, Andra SS, Makris KC, Christodoulou M, Christophi C, Kargaki S, et al. Household cleaning activities as non-ingestion exposure determinants of urinary trihalomethanes. Environ Sci Technol. 2014;48(1):770–80.

76. Gängler S, Makris KC, Bouhamra W, Dockery DW. Coupling external with internal exposure metrics of trihalomethanes in young females from Kuwait and Cyprus. J Expo Sci Environ Epidemiol. 2018 Mar;28(2):140–6.

77. WHO | Ambient air pollution: Health impacts [Internet]. WHO. [cited 2018 Aug 5]. Available from: http://www.who.int/airpollution/ambient/health-impacts/en/

78. Achilleos S, Evans JS, Yiallouros PK, Kleanthous S, Schwartz J, Koutrakis P. PM10 concentration levels at an urban and background site in Cyprus: the impact of urban sources and dust storms. J Air Waste Manag Assoc. 2014 Dec;64(12):1352–60.

79. Massoud MA, Maroun R, Abdelnabi H, Jamali II, El-Fadel M. Public perception and economic implications of bottled water consumption in underprivileged urban areas. Environ Monit Assess. 2013 Apr;185(4):3093–102.

80. Andrianou XD, Andrianou XD, Lek C van der, Charisiadis P, Ioannou S, Fotopoulou KN, et al. Application of the urban exposome framework using drinking water and quality of life indicators: a proof-of-concept study in Limassol, Cyprus. PeerJ. 2019;7:e6851.

81. Eze IC, Esse C, Bassa FK, Kone S, Acka F, Yao L, et al. Cote d'Ivoire Dual Burden of Disease (CoDuBu): Study Protocol to Investigate the Co-occurrence of Chronic

Infections and Noncommunicable Diseases in Rural Settings of Epidemiological Transition. JMIR Res Protoc. 2017 Oct 27;6(10):e210.

82. Cyprus - Country Health Profile 2017 [Internet]. European Observatory of Health Systems and Policies. 2019 [cited 2019 Jul 4]. Available from: http://www.euro.who.int/en/about-us/partners/observatory/publications/country-health-profiles

83. Country profile for Cyprus - Risk assessment on measles, May 2019 [Internet]. European Centre for Disease Prevention and Control. [cited 2019 Jul 3]. Available from: http://ecdc.europa.eu/en/publications-data/country-profile-cyprus-6

84. Lake IR, Colón-González FJ, Takkinen J, Rossi M, Sudre B, Dias JG, et al. Exploring Campylobacter seasonality across Europe using The European Surveillance System (TESSy), 2008 to 2016. Eurosurveillance. 2019 Mar 28;24(13):1800028.

85. Tuberculosis surveillance and monitoring in Europe, 2019 [Internet]. [cited 2019 Apr 23]. Available from: https://ecdc.europa.eu/en/publications-data/tuberculosis-surveillance-and-monitoring-europe-2019

86. Cyprus Open Data Portal | Quarters map [Internet]. Cypriot National Open Data Portal. 2018 [cited 2019 May 24]. Available from: https://www.data.gov.cy/dataset/%CE%B4%CE%B9%CE%BF%CE%B9%CE%BA%CE%B7%CF%84%CE%B9%CE%BA%CE%AC-%CF%8C%CF%81%CE%B9%CE%B1-%CE%B5%CE%BD%CE%BF%CF%81%CE%B9%CF%8E%CE%BD-%CE%B4%CE%B9%CE%BF%CE%B9%CE%BA%CE%B7%CF%84%CE%B9%CE%BA%CF%8C%CF%82-%CF%87%CE%AC%CF%81%CF%84%CE%B7%CF%82

87. Cyprus Open Data Portal | Postal code maps [Internet]. Cypriot National Open Data Portal. 2018 [cited 2019 May 24]. Available from: https://www.data.gov.cy/node/841?language=en

88. Kowarik A, Templ M. Imputation with the R Package VIM. J Stat Softw. 2016 Oct 20;74(1):1–16.

89. Khana D, Rossen LM, Hedegaard H, Warner M. A bayesian spatial and temporal modeling approach to mapping geographic vairation in mortality rates for subnational areas with R-INLA. J Data Sci JDS. 2018 Jan;16(1):147–82.

90. Besag J, York J, Mollié A. Bayesian image restoration, with two applications in spatial statistics. Ann Inst Stat Math. 1991 Mar 1;43(1):1–20.

91. Blangiardo M, Cameletti M, Baio G, Rue H. Spatial and spatio-temporal models with R-INLA. Spat Spatio-Temporal Epidemiol. 2013 Dec;7:39–55.

92. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. PLOS Med. 2015 Oct;12(10):e1001885–e1001885.

93. R Core Team. R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2019. Available from: https://www.R-project.org

94. Nieuwenhuijsen MJ, Agier L, Basagaña X, Urquiza J, Tamayo-Uria I, Giorgis-Allemand L, et al. Influence of the Urban Exposome on Birth Weight. Environ Health Perspect. 2019 Apr;127(4):47007.

95. Death rate, crude (per 1,000 people) | Data [Internet]. [cited 2019 Aug 21]. Available from: https://data.worldbank.org/indicator/SP.DYN.CDRT.IN?end=2017&locations=CY&start=2007

96. Life expectancy at birth, total (years) | Data [Internet]. [cited 2019 Aug 21]. Available from: https://data.worldbank.org/indicator/SP.DYN.LE00.IN?end=2017&locations=CY&start=2006

97. Life expectancy at birth [Internet]. OECD; [cited 2019 Aug 21]. Available from: https://www.oecd-ilibrary.org/social-issues-migration-health/life-expectancy-at-birth/indicator/english_27e0fc9d-en

98. Halonen JI, Blangiardo M, Toledano MB, Fecht D, Gulliver J, Ghosh R, et al. Is long-term exposure to traffic pollution associated with mortality? A small-area study in London. Environ Pollut Barking Essex 1987. 2016 Jan;208(Pt A):25–32.

99. Benmarhnia T, Kihal-Talantikite W, Ragettli MS, Deguen S. Small-area spatiotemporal analysis of heatwave impacts on elderly mortality in Paris: A cluster analysis approach. Sci Total Environ. 2017 Aug 15;592:288–94.

100. Boscoe FP, Talbot TO, Kulldorff M. Public domain small-area cancer incidence data for New York State, 2005-2009. Geospatial Health. 2016 Apr 18;11(1):304.

101. Zannetos S, Zachariadou T, Adamidi T, Georgiou A. The economic burden of tuberculosis in Cyprus. A probabilistic cost of illness study. Epidemiol Biostat Public Health [Internet]. 2018 Jun 20 [cited 2019 Jul 3];15(2). Available from: https://ebph.it/article/view/12780

102. Voniatis C, Migliori GB, Voniatis M, Georgiou A, D'Ambrosio L, Centis R, et al. Tuberculosis elimination: dream or reality? The case of Cyprus. Eur Respir J. 2014 Aug 1;44(2):543–6.

103. Alverti MN, Themistocleous K, Kyriakidis PC, Hadjimitsis DG. A Human Centric Approach on the Analysis of the Smart City Concept: the case study of the Limassol city in Cyprus. Adv Geosci. 2018 Oct 22;45:305–20.

104. Lamnisos D, Lambrianidou G, Middleton N. Small-area socioeconomic deprivation indices in Cyprus: development and association with premature mortality. BMC Public Health. 2019 May 22;19(1):627.

105. Pyrgou A, Santamouris M. Increasing Probability of Heat-Related Mortality in a Mediterranean City Due to Urban Warming. Int J Environ Res Public Health. 2018 Jul 25;15(8).

106. Pilavaki P, Giallouros G, Yiallourou AI, Pantavou K, Marcou Y, Demetriou A, et al. Epidemiology of breast cancer in Cyprus: Data on newly diagnosed cases and survival rates. Data Brief. 2018 May 19;19:353–69.

107. Vineis P. From John Snow to omics: the long journey of environmental epidemiology. Eur J Epidemiol. 2018 Apr;33(4):355–63.

108. Kostova D, Husain MJ, Sugerman D, Hong Y, Saraiya M, Keltz J, et al. Synergies between Communicable and Noncommunicable Disease Programs to Enhance Global Health Security. Emerg Infect Dis. 2017;23(13).

APPENDIX A (1 Introduction)

Table S1. 1 List of references for PubMed records on studies with the terms Limassol (or Lemesos) and health, or Nicosia (or Lefkosia) and health, retrieved on 6 July, 2019.

Search details: (“Limassol[Text Word] OR Lemesos[Text Word]) AND health[Text Word]”
1. Andrianou XD, van der Lek C, Charisiadis P, Ioannou S, Fotopoulou KN, Papapanagiotou Z, et al. Application of the urban exposome framework using drinking water and quality of life indicators: a proof-of-concept study in Limassol, Cyprus. PeerJ. 2019;7:e6851. 2. Andrianou XD, Makris KC. The framework of urban exposome: Application of the exposome concept in urban health studies. Sci Total Environ. 2018 Sep 15;636:963–7. 3. Diakou A, Sofroniou D, Di Cesare A, Kokkinos P, Traversa D. Occurrence and zoonotic potential of endoparasites in cats of Cyprus and a new distribution area for Troglostrongylus brevior. Parasitol Res. 2017 Dec;116(12):3429–35. 4. Botsaris G, Kanetis L, Slany M, Parpouna C, Makris KC. Microbial quality and molecular identification of cultivable microorganisms isolated from an urban drinking water distribution system (Limassol, Cyprus). Environ Monit Assess. 2015 Dec;187(12):739. 5. Sabbagh MN, Messis C, Friedland RP, Geula C. The 5th International Conference on Alzheimer’s Disease and related disorders in the Middle East, 15-17 May 2009, Limassol Cyprus. J Alzheimers Dis. 2012;30(3):711–27. 6. Papaevangelou V, Rousounides A, Hadjipanagis A, Katsioulis A, Theodoridou M, Hadjichristodoulou C. Decrease of antibiotic consumption in children with upper respiratory tract infections after implementation of an intervention program in Cyprus. Antimicrob Agents Chemother. 2012 Mar;56(3):1658–61. 7. Paximadi E, Karakasiliotis I, Papaventsis D, Papageorgiou G, Markoulatos P. Recombinant Sabin environmental isolates in Greece and Cyprus. J Appl Microbiol. 2008 Apr;104(4):1153–62. 8. Kontoghiorghes GJ. Ethical issues and risk/benefit assessment of iron chelation therapy: advances with deferiprone/deferoxamine combinations and concerns about the safety, efficacy and costs of deferasirox. Hemoglobin. 2008;32(1–2):1–15. 9. Papaventsis D, Siafakas N, Markoulatos P, Papageorgiou GT, Kourtis C, Chatzichristou E, et al. Membrane adsorption with direct cell culture combined with reverse transcription-PCR as a fast method for identifying enteroviruses from sewage. Appl Environ Microbiol. 2005 Jan;71(1):72–9. 10. Lyden CJ, Robertson JG. Families clinic, Limassol. A study of a unique British expatriate general practice in Cyprus. J R Coll Gen Pract. 1970 Oct;20(99):212–23.
Search detiails: (“Nicosia[Text Word] OR Lefkosia[Text Word]) AND health[Text Word]”
1. Pyrgou A, Santamouris M. Increasing Probability of Heat-Related Mortality in a Mediterranean City Due to Urban Warming. Int J Environ Res Public Health. 2018 Jul 25;15(8). 2. Asut O, Ozenli O, Gur G, Deliceo E, Cagin B, Korun O, et al. The knowledge and perceptions of the first year medical students of an International University on family planning and emergency contraception in Nicosia (TRNC). BMC Womens Health. 2018 Sep 15;18(1):149.

3. Tsangari X, Andrianou XD, Agapiou A, Mochalski P, Makris KC. Spatial characteristics of urinary BTEX concentrations in the general population. Chemosphere. 2017 Apr;173:261–6.
4. Diakou A, Sofroniou D, Di Cesare A, Kokkinos P, Traversa D. Occurrence and zoonotic potential of endoparasites in cats of Cyprus and a new distribution area for Troglostrongylus brevior. Parasitol Res. 2017 Dec;116(12):3429–35.
5. Zinonos S, Zachariadou T, Zannetos S, Panayiotou AG, Georgiou A. Smoking prevalence and associated risk factors among healthcare professionals in Nicosia general hospital, Cyprus: a cross-sectional study. Tob Induc Dis. 2016;14:14.
6. Heaviside C, Tsangari H, Paschalidou A, Vardoulakis S, Kassomenos P, Georgiou KE, et al. Heat-related mortality in Cyprus for current and future climate scenarios. Sci Total Environ. 2016 Nov 1;569–570:627–33.
7. Canakci T, Kurtdede A, Pasa S, Toz Ozensoy S, Ozbel Y. Seroprevalence of Canine Leishmaniasis in Northern Cyprus. Turkiye Parazitol Derg. 2016 Sep;40(3):117–20.
8. Petrou P. The Ariadne's thread in co-payment, primary health care usage and financial crisis: findings from Cyprus public health care sector. Public Health. 2015 Nov;129(11):1503–9.
9. Andrioti D, Kyprianou K, Charalambous G. How much do rheumatologists and orthopaedists doctors' modalities impact the cost of arthritis in Cyprus? BMC Musculoskelet Disord. 2015 Aug 14;16:193.
10. Kalyvas H, Andra SS, Charisiadis P, Karaolis C, Makris KC. Influence of household cleaning practices on the magnitude and variability of urinary monochlorinated bisphenol A. Sci Total Environ. 2014 Aug 15;490:254–61.
11. Andrianou XD, Charisiadis P, Andra SS, Makris KC. Spatial and seasonal variability of urinary trihalomethanes concentrations in urban settings. Environ Res. 2014 Nov;135:289–95.
12. Panayiotopoulos C, Pavlakis A, Apostolou M. Family burden of schizophrenic patients and the welfare system; the case of Cyprus. Int J Ment Health Syst. 2013 May 2;7(1):13.
13. Neophytou AM, Yiallouros P, Coull BA, Kleanthous S, Pavlou P, Pashiardis S, et al. Particulate matter concentrations during desert dust outbreaks and daily mortality in Nicosia, Cyprus. J Expo Sci Environ Epidemiol. 2013 Jun;23(3):275–80.
14. Direktor S, Ozer E. Evaluating dietary quality in diabetes by the Healthy Eating Index. Asia Pac J Clin Nutr. 2013;22(4):620–5.
15. Odame I, Kulkarni R, Ohene-Frempong K. Concerted global effort to combat sickle cell disease: the first global congress on sickle cell disease in Accra, Ghana. Am J Prev Med. 2011 Dec;41(6 Suppl 4):S417-421.
16. Nicosia N, Wynn BO, Romley JA. Assessing the Performance of Military Treatment Facilities. Rand Health Q. 2011 Fall;1(3):5.
17. Regalbuto C, Scollo G, Pandini G, Ferrigno R, Pezzino V. Effects of prophylaxis with iodised salt in an area of endemic goitre in north-eastern Sicily. J Endocrinol Invest. 2010 May;33(5):300–5.
18. Lambrou P, Kontodimopoulos N, Niakas D. Motivation and job satisfaction among medical and nursing staff in a Cyprus public general hospital. Hum Resour Health. 2010 Nov 16;8:26.
19. Kyprianou M, Kapsou M, Raftopoulos V, Soteriades ES. Knowledge, attitudes and beliefs of Cypriot nurses on the handling of antineoplastic agents. Eur J Oncol Nurs. 2010 Sep;14(4):278–82.
20. Eftychiou C, Georgiou M, Andreou A, Michaelides A, Yiangou K, Deligeorgis A, et al. Nicosia General Hospital cardiac arrest team: first year's practice and outcomes of in-hospital resuscitation. Hellenic J Cardiol. 2009 Aug;50(4):264–8.

21. Paximadi E, Karakasiliotis I, Papaventsis D, Papageorgiou G, Markoulatos P. Recombinant Sabin environmental isolates in Greece and Cyprus. J Appl Microbiol. 2008 Apr;104(4):1153–62.
22. Middleton N, Yiallouros P, Kleanthous S, Kolokotroni O, Schwartz J, Dockery DW, et al. A 10-year time-series analysis of respiratory and cardiovascular morbidity in Nicosia, Cyprus: the effect of short-term changes in air pollution and dust storms. Environ Health. 2008 Jul 22;7:39.
23. Bekos C, Pieri L, Angelides N, Moros I. Prevalence of multifocal atherosclerosis and comorbidity on symptomatic Cypriot inpatients. Int Angiol. 2008 Oct;27(5):419–25.
24. Tolma EL, Reininger BM, Ureda J. What predicts a Cypriot woman's decision to obtain or not obtain a screening mammogram? Implications for the promotion of screening mammography in Cyprus. Eur J Cancer Prev. 2006 Apr;15(2):149–57.
25. Tolma EL, Reininger BM, Evans A, Ureda J. Examining the theory of planned behavior and the construct of self-efficacy to predict mammography intention. Health Educ Behav. 2006 Apr;33(2):233–51.
26. Rikers RMJP, de Bruin ABH. Introduction to the special issue on innovations in problem-based learning. Adv Health Sci Educ Theory Pract. 2006 Nov;11(4):315–9.
27. Papaventsis D, Siafakas N, Markoulatos P, Papageorgiou GT, Kourtis C, Chatzichristou E, et al. Membrane adsorption with direct cell culture combined with reverse transcription-PCR as a fast method for identifying enteroviruses from sewage. Appl Environ Microbiol. 2005 Jan;71(1):72–9.
28. Demoliou CD, Charalambous A. Blood lead levels in preprimary school-age children in Nicosia, Cyprus, and their relationship with leaded soil dust exposure. Arch Environ Health. 2004 Sep;59(9):455–61.
29. Tolma EL, Reininger BM, Ureda J, Evans A. Cognitive motivations associated with screening mammography in Cyprus. Prev Med. 2003 Mar;36(3):363–73.
30. GESER A. THE LONG-TERM TREND IN PREVALENCE OF TUBERCULOSIS INFECTION IN CYPRUS. Bull World Health Organ. 1964;30:601–8.
31. KONSTANTINIDOU TP. [Hygiene service in the grade schools of Nicosia]. Cyprus Med J. 1957 Jul;9(7):125–7.

APPENDIX B (3 Application of the urban exposome framework using drinking water and quality of life indicators: a proof-of-concept study in Limassol, Cyprus)

Supplementary tables

Table S3. 1 Population by quarter, sample size estimation and number of participants.

	GEO CODE*	Area	Total (Census 2011**)	Estimated sample size	Recruited
Municipality	**5000**	**Limassol**	**101000**	120	132
Quarters	**500017**	**Agios Nikolaos**	**5631**	7	5
	500013	**Agios Nektarios**	**3397**	4	3
	500012	**Kapsalos**	**6660**	8	7
	500015	**Agia Trias**	**2786**	3	3
	500016	**Neapoli**	**7229**	9	10
	500008	**Omonoia**	**3839**	5	5
	500014	**Agia Zoni**	**4456**	5	5
	500020	**Agios Spyridon**	**9439**	11	11
	500021	**Zakaki**	**5874**	7	8
	500011	**Apostoloi Petros kai Pavlos**	**10412**	12	14
	500009	**Apostolos Andreas**	**9207**	11	14
	500010	**Agios Georgios**	**5060**	6	9
	500005	**Katholiki**	**4647**	6	12
Combined quarters (presented separately and summed together)	**500004**	**Agia Napa**	**534**	1	1
	500002	**Tziami Tzentit**	**434**	1	1
	500007	**Tsiflikoudia**	**579**	1	1
		(Beachfront quarters)	**1547**	3	3
	500018	**Agia Fylaxis**	**14451**	17	17
	500019	**Panagia Evangelistria**	**693**	1	1
		(Agia Fylaxis and Panagia Evangelistria)	**15144**	18	18
	500003	**Arnaoutogeitonia**	**905**	1	1
	500006	**Agios Ioannis**	**4767**	6	4
		(Arnaoutogeitonia and Agios Ioannis)	**5672**	7	5

*Based on the 2011 Population Census of Cyprus

**Source: Population Census 2011 [Internet]. Statistical Service, Republic of Cyprus. 2014 [cited 2014 Sep 9]. Available from: http://www.mof.gov.cy/mof/cystat/statistics.nsf/census-2011_cystat_en/census-2011_cystat_en?OpenDocument

Table S3. 2 Variables from the urban population study questionnaire used in the environment-wide association study (EWAS) analysis. Part A of the table lists the outcomes, and Part B the predictors by block/group.

Part A	Outcomes		
Comment on the predictors	Variable	Categories(if applicable)	Score
Predictors from blocks/groups 1-6 (number of predictor variables=36)	General health	Very good	2
		Good	1
		So and so	0
		Bad	-1
		Very bad	-2
	Chronic disease	Yes	1
		No	0
		I don't know/I don't want to answer	NA
Predictors from blocks/groups 1-5 (number of predictor variables=25)	Any disease past year	Yes	1
		No	0
Part B	**Predictors**		
Block/Group (number of variables)	Description of variables	Categories (if applicable)	Score
(B1) Chemical water indicators (n=7)	Trihalomethanes (Total THM, BrTHM, TCM, BDCM, DBCM, TBM; units: μg/L)		
	Free chlorine (units mg/L; ND=0)		
(B2) Drinking water habits (n=5)	Number of glasses of water per day by source		
(B3) Cleaning activities (n=3)	Mopping, bathroom cleaning, dishwashing (times per week)		
(B4) Questionnaire variables (n=5)		I don't want to answer	NA
	Delays in access to health care services due to long waiting lists	No, I didn't face any delays (reference)	+1
		No, I didn't need care	0
		Yes	-1
		I don't want to answer	NA
	Financial constraints in access to dental care	No, I could afford it (reference)	+1
		No, I didn't need	0
		Yes	-1
	Living close to green space (proximity) Can do many activities in the green space nearby There is always someone to help you in the neighborhood	Completely agree (reference)	+2
		Probably agree	+1
		Do not know	0
		Probably disagree	-1
		Completely disagree	-2
(B5) Participant characteristics (n=5)	Age (years) BMI (kg/m^2) Number of cigarettes smoking daily		
	Sex	Female (reference)	0
		Male	1
(B6) Self-reported diseases the past year (n=11)	Asthma, respiratory diseases, hypertension, cardiovascular diseases, joint or other muscloskeletal problems, diabetes, allergies, liver disorders, cancer, depression	Yes	1
		No (reference)	0
		I don't know/ I don't want to answer	NA

Notes: NA: excluded as missing

Table S3. 3 R packages used in the data analysis.

Packages used in the analysis
[1] mixOmics_6.3.2 MASS_7.3-50gdtools_0.1.7
[4] bindrcpp_0.2.2 rJava_0.9-10 xlsx_0.6.1
[7] officer_0.3.2rvg_0.1.9scales_0.5.0
[10] viridis_0.5.1viridisLite_0.3.0broom_0.4.5
[13] reshape2_1.4.3 knitr_1.20 tableone_0.9.3
[16] ISOweek_0.6-2summarytools_0.8.5 corrplot_0.84
[19] Hmisc_4.1-1Formula_1.2-3survival_2.42-3
[22] lattice_0.20-35forcats_0.3.0stringr_1.3.1
[25] purrr_0.2.5readr_1.1.1tidyr_0.8.1
[28] tibble_1.4.2 tidyverse_1.2.1lubridate_1.7.4
[31] readxl_1.1.0 RColorBrewer_1.1-2 dplyr_0.7.6
[34] data.table_1.11.4rgdal_1.3-3sp_1.3-1
[37] plyr_1.8.4 ggplot2_3.0.0

Table S3. 4 Additional characteristics of the study population based on the questionnaire responses of the urban population study.

	Overall (n=132)
Years living in Cyprus (%)	
Less than a year	3 (2.3)
1-5 years	6 (4.5)
6-10 years	4 (3.0)
11-20 years	3 (2.3)
More than 20 years	20 (15.2)
All my life	96 (72.7)
Place of birth (%)	
Cyprus	114 (86.4)
Other EU country	13 (9.8)
Other non-EU country	5 (3.8)
Smoking status (%)	
I don't want to answer	1 (0.8)
Non-smokers	81 (61.8)
Smokers	41 (31.3)
Occasional smoking	8 (6.1)
Exposure to secondhand smoke (hours per day) (%)	
I don't know/I don't remember	8 (6.2)
I don't want to answer	1 (0.8)
Less than 1 hour per day	35 (27.3)
More than 1 hour per day	32 (25.0)
Never or almost never	52 (40.6)
Alcoholic consumption the past 12 months (%)	
Daily or almost daily	11 (8.4)
5-6 times per week	2 (1.5)
3-4 times per week	15 (11.5)
1-2 times per week	33 (25.2)
2-3 days per month	23 (17.6)
1 time per month	8 (6.1)
Less than 1 time per month	15 (11.5)
Never consumed alcohol in the past 12 months	7 (5.3)
Never or I have consumed alcohol only a few times in my life	13 (9.9)
I don't want to answer	4 (3.1)

Table S3. 5 Summary of the responses to different questions relating to health care access, lifestyle and quality of life in the neighborhood.

		Overall (n=132)
Delays in access to health care services		
Delays in health care due to long waiting list (%)	I don't want to answer	6 (4.5)
	No, I didn't face any delays	43 (32.6)
	No, I didn't need care	68 (51.5)
	Yes	15 (11.4)
Delays in health care due to lack of transport (%)	I don't want to answer	20 (15.2)
	No, I didn't face any delays	43 (32.6)
	No, I didn't need care	67 (50.8)
	Yes	2 (1.5)
Financial constraints in access to medical care (%)	I don't want to answer	9 (6.8)
	No, I could afford it	45 (34.1)
	No, I didn't need	75 (56.8)
	Yes	3 (2.3)
Financial constraints in access to dental care (%)	I don't want to answer	4 (3.0)
	No, I could afford it	40 (30.3)
	No, I didn't need	70 (53.0)
	Yes	18 (13.6)
Financial constraints in access to buy any medications (%)	I don't want to answer	6 (4.5)
	No, I could afford it	45 (34.1)
	No, I didn't need	76 (57.6)
	Yes	5 (3.8)
Financial constraints in access to mental health care (%)	I don't want to answer	11 (8.3)
	No, I could afford it	5 (3.8)
	No, I didn't need	113 (85.6)
	Yes	3 (2.3)
Opinions about green space near the residence		
Enough green spaces (%)	Completely agree	18 (13.6)
	Probably agree	29 (22.0)
	Do not know	8 (6.1)
	Probably disagree	45 (34.1)
	Completely disagree	32 (24.2)
Access to green spaces is easy (%)	Completely agree	38 (28.8)
	Probably agree	39 (29.5)

	Do not know	9 (6.8)
	Probably disagree	24 (18.2)
	Completely disagree	22 (16.7)
Living close to green space (proximity) (%)	Completely agree	45 (34.1)
	Probably agree	40 (30.3)
	Do not know	7 (5.3)
	Probably disagree	17 (12.9)
	Completely disagree	23 (17.4)
Green spaces nearby are well-maintained (%)	Completely agree	11 (8.3)
	Probably agree	39 (29.5)
	Do not know	12 (9.1)
	Probably disagree	39 (29.5)
	Completely disagree	31 (23.5)
Relaxing in the green spaces nearby (%)	Completely agree	14 (10.6)
	Probably agree	26 (19.7)
	Do not know	6 (4.5)
	Probably disagree	39 (29.5)
	Completely disagree	47 (35.6)
Can do many activities in green space (%)	Completely agree	8 (6.1)
	Probably agree	18 (13.6)
	Do not know	9 (6.8)
	Probably disagree	46 (34.8)
	Completely disagree	51 (38.6)
Opinions about different aspects of life in the neighborhood		
The neighbors are willing to help each other (%)	Completely agree	41 (31.1)
	Probably agree	59 (44.7)
	Do not know	13 (9.8)
	Probably disagree	14 (10.6)
	Completely disagree	5 (3.8)
Neighbors share the same values (%)	Completely agree	34 (25.8)
	Probably agree	57 (43.2)
	Do not know	23 (17.4)
	Probably disagree	12 (9.1)
	Completely disagree	6 (4.5)
There is always someone to ask help you(%)	Completely agree	51 (38.6)
	Probably agree	56 (42.4)
	Do not know	15 (11.4)
	Probably disagree	6 (4.5)
	Completely disagree	4 (3.0)

Table S3. 6 Parameters from the univariate models ranked by FDR adjusted p-value. In the categorical outcomes (i.e. chronic disease and any disease the past year, noted as "ChronicDisease" and "Disease12M" in the column "Outcome") the estimate is the odds ratio.

variable	term	estimate	std.error	statistic	p.value	conf.low	conf.high	n (%)	Outcome	FDR
FinancialIssuesDentalCareREC	valueYes	-0.794	0.188	-4.223	0	-1.167	-0.422	18 (14.1)	GeneralHealth	0
Depression12MREC	valueYes	-1.448	0.377	-3.839	0	-2.195	-0.7	3 (2.8)	GeneralHealth	0
Hypertension12MREC	valueYes	11.714	0.58	4.24	0	3.858	38.429	19 (16.2)	ChronicDisease	0
Age	value	3.293	0.233	5.105	0	2.128	5.337	NA	Disease12M	0
JointProblems12MREC	valueYes	-0.621	0.19	-3.266	0.001	-0.998	-0.244	12 (10.8)	GeneralHealth	0.0215
BackProblems12MREC	valueYes	-0.5	0.142	-3.511	0.001	-0.782	-0.218	37 (32.2)	GeneralHealth	0.0215
Age	value	-0.194	0.063	-3.084	0.002	-0.318	-0.07	NA	GeneralHealth	0.036857
NeckProblems12MREC	valueYes	-0.479	0.157	-3.052	0.003	-0.79	-0.168	20 (17.5)	GeneralHealth	0.043
BackProblems12MREC	valueYes	4.402	0.501	2.957	0.003	1.67	12.124	37 (32.2)	ChronicDisease	0.043
Age	value	2.074	0.256	2.844	0.004	1.297	3.589	NA	ChronicDisease	0.046909
NeckProblems12MREC	valueYes	4.657	0.541	2.845	0.004	1.602	13.623	20 (17.5)	ChronicDisease	0.046909
Asthma12MREC	valueYes	6.071	0.695	2.595	0.009	1.515	24.61	10 (8.5)	ChronicDisease	0.09675
ProximityGreenSpace	valueDo not know	-0.708	0.295	-2.4	0.018	-1.292	-0.124	7 (5.3)	GeneralHealth	0.175071
LongWaitingListHCDelay12MREC	valueYes	4.5	0.641	2.346	0.019	1.311	16.672	15 (11.9)	ChronicDisease	0.175071
Hypertension12MREC	valueYes	-0.354	0.155	-2.279	0.024	-0.661	-0.046	19 (16.2)	GeneralHealth	0.2064
Alergies12MREC	valueYes	3.846	0.607	2.22	0.026	1.129	12.624	17 (15.5)	ChronicDisease	0.209625
Mopping_days_week	value	-0.135	0.064	-2.131	0.035	-0.261	-0.01	NA	GeneralHealth	0.265588
ActivitiesInGreenSpace	valueDo not know	-0.736	0.354	-2.078	0.04	-1.437	-0.035	9 (6.8)	GeneralHealth	0.278368
Spring_water_glasses_day	value	0.506	0.333	-2.045	0.041	0.191	0.835	NA	Disease12M	0.278368
Dish_washing_days_week	value	1.431	0.181	1.983	0.047	1.009	2.058	NA	Disease12M	0.30315
BMI	value	-0.118	0.061	-1.937	0.055	-0.238	0.003	NA	GeneralHealth	0.306375
LiverDisorders12MREC	valueYes	-0.927	0.478	-1.939	0.055	-1.875	0.02	2 (1.8)	GeneralHealth	0.306375
Depression12MREC	valueYes	10.933	1.257	1.904	0.057	0.988	244.238	3 (2.8)	ChronicDisease	0.306375
Mopping_days_week	value	1.423	0.184	1.921	0.055	0.998	2.058	NA	Disease12M	0.306375
FinancialIssuesDentalCareREC	valueYes	3.178	0.615	1.881	0.06	0.995	11.485	18 (14.1)	Disease12M	0.3096
CVD12MREC	valueYes	-0.907	0.483	-1.879	0.063	-1.864	0.05	2 (1.7)	GeneralHealth	0.312577
FreeChlorine	value	1.475	0.211	1.837	0.066	0.974	2.251	NA	ChronicDisease	0.315333
LongWaitingListHCDelay12MREC	valueNo, I didn't need care	0.244	0.141	1.736	0.085	-0.034	0.523	68 (54)	GeneralHealth	0.382552
Mopping_days_week	value	1.462	0.221	1.717	0.086	0.95	2.275	NA	ChronicDisease	0.382552
Spring_water_glasses_day	value	0.102	0.063	1.615	0.109	-0.023	0.226	NA	GeneralHealth	0.393973
Bathroom_cleaning_days_week	value	-0.103	0.064	-1.607	0.111	-0.23	0.024	NA	GeneralHealth	0.393973
Alergies12MREC	valueYes	-0.286	0.179	-1.6	0.113	-0.64	0.068	17 (15.5)	GeneralHealth	0.393973
LongWaitingListHCDelay12MREC	valueNo, I didn't need care	0.421	0.525	-1.647	0.1	0.146	1.176	68 (54)	ChronicDisease	0.393973
FinancialIssuesDentalCareREC	valueYes	2.917	0.642	1.667	0.095	0.824	10.518	18 (14.1)	ChronicDisease	0.393973
LongWaitingListHCDelay12MREC	valueNo, I didn't need care	0.527	0.398	-1.61	0.107	0.238	1.14	68 (54)	Disease12M	0.393973
ActivitiesInGreenSpace	valueDo not know	5.833	1.085	1.626	0.104	0.777	61.719	9 (6.8)	Disease12M	0.393973

ActivitiesInGreenSpace	valueProbably agree	4.333	0.9	1.629	0.103	0.777	28.663	18 (13.6)	Disease12M	0.393973
LongWaitingListHCDelay12MREC	valueYes	-0.322	0.217	-1.489	0.139	-0.751	0.106	15 (11.9)	GeneralHealth	0.415667
FinancialIssuesDentalCareREC	valueNo, I didn't need	0.193	0.131	1.468	0.145	-0.067	0.453	70 (54.7)	GeneralHealth	0.415667
ProximityGreenSpace	valueProbably disagree	-0.305	0.207	-1.474	0.143	-0.714	0.104	17 (12.9)	GeneralHealth	0.415667
Diabetes12MREC	valueYes	-0.43	0.282	-1.523	0.131	-0.989	0.129	6 (5.3)	GeneralHealth	0.415667
TCM	value	0.655	0.284	-1.489	0.136	0.351	1.081	NA	ChronicDisease	0.415667
TBM	value	0.654	0.29	-1.464	0.143	0.346	1.081	NA	ChronicDisease	0.415667
Water_from_vending_machines_glasses_day	value	1.36	0.21	1.462	0.144	0.892	2.152	NA	ChronicDisease	0.415667
ProximityGreenSpace	valueProbably disagree	2.567	0.62	1.521	0.128	0.751	8.781	17 (12.9)	ChronicDisease	0.415667
Asthma12MREC	valueYes	-0.321	0.224	-1.428	0.156	-0.765	0.124	10 (8.5)	GeneralHealth	0.437478
Sex	valueMale	0.172	0.132	1.3	0.196	-0.09	0.433	50 (37.9)	GeneralHealth	0.473
ActivitiesInGreenSpace	valueProbably agree	-0.403	0.31	-1.3	0.196	-1.016	0.21	18 (13.6)	GeneralHealth	0.473
Resporatory12MREC	valueYes	0.418	0.312	1.338	0.183	-0.201	1.037	5 (4.3)	GeneralHealth	0.473
TTHMs	value	0.695	0.278	-1.312	0.19	0.377	1.128	NA	ChronicDisease	0.473
BrTHMs	value	0.701	0.275	-1.288	0.198	0.382	1.135	NA	ChronicDisease	0.473
SomeonetoHelpinNeighborhood	valueDo not know	0.231	1.09	-1.345	0.179	0.012	1.356	15 (11.4)	ChronicDisease	0.473
JointProblems12MREC	valueYes	2.406	0.671	1.308	0.191	0.586	8.673	12 (10.8)	ChronicDisease	0.473
ProximityGreenSpace	valueDo not know	4.385	1.121	1.318	0.188	0.672	86.452	7 (5.3)	Disease12M	0.473
ActivitiesInGreenSpace	valueCompletely disagree	-0.35	0.277	-1.264	0.208	-0.899	0.198	51 (38.6)	GeneralHealth	0.487855
ActivitiesInGreenSpace	valueProbably agree	4.2	1.187	1.209	0.227	0.541	88.738	18 (13.6)	ChronicDisease	0.502881
LongWaitingListHCDelay12MREC	valueYes	2.37	0.718	1.201	0.23	0.635	11.558	15 (11.9)	Disease12M	0.502881
FinancialIssuesDentalCareREC	valueNo, I didn't need	1.63	0.399	1.223	0.221	0.748	3.596	70 (54.7)	Disease12M	0.502881
ActivitiesInGreenSpace	valueCompletely disagree	2.583	0.785	1.21	0.226	0.571	13.743	51 (38.6)	Disease12M	0.502881
Cigarettes_daily_on_average	value	-0.078	0.068	-1.152	0.252	-0.213	0.056	NA	GeneralHealth	0.528484
Tap_water_glasses_day	value	0.744	0.257	-1.147	0.252	0.424	1.182	NA	ChronicDisease	0.528484
SomeonetoHelpinNeighborhood	valueDo not know	0.506	0.598	-1.14	0.254	0.149	1.612	15 (11.4)	Disease12M	0.528484
CVD12MREC	valueYes	4.833	1.438	1.096	0.273	0.185	126.104	2 (1.7)	ChronicDisease	0.559
DBCM	value	1.222	0.187	1.069	0.285	0.858	1.804	NA	Disease12M	0.574453
DBCM	value	0.758	0.262	-1.059	0.29	0.425	1.202	NA	ChronicDisease	0.575538
SomeonetoHelpinNeighborhood	valueProbably disagree	0.333	0.32	1.041	0.3	-0.3	0.967	6 (4.5)	GeneralHealth	0.577612
BDCM	value	0.763	0.261	-1.036	0.3	0.428	1.211	NA	ChronicDisease	0.577612
Water_from_vending_machines_glasses_day	value	1.235	0.209	1.008	0.314	0.853	2.031	NA	Disease12M	0.594522
Other_glasses_day	value	1.555	0.442	0.999	0.318	0.897	5.212	NA	Disease12M	0.594522
BDCM	value	-0.059	0.065	-0.909	0.365	-0.186	0.069	NA	GeneralHealth	0.645
DBCM	value	-0.06	0.065	-0.926	0.356	-0.187	0.068	NA	GeneralHealth	0.645
Spring_water_glasses_day	value	0.73	0.345	-0.913	0.361	0.243	1.211	NA	ChronicDisease	0.645
Bathroom_cleaning_days_week	value	1.179	0.181	0.913	0.361	0.831	1.693	NA	Disease12M	0.645
Dish_washing_days_week	value	-0.055	0.065	-0.852	0.396	-0.183	0.073	NA	GeneralHealth	0.690324
BMI	value	1.199	0.218	0.834	0.404	0.777	1.841	NA	ChronicDisease	0.69488
Dish_washing_days_week	value	1.217	0.238	0.823	0.411	0.784	2.032	NA	ChronicDisease	0.697618
BDCM	value	1.158	0.183	0.801	0.423	0.816	1.689	NA	Disease12M	0.708662
ProximityGreenSpace	valueCompletely disagree	0.579	0.726	-0.753	0.452	0.118	2.218	23 (17.4)	ChronicDisease	0.738076

BMI	value	1.147	0.181	0.757	0.449	0.806	1.648	NA	Disease12M	0.738076
TTHMs	value	-0.045	0.065	-0.69	0.492	-0.172	0.083	NA	GeneralHealth	0.757107
BrTHMs	value	-0.045	0.065	-0.698	0.487	-0.173	0.083	NA	GeneralHealth	0.757107
Bathroom_cleaning_days_week	value	1.169	0.216	0.723	0.47	0.756	1.779	NA	ChronicDisease	0.757107
Cancer12MREC	valueYes	2.361	1.252	0.686	0.493	0.106	25.962	3 (2.6)	ChronicDisease	0.757107
SomeonetoHelpinNeighborhood	valueCompletely disagree	2.276	1.189	0.692	0.489	0.27	47.74	4 (3)	Disease12M	0.757107
ProximityGreenSpace	valueCompletely disagree	-0.118	0.186	-0.633	0.528	-0.486	0.25	23 (17.4)	GeneralHealth	0.766753
Other_glasses_day	value	1.121	0.181	0.629	0.529	0.714	1.681	NA	ChronicDisease	0.766753
TTHMs	value	1.121	0.182	0.63	0.529	0.791	1.636	NA	Disease12M	0.766753
BrTHMs	value	1.127	0.182	0.657	0.511	0.795	1.646	NA	Disease12M	0.766753
FreeChlorine	value	1.123	0.178	0.652	0.514	0.794	1.604	NA	Disease12M	0.766753
SomeonetoHelpinNeighborhood	valueDo not know	0.133	0.218	0.612	0.542	-0.298	0.565	15 (11.4)	GeneralHealth	0.776867
SomeonetoHelpinNeighborhood	valueProbably agree	-0.083	0.144	-0.58	0.563	-0.367	0.201	56 (42.4)	GeneralHealth	0.797837
Cigarettes_daily_on_average	value	0.862	0.261	-0.569	0.569	0.481	1.375	NA	ChronicDisease	0.797837
FinancialIssuesDentalCareREC	valueNo, I didn't need	0.75	0.517	-0.556	0.578	0.273	2.127	70 (54.7)	ChronicDisease	0.801742
TCM	value	-0.032	0.065	-0.501	0.618	-0.16	0.096	NA	GeneralHealth	0.805273
Other_glasses_day	value	0.032	0.064	0.503	0.616	-0.094	0.159	NA	GeneralHealth	0.805273
ActivitiesInGreenSpace	valueProbably disagree	-0.147	0.279	-0.525	0.6	-0.699	0.406	46 (34.8)	GeneralHealth	0.805273
Bottled_water_glasses_day	value	1.1	0.18	0.529	0.597	0.776	1.584	NA	Disease12M	0.805273
Cigarettes_daily_on_average	value	1.107	0.189	0.538	0.591	0.77	1.633	NA	Disease12M	0.805273
Sex	valueMale	0.832	0.362	-0.51	0.61	0.409	1.694	50 (37.9)	Disease12M	0.805273
SomeonetoHelpinNeighborhood	valueCompletely disagree	0.167	0.385	0.433	0.666	-0.596	0.929	4 (3)	GeneralHealth	0.821914
ProximityGreenSpace	valueDo not know	0.611	1.144	-0.431	0.667	0.03	4.261	7 (5.3)	ChronicDisease	0.821914
SomeonetoHelpinNeighborhood	valueProbably agree	0.811	0.461	-0.456	0.649	0.325	2.007	56 (42.4)	ChronicDisease	0.821914
ProximityGreenSpace	valueCompletely disagree	0.797	0.515	-0.44	0.66	0.288	2.204	23 (17.4)	Disease12M	0.821914
ActivitiesInGreenSpace	valueProbably disagree	1.4	0.788	0.427	0.669	0.306	7.478	46 (34.8)	Disease12M	0.821914
SomeonetoHelpinNeighborhood	valueProbably disagree	1.517	0.911	0.458	0.647	0.27	11.66	6 (4.5)	Disease12M	0.821914
TBM	value	-0.026	0.065	-0.398	0.691	-0.154	0.102	NA	GeneralHealth	0.833075
ActivitiesInGreenSpace	valueDo not know	1.714	1.345	0.401	0.689	0.13	42.528	9 (6.8)	ChronicDisease	0.833075
ActivitiesInGreenSpace	valueCompletely disagree	1.538	1.137	0.379	0.705	0.225	30.793	51 (38.6)	ChronicDisease	0.842083
Bottled_water_glasses_day	value	0.923	0.226	-0.356	0.722	0.572	1.405	NA	ChronicDisease	0.846709
Sex	valueMale	0.847	0.459	-0.361	0.718	0.332	2.045	50 (37.9)	ChronicDisease	0.846709
ProximityGreenSpace	valueProbably disagree	0.822	0.572	-0.342	0.732	0.266	2.564	17 (12.9)	Disease12M	0.850703
SomeonetoHelpinNeighborhood	valueProbably disagree	0.692	1.164	-0.316	0.752	0.034	5.238	6 (4.5)	ChronicDisease	0.866143
ProximityGreenSpace	valueProbably agree	0.893	0.438	-0.258	0.797	0.377	2.114	40 (30.3)	Disease12M	0.90985
Tap_water_glasses_day	value	0.013	0.064	0.208	0.835	-0.113	0.14	NA	GeneralHealth	0.912839
ProximityGreenSpace	valueProbably agree	0.885	0.565	-0.216	0.829	0.284	2.673	40 (30.3)	ChronicDisease	0.912839
TBM	value	1.044	0.178	0.242	0.809	0.737	1.508	NA	Disease12M	0.912839
Tap_water_glasses_day	value	1.042	0.178	0.23	0.818	0.736	1.492	NA	Disease12M	0.912839
SomeonetoHelpinNeighborhood	valueProbably agree	1.088	0.392	0.216	0.829	0.504	2.354	56 (42.4)	Disease12M	0.912839
ProximityGreenSpace	valueProbably agree	0.028	0.158	0.176	0.861	-0.284	0.34	40 (30.3)	GeneralHealth	0.917926
Cancer12MREC	valueYes	-0.072	0.396	-0.182	0.856	-0.858	0.713	3 (2.6)	GeneralHealth	0.917926

TCM	value	1.033	0.177	0.183	0.854	0.731	1.481	NA	Disease12M	0.917926
ActivitiesInGreenSpace	valueProbably disagree	1.2	1.157	0.158	0.875	0.165	24.501	46 (34.8)	ChronicDisease	0.925205
FreeChlorine	value	-0.009	0.065	-0.142	0.888	-0.137	0.119	NA	GeneralHealth	0.929008
Resporatory12MREC	valueYes	1.167	1.148	0.134	0.893	0.058	8.484	5 (4.3)	ChronicDisease	0.929008
Water_from_vending_machines_glasses_day	value	-0.007	0.064	-0.108	0.914	-0.134	0.12	NA	GeneralHealth	0.943248
Bottled_water_glasses_day	value	-0.004	0.064	-0.058	0.954	-0.13	0.123	NA	GeneralHealth	0.976714
SomeonetoHelpinNeighborhood	valueCompletely disagree	0	1199.772	-0.013	0.99	NA	6.62E+52	4 (3)	ChronicDisease	0.992
Diabetes12MREC	valueYes	2.44E+08	1978.09	0.01	0.992	0	NA	6 (5.3)	ChronicDisease	0.992
LiverDisorders12MREC	valueYes	84126064	1696.734	0.011	0.991	0	NA	2 (1.8)	ChronicDisease	0.992

Supplementary figures

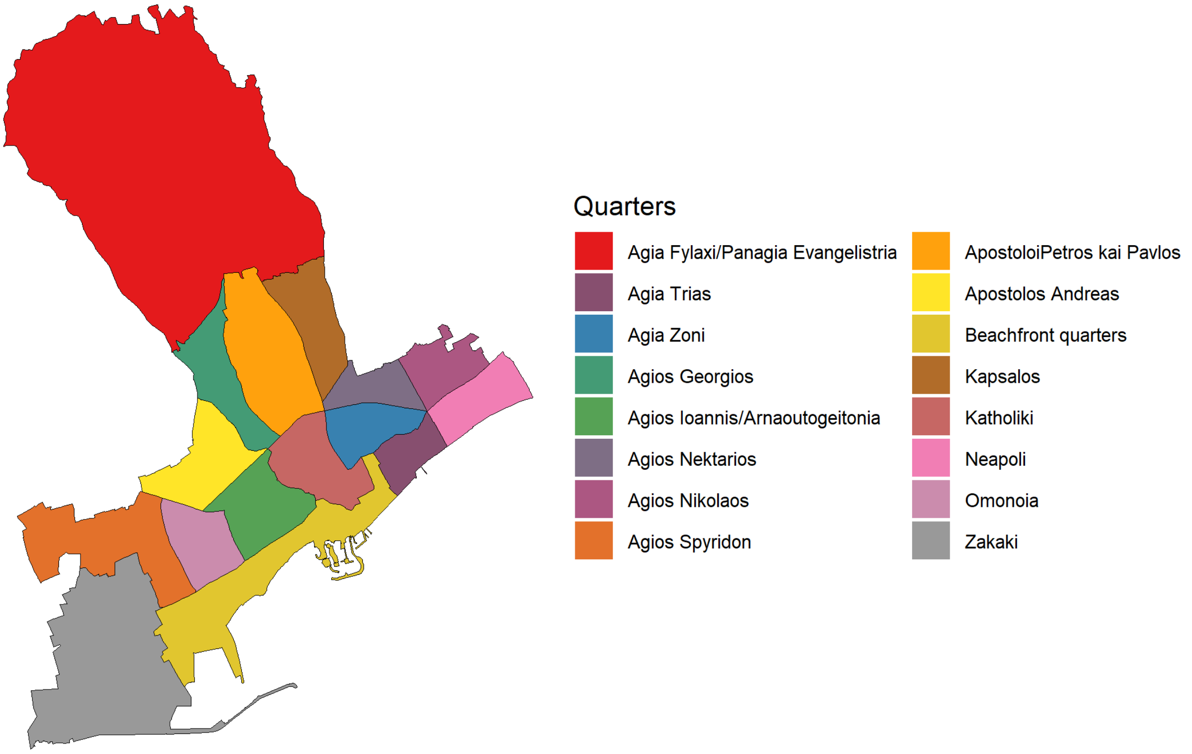


Figure S3. 1 Map of the quarters of the Limassol municipality as they are used in the analysis.

Supplementary methods

Microbiological analysis

Total viable counts at 22 and 37 °C

Enumeration of heterotrophic bacteria in water was performed by the pour plate method with yeast extract agar (YEA; Oxoid, CM0019, Basingstoke, UK) (Suthar et al. 2009). Briefly, 1 ml of water sample was transferred onto sterile 90-mm Petri dishes, followed by the addition of 15 ml of YEA (previously autoclaved and cooled to 45–50 °C). The contents were mixed by a combination of rapid end-to end shaking and circular movements lasting over a period of 5–10 s. The agar was then allowed to solidify, and incubation of duplicate sets of plates for 3 days at 37 and at 22 °C was practiced.

Membrane filtration analysis for *E. coli*, coliforms, *Pseudomonas aeruginosa*, and *Enterococus* spp.

The membrane filtration technique was applied for the detection and enumeration of *E. coli*, coliforms, *Pseudomonas aeruginosa*, and *Enterococcus* spp., followed by incubation onto selective media. A volume of 250 ml of the sample was filtered through a 0.45-mm, gridded, sterile membrane, and the filter was then aseptically transferred onto the appropriate agar medium in Petri dish, avoiding air bubbles beneath the membrane. For the *E. coli* and coliform analysis, a cromogenic medium was used (ChromoCult® Coliform Agar, Merck, Darmstadt, Germany), which was able to differentiate between *E. coli* and other coliform bacteria. Plates were incubated inverted at 37 °C for 24 h with red color colonies, indicating the presence of coliform bacteria, whereas the presence of blue colonies indicated the presence of *E. coli* (see Ouattara et al. 2011).

The analysis for *Pseudomonas aeruginosa* was performed onto Pseudomonas Agar (OXOID CM0559, plus Pseudomonas CN selective agar supplement SR0102, Basingstoke, UK). Incubation was set at 25 °C for 2 days with positive colonies of *Pseudomonas aeruginosa* coming up with light green color and fluoresced under UV light at 365 nm. Finally, for enumerating enterococci from the water samples, the membrane filters were incubated onto Slanetz and Bartley medium (OXOID CM0377, Basingstoke, UK) at 44 °C for 4 h and at 37 °C for 2 days. Colonies with red-brown color were enumerated as *Enterococcus* spp. All suspicious colonies were confirmed molecularly via 16S rRNA sequencing as previously described by Botsaris et al. (2015).

References

Botsaris, G., Kanetis, L., Slaný, M. et al. Environ Monit Assess (2015) 187: 739.

Ouattara, K. N., Passerat, J., & Servais, P. (2011). Faecal contamination of the water and sediment in the rivers of the Scheldt drainage network. Environmental Monitoring and Assessment, 183(1–4), 243–257.

Suthar, S., Chhimpa, V., & Singh, S. (2009). Bacterial contamination in drinking water: a case study in rural areas of northern Rajasthan, India. Environmental Monitoring and Assessment, 159(1–4), 43–50.

Supplementary information

STROBE Statement

Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Inclusion in the relevant section (yes if included in the manuscript/not applicable/explanations if necessary)
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes (introduction)
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes (introduction)
Methods			
Study design	4	Present key elements of study design early in the paper	Yes
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Yes
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes (mapping of indicators and general health/chronic diseases/any disease in the past year) were included in an agnostic approach for proof-of-concept analysis.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Questionnaires and water sample analysis were conducted details can be found in the methods section.
Bias	9	Describe any efforts to address potential sources of bias	Addressed in the methods section.

Study size	10	Explain how the study size was arrived at	Addressed in the methods section.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Addressed in the methods section.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Addressed in the methods section.
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	Addressed in the methods section.
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes
		(b) Indicate number of participants with missing data for each variable of interest	Yes
Outcome data	15*	Report numbers of outcome events or summary measures	Included in the results
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Provided in the environment-wide associations part of the analysis
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	Yes
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes
Generalisability	21	Discuss the generalisability (external validity) of the study results	The study is for proof-of-concept.
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Not applicable

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Questionnaires

Questionnaire 1 – Perceptions study

Note: Questions used in for the study about the drinking water and quality of life indicators are highlighted.

Personal information

Q1 What is your gender?

- Male
- Female
- I don't want to answer this question

Q2 What is your age?

Q3 What is the highest education leaving certificate, diploma or education degree you have obtained?

- Never attended school
- Not completed primary
- Primary
- Gymnasium (3 years)
- Lyceum (secondary completed)
- Post Secondary non-tertiary
- Tertiary level (non-university)
- University (1st degree)
- University (Master's degree)
- University (Doctorate degree)

Q4 Where were you born?

- Born on Cyprus
- Born in another EU country:

____

- Born in a non-EU country

____

Q5 In which of the following areas, did you spend most of childhood (until you turned 18 years old)?

- Nicosia (city)
- Limassol (city)
- Paphos (city)
- Larnaca (city)
- A village
- Not in Cyprys

Q6 What is your current place of residence?

- Nicosia (city)
- Limassol (city)
- Paphos (city)
- Larnaca (city)
- A village

Display This Question:

If What is your current place of residence? Limassol (city) Is Selected:

Q6B What is your zipcode?

47

Q7 What is your marital status?

- Single, never married
- Cohabiting
- Married (including registered partnership)
- Widowed and not remarried
- Divorced and not remarried

Q8 Do you have children?

- Yes
- No

Personal norms and values

48

Q9 How do perceive your life being controlled? (max. 1 answer)

- My life is controlled by me, I decide on what I want to do and achieve in life
- My life is controlled by me and my family/friends, I involve others in the decision-making but make the final decision myself
- My life is mainly controlled by my family and/or friends
- My life is mainly controlled by my family/friends and the government
- My life is mainly controlled by the government

Q10 When something bad happens, what do you often see as the cause? (max. 1 answer)

- A higher power, for example God, caused it
- I have caused it personally
- It is a result of other powers in my environment, for example other people
- Injustice is the cause, societal inequalities (for example discrimination)

Q11 Whose wellbeing is most important to you? (max. 1 answer)

- My community
- My friends
- My family
- My own wellbeing

Q12 How do you perceive yourself? (max. 1 answer)

- As autonomous
- As a part of a social community
- As a part of traditions and culture

Q13 How do you consider nature and environment? As basically (max. 1 answer):

- Stable, but there are certain limits of human induced pressure
- Good and giving, mother earth provides
- Flexible, after damage nature will restore itself
- Overwhelming, the nature makes me feel small
- Fragile, we are responsible and should thread very lightly
- Complex, small changes we induce can have big and unforeseen consequences

Q14 According to your own opinion, what terms do reflect your character best? You being (max. 1 answer):

- Righteous
- Goodhearted
- Optimistic
- Flexible
- Independent
- Open minded

Q15 According to your own opinion, what terms do reflect your character best? You being: (max. 1 answer)

- ◯ Conscientious
- ◯ Amiable
- ◯ Ambitious
- ◯ Realistic
- ◯ Autonomous
- ◯ Dynamic

Q16 What do you consider MOST important for a well-functioning society? (max. 1 answer)

- ◯ Truthfulness
- ◯ Kindness
- ◯ Intelligence
- ◯ Adaptability
- ◯ Independence
- ◯ Loyalty

Q17 Do you think a higher social position (for example wealth) could protect people from environmental hazards? (max. 1 answer)

- Definitely yes
- Probably yes
- Might or might not
- Probably not
- Definitely not

Q18 Do you think a lower social position (for example poorness) could increase people's exposure to environmental hazards? (max. 1 answer)

- Definitely yes
- Probably yes
- Might or might not
- Probably not
- Definitely not

Environment

Q19 On what do you think the focus should be in order to tackle environmental problems? (max. 1 answer)

- ○ Implementing clear rules and regulations
- ○ Raising awareness and engaging collectively for the cause
- ○ Developing innovative technologies
- ○ Cutting down on our consumption patterns
- ○ Integrate existing knowledge to better understand the complexities of the global environmental problems

Q20 Who do you think has the main responsibility to solve environmental problems? (max. 1 answer)

- ○ The government
- ○ Non Governmental Organisations (for example WWF, Greenpeace) or civil actions groups
- ○ Scientists and inventors
- ○ I and the lifestylechoices I make, daily
- ○ All joined forces together
- ○ We can't help solving (global) environmental problems: they are beyond our influence

Q21 Do you ever worry about the global environment? (max. 1 answer)

- Yes, very often
- Yes, sometimes
- No, almost never
- No, not at all

Q22 Do you ever worry about Cyprus' environment? (max. 1 answer)

- Yes, very often
- Yes, sometimes
- No, almost never
- No, not at all

Q23 Do you think you can influence Cyprus' environment with your behavior and actions? (max. 1 answer)

- Definitely yes
- Probably yes
- Might or might not
- Probably not
- Definitely not

Q24 Do you believe in climate change?

- Yes
- No
- Maybe

Display This Question:

If Do you believe in climate change? Yes Is Selected

Q25 How worried are you about climate change on a scale from 1 to 10 (1 as not concerned at all, to 10 as most concerned)

1 2 3 4 5 6 7 8 9 10

Q26 What is, on a global scale, your major environmental worry? (max. 2 answers)

☐ Air pollution

☐ Effects from climate change, such as rising temperatures, extreme weather conditions, droughts or floods

☐ Plastic in the oceans

☐ Water pollution and soil contamination

☐ Rising sea levels

☐ other: ______________________________

Q27 What are your major concerns regarding environmental problems on Cyprus, specifically in relation to industrial pollution? (max. 2 answers)

☐ Air quality

☐ Water quality

☐ Soil contamination/pollution

☐ Chemical exposure

☐ Other: ______________________________

☐ none

Q28 What are your major concerns regarding environmental problems on Cyprus, specifically in relation to agriculture? (max. 2 answers)

☐ Air quality

☐ Water quality

☐ Soil contamination

☐ Chemical exposure

☐ Other: ____

☐ None

Q29 What is your biggest environmental concern where you live? (max. 2 options)

- ☐ Air quality
- ☐ Water quality
- ☐ Soil contamination
- ☐ Chemical exposure
- ☐ Waste (waste management, cleanness of public spaces)
- ☐ Noise
- ☐ other: ______________________________
- ☐ None

Q30 Have you, and to what extent, been exposed at HOME to any of the following conditions in the past 12 months?

	Severely exposed	Somewhat exposed	Not exposed	Don't know
Noise (traffic, airplanes, factories, neighbours, animals, restaurants/bars/clubs)	○	○	○	○
Air pollution (fine dust, grime, fume, ozone	○	○	○	○
Bad smells (industry, agriculture, waste)	○	○	○	○
Water pollution (microbes or chemicals in drinking water)	○	○	○	○
Soil contamination (for example a chemical waste dump)	○	○	○	○

Q31 Have you, and to what extent, been exposed OUTSIDE OF YOUR HOUSE (at work, or during your free time) to any of the following conditions in the past 12 months?

	Severely exposed	Somewhat exposed	Not exposed	Don't know
Noise (traffic, airplanes, factories, neighbours, animals, restaurants/bars/clubs)	○	○	○	○
Air pollution (fine dust, grime, fume, ozone)	○	○	○	○
Bad smells (industry, agriculture, waste)	○	○	○	○
Water pollution (microbes or chemicals in drinking water)	○	○	○	○
Soil contamination (for example a chemical waste dump)	○	○	○	○

Q32 Are you worried about chemical exposure?

○ Yes

○ No

○ Maybe

Q33 Do you think you're exposed to chemicals on a daily basis?

- Yes
- No
- Maybe

Q34 Do you think the tap water is safe to drink?

- Yes
- No
- Maybe

Q35 Do you drink tap water?

- Yes
- No
- Only after cooking it, or using a filter

Q36 What is your main concern about the tapwater as drinking water? (max. 1 answer)

- Chemicals (e.g. heavy metals)
- Microbes (e.g. bacteria)
- Taste
- Other: ______________________________
- None

Q37 Where do you get your information about the environment and the place you live? (max. 2 answers)

- Newspapers
- Family or friends
- TV
- Internet
- Other: ______________________________
- None

Q38 Would you like to get more information about environmental hazards in your daily life?

- ○ Yes
- ○ No
- ○ Maybe

Health

Q39 How would you rate your health, on a scale from 1 to 10? (10 as excellent)

1 2 3 4 5 6 7 8 9 10

Q40 Are you worried about your health?

- ○ Yes, very much
- ○ Yes, a bit
- ○ No, not really
- ○ No, not at all

Q41 How do you think living in a city affects your health?

- Positively
- Negatively
- No influence

Q42 Which environment is healthier, and why? Please provide one or two reasons that you consider make the environment of the city or the villages more healthy

- City, because (max. 2 reasons) ________________
- Villages/rural areas, because (max. 2 reasons) ________________
- No difference

Q43 Would you like to change your city to make it a healthier environment? Why?

- Yes
- No

Display This Question:

If Would you like to change your city to make it a healthier environment? Why? Yes Is Selected

Q43.2 If yes, what would you like to change?

Thank you for participating in our research! **Please press the orange button** below to submit your answers. You can write any comments you have before submitting your answers below.

Questionnaire 2 – Urban population

Note: the questionnaire is available in Greek. Questions used in mapping the drinking water and quality of life indicators are highlighted and brief notes in English have been added.

Περιβαλλοντική υγεία: μελέτη του αστικού περιβάλλοντος
Ποιότητα ζωής και υγεία

Το μεγαλύτερο μέρος του κυπριακού πληθυσμού, με βάση τα πιο πρόσφατα δεδομένα κατοικεί σε αστικές περιοχές (>60%). Οι κυπριακές πόλεις, λοιπόν, καλούνται να αντιμετωπίσουν μια σειρά από προκλήσεις στους τομείς της δημόσιας υγείας και του περιβάλλοντος, παρόμοιες με αυτές που αντιμετωπίζουν τα αστικά κέντρα παγκοσμίως. Πρέπει ταυτοχρόνως να ακολουθήσουν πρακτικές βιώσιμης ανάπτυξης για την ανάπτυξη των τοπικών οικονομιών τους.

Το παρόν ερευνητικό έργο έχει στόχο να καταγράψει δείκτες περιβαλλοντικής υγείας στην πόλη της Λεμεσού με σκοπό να πραγματοποιηθεί μια πρώτη χαρτογράφηση δεικτών υγείας ειδικά για το αστικό περιβάλλον.

Αν είστε κάτοικος της πόλης της Λεμεσού η συμμετοχή σας θα μας βοηθήσει να συλλέξουμε δεδομένα για την καθημερινή ζωή στην πόλη.

Η έρευνα πραγματοποιείται στο πλαίσιο εκπόνησης διδακτορικής διατριβής στο Διεθνές Ινστιτούτο Κύπρου για την Περιβαλλοντική και Δημόσια Υγεία του Τεχνολογικού Πανεπιστημίου Κύπρου. Επιστημονικός υπεύθυνος: Κωνσταντίνος Χ. Μακρής, Αναπληρωτής Καθηγητής, Τεχνολογικό Πανεπιστήμιο Κύπρου (τηλ.: 2500 2398, email: konstantinos.makris@cut.ac.cy).

Περισσότερες πληροφορίες για την ερευνητική δραστηριότητα του Ινστιτούτου και του εργαστηρίου μας μπορείτε να βρείτε στις ιστοσελίδες:

- CII: http://www.cut.ac.cy/cii/
- Water and Health Laboratory: web.cut.ac.cy/waterandhealth/

Καθώς και στα μέσα κοινωνικής δικτύωσης:

- Facebook: facebook.com/waterandhealthlab.CII/
- Twitter: @waterhealth_lab

Σημαντικές πληροφορίες:

- Η συμπλήρωση του ερωτηματολογίου δεν απαιτεί την συμπλήρωση προσωπικών δεδομένων. Η μελέτη έχει εγκριθεί από την Εθνική Επιτροπή Βιοηθικής Κύπρου.

Ευχαριστούμε πολύ!

Ημερομηνία συμπλήρωσης		Κωδικός (συμπληρώνεται από τους ερευνητές)	

- **Γενικές ερωτήσεις**

1. Ταχυδρομικός κώδικας κατοικίας

2. Δήμος/Κοινότητα ______________________

3. Ενορία (αν γνωρίζετε) ______________________

4. Πόσα χρόνια μένετε στην Κύπρο; (years living in Cyprus)

- ❑ Όλη μου τη ζωή
- ❑ Λιγότερο από 1 χρόνο
- ❑ 1-5 χρόνια
- ❑ 6-10 χρόνια
- ❑ 11-20 χρόνια
- ❑ Περισσότερο από 20 χρόνια

5. Γεννηθήκατε στην …

- ❑ Κύπρο
- ❑ Σε άλλη χώρα της Ευρωπαϊκής 'Ενωσης

  Σημειώστε σε ποια άλλη χώρα της Ευρωπαϊκής Ένωσης έχετε γεννηθεί

  ____

- ❑ Σε άλλη χώρα εκτός Ευρωπαϊκής Ένωσης

  Σημειώστε σε ποια άλλη χώρα εκτός της Ευρωπαϊκής Ένωσης έχετε γεννηθεί

  ____

- Οικογενειακή κατάσταση και εκπαίδευση

1. **Ποια είναι η οικογενειακή σας κατάσταση; (marital status)**

- ❑ 'Αγαμος/η
- ❑ 'Ατομο που συζεί (σύντροφος)
- ❑ Παντρεμένος/η
- ❑ Χήρος/α που δεν ξαναπαντρέυτηκε
- ❑ Διαζευγμένος/η που δεν ξαναπαντρεύτηκε

2. **Ποιο είναι το υψηλότερο επίπεδο εκπαίδευσης που έχετε ολοκληρώσει με επιτυχία; (education)** *Παρακαλώ περιλάβετε οποιαδήποτε εκπαίδευση πήρατε στα πλαίσια της εργασίας σας.*

- ❑ Δεν έχω φοιτήσει ποτέ σε σχολείο
- ❑ Δεν έχω τελειώσει το δημοτικό
- ❑ Δημοτικό σχολείο
- ❑ Γυμνάσιο (3 χρόνια)
- ❑ Λύκειο/Τεχνική σχολή (απολυτήριο)
- ❑ Μεταλυκειακή εκπαίδευση μη τριτοβάθμια
- ❑ Τριτοβάθμια μη Πανεπιστημιακή
- ❑ Πανεπιστήμιο (πρώτο πτυχίο)
- ❑ Πανεπιστήμιο-Μεταπτυχιακό (μόνο Master's degree)
- ❑ Διδακτορικό

- Ερωτήσεις σχετικά με την επαγγελματική σας κατάσταση

1. **Ποια είναι η επαγγελματική σας κατάσταση, αυτή την περίοδο;**

- ❑ Εργαζόμενος/η πλήρους απασχόλησης
- ❑ Εργαζόμενος/η μερικής απασχόλησης
- ❑ Είμαι άνεργος/η και δεν έχω εργαστεί ποτέ
- ❑ Είμαι άνεργος/η, αλλά εργαζόμουν προηγουμένως
- ❑ Οικιακά/φροντίδα παιδιών (χωρίς μισθό)
- ❑ Δεν εργάζομαι για λόγους υγείας
- ❑ Δεν εργάζομαι διότι έχω συνταξιοδοτηθεί
- ❑ Είμαι μαθητής/φοιτητής
- ❑ Υπηρετώ τη στρατιωτική μου θητεία
- ❑ Άλλο (παρακαλώ συμπληρώστε) ______________________________

2. **Αν εργάζεστε, ποια είναι η θέση σας στην επιχείρηση/υπηρεσία ή στον οργανισμό όπου εργάζεστε;**
   - ❑ Αυτοεργοδοτούμενος με υπαλλήλους
   - ❑ Αυτοεργοδοτούμενος χωρίς υπαλλήλους
   - ❑ Υπάλληλος σε μόνιμη θέση ή σύμβαση εργασίας αορίστου χρόνου
   - ❑ Υπάλληλος σε προσωρινή θέση ή σύμβαση εργασίας ορισμένου χρόνου
   - ❑ Υπάλληλος σε οικογενειακή επιχείρηση χωρίς μισθό

3. **Αν εργάζεστε, σε ποιο τομέα εργάζεστε;**
   - ❑ Αγροτικές ή/και γεωργικές εργασίες
   - ❑ Μεσιτικά
   - ❑ Στο δημόσιο τομέα (κυβέρνηση) ή στην άμυνα (στρατός)
   - ❑ Εκπαίδευση
   - ❑ Σε εργοστάσιο
   - ❑ Στον τομέα της υγείας
   - ❑ Σε υπηρεσίες δημόσιου συμφέροντος (π.χ. ΑΗΚ, υδατοπρομήθεια)
   - ❑ Κατασκευές
   - ❑ Πωλήσεις
   - ❑ Τουρισμός (ξενοδοχεία και χώροι εστίασης)
   - ❑ Στον τομέα της επικοινωνίας
   - ❑ Άλλο: ____________________

- **Ερωτήσεις σχετικά με την προσωπική αντίληψη της κατάστασης υγείας**

1. Πώς είναι γενικά η υγεία σας; Είναι... (general health)

- ❑ Πολύ καλή
- ❑ Καλή
- ❑ Μέτρια
- ❑ Κακή
- ❑ Πολύ κακή
- ❑ Δεν γνωρίζω/δεν είμαι σίγουρος/δεν θυμάμαι
- ❑ Δεν απαντώ

2. Έχετε κάποια μακροχρόνια ασθένεια ή χρόνιο πρόβλημα υγείας (chronic disease)

- ❑ Ναι
- ❑ Όχι
- ❑ Δεν γνωρίζω/δεν είμαι σίγουρος/δεν θυμάμαι
- ❑ Δεν απαντώ

3. Κατά τους τελευταίους 12 μήνες, είχατε κάποια από τις παρακάτω ασθένειες; Σημειώστε στο αντίστοιχο κουτάκι. (diseases the past 12 months)

Ερωτηματολόγιο

	Ναι	Όχι	Δεν γνωρίζω	Δεν απαντώ
Άσθμα (περιλαμβάνεται το αλλεργικό άσθμα)	☐	☐	☐	☐
Χρόνια βρογχίτιδα, χρόνια αποφρακτική πνευμονοπάθεια, Εμφύσημα	☐	☐	☐	☐
Ψηλή αρτηριακή πίεση - Υπέρταση	☐	☐	☐	☐
Καρδιαγγειακές παθήσεις (π.χ. έμφραγμα της καρδιάς (καρδιακή προσβολή) ή χρόνιες επιπτώσεις παλαιού εμφράγματος, στεφανιαία νόσος ή στηθάγχη)	☐	☐	☐	☐
Πάθηση των αρθρώσεων (εξαιρείται η αρθρίτιδα)	☐	☐	☐	☐
Πάθηση στη μέση ή άλλα χρόνια προβλήματα μέσης (οσφυαλγία-δισκοπάθεια)	☐	☐	☐	☐
Πάθηση του αυχένα ή άλλα χρόνια προβλήματα του αυχένα	☐	☐	☐	☐
Διαβήτης (εξαιρείται ο διαβήτης της εγκυμοσύνης)	☐	☐	☐	☐
Αλλεργία (π.χ. ρινίτιδα, φλεγμονή ματιών, δερματίτιδα, τροφική αλλεργία, κλπ). Εξαιρείται το αλλεργικό άσθμα.	☐	☐	☐	☐
Παθήσεις στο συκώτι (π.χ. κίρρωση ήπατος)	☐	☐	☐	☐
Καρκίνος (κακοήθης όγκος, λευχαιμία, λέμφωμα)	☐	☐	☐	☐
Κατάθλιψη	☐	☐	☐	☐

4. Χρήση υπηρεσιών υγείας

4.1. Κατά τη διάρκεια των τελευταίων 12 μηνών, αντιμετωπίσατε καθυστέρηση στην παροχή ιατρικής φροντίδας λόγω …………………... ; (delays in access to health care)

Σημειώστε στο αντίστοιχο κουτάκι στον παρακάτω πίνακα

Λόγοι καθυστέρηση στην παροχή ιατρικής φροντίδας	Ναι	Όχι, δεν αντιμετώπισα καθυστέρηση	Όχι, δεν χρειάστηκα ιατρική φροντίδα	Δεν γνωρίζω	Δεν απαντώ
Μεγάλης λίστας αναμονής;	☐	☐	☐	☐	☐
Απόστασης ή έλλειψης μεταφορικού;	☐	☐	☐	☐	☐

4.2. Κατά τη διάρκεια των τελευταίων 12 μηνών, χρειαστήκατε κάποιο από τα

Ερωτηματολόγιο

ακόλουθα είδη φροντίδας, αλλά δεν είχατε την οικονομική ευχέρεια να το έχετε; (financial issues in access to health care)

Σημειώστε στο αντίστοιχο κουτάκι στον παρακάτω πίνακα

Είδη φροντίδας	Ναι	Όχι, είχα οικονομική ευχέρεια	Όχι, δεν χρειάστηκα	Δεν γνωρίζω	Δεν απαντώ
Ιατρική φροντίδα	☐	☐	☐	☐	☐
Οδοντιατρική φροντίδα	☐	☐	☐	☐	☐
Συνταγογραφημένα φάρμακα	☐	☐	☐	☐	☐
Φροντίδα για ψυχική υγεία	☐	☐	☐	☐	☐

- **Πρόληψη και εμβολιασμοί**

1. **Έχετε εμβολιαστεί ποτέ κατά της γρίπης;**
   - ❑ Ναι
     Πότε ήταν η τελευταία φορά που εμβολιαστήκατε κατά της γρίπης; (χρονιά) …………
   - ❑ Όχι (προχωρήστε στην ερώτηση 2)
   - ❑ Δεν γνωρίζω/δεν είμαι σίγουρος/δεν θυμάμαι (προχωρήστε στην ερώτηση 2)
   - ❑ Δεν απαντώ ((προχωρήστε στην ερώτηση 2)

2. **Πότε ήταν η τελευταία φορά που εξεταστήκατε ή μετρήθηκε κάποιος από τους παρακάτω δείκτες;**

	Τους τελευταίους 12 μήνες	1-3 χρόνια πριν	3-5 χρόνια πριν	Παλαιότερα από τα τελευταία 5 χρόνια	Ποτέ	Δεν γνωρίζω	Δεν απαντώ
Αρτηριακή πίεση	☐	☐	☐	☐	☐	☐	☐
Χοληστερίνη	☐	☐	☐	☐	☐	☐	☐
Σάκχαρο	☐	☐	☐	☐	☐	☐	☐

3. **Κάνατε ποτέ εξέταση για καρκίνο του παχέος εντέρου (π.χ. κολονοσκόπηση, εξέταση ανίχνευσης κρυφού αίματος στα κόπρανα);**
   - ❑ Ναι
   - ❑ Όχι
   - ❑ Δεν γνωρίζω/δεν είμαι σίγουρος/δεν θυμάμαι
   - ❑ Δεν απαντώ

- **Δείκτης μάζας σώματος/έτος γέννησης/φύλο**

1. **Πόσο είναι το ύψος σας χωρίς παπούτσια; ....εκατοστά (height)**
2. **Πόσο ζυγίζετε χωρίς ρούχα και παπούτσια; ....κιλά (weight)**

3. **Έτος γέννησης ____________ (year of birth)**

4. **Φύλο (sex)**
   - ❑ 'Ανδρας
   - ❑ Γυναίκα
   - ❑ Δεν θα ήθελα να απαντήσω

- **Ερωτήσεις για γυναίκες**

1. **Κάνατε ποτέ μαστογραφία;**
   - ❑ Ναι
   - ❑ Όχι
   - ❑ Δεν γνωρίζω/δεν είμαι σίγουρος/δεν θυμάμαι
   - ❑ Δεν απαντώ
2. **Κάνατε ποτέ τεστ Παπανικολάου;**
   - ❑ Ναι
   - ❑ Όχι
   - ❑ Δεν γνωρίζω/δεν είμαι σίγουρος/δεν θυμάμαι
   - ❑ Δεν απαντώ
3. **Πότε ήταν η τελευταία φορά που κάνατε τεστ Παπανικολάου**
   - ❑ Εντός των τελευταίων 12 μηνών
   - ❑ 1-2 έτη πριν
   - ❑ 2-3 έτη πριν
   - ❑ Παλαιότερα από τα τελευταία 3 έτη
   - ❑ Δεν γνωρίζω/δεν είμαι σίγουρη/δεν θυμάμαι
   - ❑ Δεν απαντώ

- Σωματική δραστηριότητα και διατροφικές συνήθειες

1. Κάνετε σωματική άσκηση τουλάχιστον 30 λεπτά (π.χ. γρήγορο περπάτημα,τρέξιμο, αεροβική άσκηση, ποδήλατο) τη μέρα, στον ελεύθερό σας χρόνο;

- ❑ Καθημερινά
- ❑ 4-6 φορές τη εβδομάδα
- ❑ 2-3 φορές την εβδομάδα
- ❑ 1 φορά την εβδομάδα
- ❑ 2-3 φορές το μήνα
- ❑ Μερικές φορές το χρόνο
- ❑ Δεν ασκούμαι λόγω προβλημάτων υγείας
- ❑ Δεν ασκούμαι λόγω προβλημάτων κινητικότητας
- ❑ Δεν ασκούμαι ποτέ

2. Πόσο συχνά τρώτε πρωινό (π.χ. δημητριακά με γάλα, σάντουιτς κτλ)

- ❑ Περισσότερο από 4 φορές την εβδομάδα
- ❑ Λιγότερο από 4 φορές την εβδομάδα

3. Κατά μέσο όρο πόσες μερίδες φρούτων καταναλώνετε τη μέρα;

…… μερίδες

Σημείωση: Μια μερίδα ισοδυναμεί περίπου με: 1 μήλο, 1 αχλάδι, 1 ροδάκινο, 1 πορτοκάλι, 2 μανταρίνια, 1 φέττα καρπούζι/πεπόνι (μερίδα εστιατορίου), 7 μικρές φράουλες, 14 κεράσια, 2 δαμάσκηνα, 2 φορμόζες, 2 ακτινίδια, 3 κουταλιές φρουτοσαλάτα (χωρίς κομπόστο ή ζάχαρη), 1 μικρό ποτήρι (150ml) φρέσκο χυμό φρούτων

4. Κατά μέσο όρο πόσες μερίδες λαχανικών καταναλώνετε τη μέρα;

…… μερίδες

Σημείωση: Μια μερίδα αντιστοιχεί σε: 2 κομμάτια μπρόκολο, 2 μεγάλα κομμάτια κουνουπίδι, 4 κουταλιές λάχανο/σπανάκι/φασολάκι, 1 μέτρια ντομάτα, 1 αγγουράκι, 1 καρότο, 3 κουταλιές λαχανάκια Βρυξελλών, 3 κουταλιές σαλάτα από φρέσκα λαχανικά, 1 μικρό ποτήρι (150ml) φρέσκο χυμό λαχανικών

- Ερωτήσεις σχετικά με τη ζωή στη γειτονιά και την πόλη

1. **Κατά μέσο όρο τους τελευταίους 12 μήνες, πόσο συχνά συναντούσατε την οικογένεια και τους συγγενείς σας;**
   - ❑ Καθημερινά
   - ❑ Κάθε εβδομάδα, αλλά όχι κάθε μέρα
   - ❑ Μερικές φορές το μήνα, αλλά όχι κάθε εβδομάδα
   - ❑ Ποτέ

2. **Πόσο συχνά συναντάτε τους φίλους σας**
   - ❑ Καθημερινά
   - ❑ Κάθε εβδομάδα, αλλά όχι κάθε μέρα
   - ❑ Μερικές φορές το μήνα, αλλά όχι κάθε εβδομάδα
   - ❑ Ποτέ

3. **Πόσο συχνά επικοινωνείτε με τους φίλους σας μέσω τηλεφώνου ή του διαδικτύου (με email, στα μέσα κοινωνικής δικτύωσης π.χ. facebook)**
   - ❑ Καθημερινά
   - ❑ Κάθε εβδομάδα, αλλά όχι κάθε μέρα
   - ❑ Μερικές φορές το μήνα, αλλά όχι κάθε εβδομάδα
   - ❑ Ποτέ

4. **Πόσο πολύ αισθάνεστε ότι είστε μέλος ή ταυτίζεστε με τα παρακάτω μέρη;**

	Πάρα πολύ (1)	2	3	4	Καθόλου (5)	Δε γνωρίζω
Τη γειτονιά	☐	☐	☐	☐	☐	☐
Την περιοχή (περίπου σε απόσταση 15-20 λεπτά από την κύρια κατοικίας σας π.χ. δήμος, ενορία)	☐	☐	☐	☐	☐	☐
Την πόλη	☐	☐	☐	☐	☐	☐

5. **Πόσα χρόνια μένετε στην ίδια γειτονιά;**
   - ❑ 0-6 μήνες
   - ❑ 6-12 μήνες
   - ❑ 1-5 χρόνια
   - ❑ Πάνω από 5 χρόνια

6. Σημειώστε αν συμφωνείτε ή διαφωνείτε με τα παρακάτω (life in the neighborhood)

	Συμφωνώ απόλυτα	Μάλλον συμφωνώ	Μάλλον διαφωνώ	Διαφωνώ απόλυτα	Δεν γνωρίζω
Οι γείτονες μου είναι διατεθειμένοι να βοηθήσουν ο ένας τον άλλον	☐	☐	☐	☐	☐
Οι άνθρωποι στη γειτονιά μου δεν έχουν όλοι τις ίδιες αξίες και ιδανικά	☐	☐	☐	☐	☐
Πάντα υπάρχει κάποιος να σε βοηθήσει στην γειτονιά	☐	☐	☐	☐	☐

- Ερωτήσεις σχετικά με το περιβάλλον στο οποίο ζείτε

1. Πόσο μακριά απέχει το σπίτι σας από τον κοντινότερο δρόμο με πολύ κίνηση;

❑ Λιγότερο από 20 μέτρα

❑ 20-50 μέτρα

❑ 50-150 μέτρα

❑ Περισσότερο από 150 μέτρα

2. Σημειώστε την απάντηση που ισχύει στο κατάλληλο κουτάκι

	Συνεχώς (σχεδόν πάντα)	Σπάνια	Ποτέ
Πόσο συχνά περνάνε αυτοκίνητα μπροστά από το σπίτι σας;	☐	☐	☐
Πόσο συχνά περνάνε οχήματα μεγάλου κυβισμού, π.χ. φορτηγά, λεωφορεία	☐	☐	☐

3. Κατά τους τελευταίους 12 μήνες σε τι βαθμό εκτεθήκατε, στο σπίτι σας από θορύβους, π.χ. από αυτοκίνητα και κίνηση, από τους γείτονες, από ζώα, από δραστηριότητες εργοστασίων, από εστιατόρια ή καφέ;

❑ Δεν εκτέθηκα καθόλου

❑ Εκτέθηκα πολύ λίγο

❑ Εκτέθηκα πάρα πολύ

- **Οι επόμενες ερωτήσεις αφορούν στους χώρους πρασίνου**

1. Σημειώστε σε τι βαθμό συμφωνείτε ή διαφωνείτε με τις παρακάτω δηλώσεις σχετικά με τους χώρους πρασίνου στη γειτονιά σας (green space)

	Συμφωνώ απόλυτα	Μάλλον συμφωνώ	Μάλλον διαφωνώ	Διαφωνώ απόλυτα	Δεν γνωρίζω
Οι χώροι πρασίνου στη γειτονιά μου είναι...					
επαρκείς	☐	☐	☐	☐	☐
εύκολα προσβάσιμοι	☐	☐	☐	☐	☐
είναι κοντά στο σπίτι μου	☐	☐	☐	☐	☐
καλά διατηρημένοι	☐	☐	☐	☐	☐

	Συμφωνώ απόλυτα	Μάλλον συμφωνώ	Μάλλον διαφωνώ	Διαφωνώ απόλυτα	Δεν γνωρίζω
Στους χώρους πρασίνου στη γειτονιά μου...					
μπορώ να πάω και να χαλαρώσω στους χώρους πρασίνου στη γειτονιά μου	☐	☐	☐	☐	☐
μπορώ να κάνω πολλές δραστηριότητες	☐	☐	☐	☐	☐

Ευχαριστούμε πολύ!

Τεχνολογικό Πανεπιστήμιο Κύπρου | Διεθνές Ινστιτούτο Κύπρου για την Περιβαλλοντική και Δημόσια Υγεία | Εργαστήριο Νερό και Υγεία

Περιβαλλοντική υγεία: μελέτη του αστικού περιβάλλοντος
Περιβαλλοντικές εκθέσεις

Το μεγαλύτερο μέρος του κυπριακού πληθυσμού, με βάση τα πιο πρόσφατα δεδομένα κατοικεί σε αστικές περιοχές (>60%). Οι κυπριακές πόλεις, λοιπόν, καλούνται να αντιμετωπίσουν μια σειρά από προκλήσεις στου τομείς της δημόσιας υγείας και του περιβάλλοντος, παρόμοιες με αυτές που αντιμετωπίζουν τα αστικά κέντρα παγκοσμίως. Πρέπει ταυτοχρόνως να ακολουθήσουν πρακτικές βιώσιμης ανάπτυξης για την ανάπτυξη των τοπικών οικονομιών τους.

Το παρόν ερευνητικό έργο έχει στόχο να καταγράψει δείκτες περιβαλλοντικής υγείας στην πόλη της Λεμεσού με σκοπό να πραγματοποιηθεί μια πρώτη χαρτογράφηση δεικτών υγείας ειδικά για το αστικό περιβάλλον.

Σημαντικές πληροφορίες:

- Πριν την συμπλήρωση του ερωτηματολογίου και τη δειγματοληψία θα πρέπει να διαβάσετε προσεκτικά και να συμπληρώσετε το έντυπο συγκατάθεσης.
- Επεξεργασία και ανάλυση των δεδομένων θα γίνει κατόπιν ανωνυμοποίησης όλων των πληροφοριών
- Η μελέτη έχει εγκριθεί από την Εθνική Επιτροπή Βιοηθικής Κύπρου

Η έρευνα πραγματοποιείται στα πλαίσια εκπόνησης διδακτορικής διατριβής στο Διεθνές Ινστιτούτο Κύπρου για την Περιβαλλοντική και Δημόσια Υγεία του Τεχνολογικού Πανεπιστημίου Κύπρου. Επιστημονικός υπεύθυνος: Κωνσταντίνος Χ. Μακρής, Αναπληρωτής Καθηγητής, Τεχνολογικό Πανεπιστήμιο Κύπρου (τηλ.: 2500 2398, email: konstantinos.makris@cut.ac.cy).

Περισσότερες πληροφορίες για την ερευνητική δραστηριότητα του Ινστιτούτου και του εργαστηρίου μας μπορείτε να βρείτε στις ιστοσελίδες:

- CII: http://www.cut.ac.cy/cii/
- Water and Health Laboratory: web.cut.ac.cy/waterandhealth/

Καθώς και στα μέσα κοινωνικής δικτύωσης:

- Facebook: facebook.com/waterandhealthlab.CII/
- Twitter: @waterhealth_lab

Ευχαριστούμε πολύ!

Ημερομηνία συμπλήρωσης		Κωδικός (συμπληρώνεται από τους ερευνητές)	

- Συνήθειες κατανάλωσης νερού και δραστηριοτήτων καθαριότητας

1. Από ποιες πηγές καταναλώνετε νερό; (water sources)

❑ Υδατοπρομήθεια

❑ Εμφιαλωμένο νερό

❑ Νερό από αυτόματους πωλητές (κερματοδέκτες)

❑ Νερό πηγής

❑ Άλλο (παρακαλώ συμπληρώστε) ....

Χρησιμοποιείτε φίλτρο στην κεντρική βρύση του σπιτιού; (use of filter in the main tap) ❑ Ναι ❑ Όχι

2. Πόσα ποτήρια νερό καταναλώνετε τη μέρα από κάθε πηγή (water consumption)

1 ποτήρι νερό αντιστοιχεί περίπου σε ποσότητα 250ml. Σημειώστε τον αριθμό ποτηριών ανά πηγή νερού που χρησιμοποιείτε.

	Αριθμός ποτηριών
Υδατοπρομήθεια	
Εμφιαλωμένο νερό	
Νερό από αυτόματους πωλητές	
Νερό πηγής	
Άλλο (παρακαλώ συμπληρώστε) ________________________	

3. Πόσες μέρες την εβδομάδα εκτελείτε κατά μέσο όρο της παρακάτω δραστηριότητες; (cleaning activities)

	Μέρες την εβδομάδα
Πλύσιμο πιάτων	
Σφουγγάρισμα χώρων σπιτιού	
Καθαρισμός μπάνιου	

- Χρήση πλαστικών δοχείων

1. Χρησιμοποιείτε πλαστικά δοχεία για την αποθήκευση φαγητού;

❑ Ναι (απαντήστε και στην ερώτηση από κάτω)

Κάνετε καθημερινή χρήση των πλαστικών δοχείων (π.χ. για μεταφορά γευμάτων στη δουλειά); ❑ Ναι ❑ Όχι καθημερινά

❑ Όχι

2. Πόσες φορές την εβδομάδα χρησιμοποιείτε πλαστικές συσκευασίες στον

φούρνο μικροκυμάτων;

___________ φορές

- Χρήση αλατιού

1. **Χρησιμοποιείτε ιωδιούχο αλάτι;**
   - ❑ Ναι, πάντα
   - ❑ Δεν γνωρίζω/δεν προσέχω την ετικέτα
   - ❑ Χρησιμοποιώ υποκατάστατο αλατιού
   - ❑ Γνωρίζω τι είναι το ιωδιούχο αλάτι αλλά δεν χρησιμοποιώ

- Χρήση φυτοφαρμάκων και εντομοκτόνων

1. **Χρησιμοποιείτε φυτοφάρμακα στον κήπο, την αυλή, ή στα λουλούδια σας;**
   - ❑ Ναι
   - ❑ Όχι

Εάν απαντήσατε «Ναι» στην προηγούμενη ερώτηση

1.1. Πότε ήταν η τελευταία φορά που χρησιμοποιήσατε φυτοφάρμακα;
Μήνας ………………… Χρονιά …………..
Ποια ήταν η μάρκα των φυτοφαρμάκων που χρησιμοποιήσατε;
………………………………..

2. **Χρησιμοποιείτε εντομοκτόνα ή εντομοαπωθητικά;**
   - ❑ Ναι, σε χώρους (π.χ. στο σπίτι) και σώματος
   - ❑ Ναι, μόνο σε χώρους
   - ❑ Ναι, μόνο σώματος
   - ❑ Δεν χρησιμοποιώ καθόλου (*συνεχίστε στην επόμενη ενότητα*)
   - ❑ Δεν γνωρίζω/δεν είμαι σίγουρος/δεν θυμάμαι (*συνεχίστε στην επόμενη ενότητα*)

Εάν απαντήσατε «Ναι» στην προηγούμενη ερώτηση

2.1. Πότε ήταν η τελευταία φορά που χρησιμοποιήσατε εντομοκτόνα ή εντομοαπωθητικά;
Μήνας......... Χρονιά .... τελευταίας χρήσης

- Κατανάλωση ψαριών

1. **Πόσες φορές την εβδομάδα καταναλώνετε φρέσκα ψάρια; ....** φορές

2. **Πόσες φορές την εβδομάδα καταναλώνετε ψάρια σε κονσέρβες (π.χ. τόνος); ....** φορές

- Κάπνισμα και κατανάλωση αλκοόλ

1. Καπνίζετε; (smoking)

- ❑ Ναι, καθημερινά
- ❑ Ναι, περιστασιακά
- ❑ Καθόλου (προχωρήστε στην ερώτηση 2)
- ❑ Δεν γνωρίζω/δεν είμαι σίγουρος/δεν θυμάμαι (προχωρήστε στην ερώτηση 2)
- ❑ Δεν απαντώ (προχωρήστε στην ερώτηση 2)

Εάν απαντήσατε «Ναι» στην προηγούμενη ερώτηση

1.1. Ποιο προϊόν καπνίζετε κυρίως;

- ❑ Τσιγάρα (βιομηχανοποιημένα ή στριφτά)
- ❑ Πούρα
- ❑ Πίπα
- ❑ Άλλα προϊόντα
- ❑ Δεν γνωρίζω/δεν είμαι σίγουρος/δεν θυμάμαι

1.2. Κατά μέσο όρο, πόσα τσιγάρα καπνίζετε καθημερινά; (number of cigarettes smoking per day)

Αριθμός τσιγάρων (βιομηχανοποιημένων ή στριφτών) …………………

- ❑ Δεν γνωρίζω/δεν είμαι σίγουρος/δεν θυμάμαι
- ❑ Δεν απαντώ

2. Πόσο συχνά εκτίθεστε σε καπνό από προϊόντα που καπνίζουν άλλοι σε κλειστό χώρο, π.χ. στο σπίτι, στην εργασία, σε δημόσιους χώρους, σε εστιατόρια και στα μέσα μαζικής μεταφοράς; (secondhand smoking)

- ❑ Ποτέ ή σχεδόν ποτέ
- ❑ Λιγότερο από 1 ώρα ημερησίως
- ❑ Περισσότερο από 1 ώρα ημερησίως
- ❑ Δεν γνωρίζω/δεν είμαι σίγουρος/δεν θυμάμαι
- ❑ Δεν απαντώ

3. Κατά τη διάρκεια των τελευταίων 12 μηνών, πόσο συχνά καταναλώσατε αλκοολούχα ποτά, οποιουδήποτε είδους (μπύρα, κρασί, κονιάκ, ζιβανία, ουίσκι, ούζο, λικέρ, κοκτέιλς με αλκοόλ, breezers ή άλλα); (alcohol consumption)

- ❑ Καθημερινά ή σχεδόν καθημερινά
- ❑ 5-6 μέρες την εβδομάδα
- ❑ 3-4 μέρες την εβδομάδα
- ❑ 1-2 μέρες την εβδομάδα
- ❑ 2-3 μέρες το μήνα
- ❑ 1 φορά το μήνα
- ❑ Λιγότερο από 1 φορά το μήνα
- ❑ Ποτέ τους τελευταίους 12 μήνες, το έκοψα
- ❑ Ποτέ ή μόνο ελάχιστες φορές στη ζωή μου
- ❑ Δεν γνωρίζω/δεν είμαι σίγουρος/δεν θυμάμαι
- ❑ Δεν απαντώ

Ευχαριστούμε πολύ!

Scripts and output – available in electronic form

APPENDIX C (4 Routine public health surveillance within the urban exposome framework: a proof-of-concept study in Limassol district, Cyprus)

Supplementary table

Table S4. 1 Population size and coefficients of change from the 2011 census for the total population and the district of Limassol.

Year	Total end-year population	Total mid-year population	Limassol District (end of year)	Change coefficient (for end-year estimates) Reference: Census 2011	Proportion of Limassol district population to the total population (end-year)	Mid-year Limassol district population = proportion of total * total mid-year
2007	776,400	766,400	219,000	**0.931**	0.282	216,179
2008	796,900	785,700	224,400	**0.954**	0.282	221,246
2009	819,100	807,100	230,200	**0.978**	0.281	226,828
2010	839,800	827,700	235,500	**1.001**	0.280	232,107
2011	862,000	849,000	241,300	**1.025**	0.280	237,661
2012	865,900	863,900	241,900	**1.028**	0.279	241,341
2013	858,000	861,900	239,700	**1.019**	0.279	240,790
2014	847,000	853,200	236,600	**1.005**	0.279	238,332
2015	848,300	843,100	237,000	**1.007**	0.279	235,547
2016	854,800	849,800	239,400	**1.017**	0.280	238,000
2017	864,200	860,200	242,000	**1.028**	0.280	240,880
Census	840,407		235,330		0.280	
Corrected	856,960		241,300			

Comments:
The population refers to the Government controlled areas.
Date of reference for the estimates: December 31 of each year.
Census population date of reference: October 1 in the datasets from the census the population is reported to be 840,407 while the corrected total population at the census is estimated to be 856,960.
Using the late demographic report of 2017, published in 2018.

Table S4. 2 List of the R packages used in the data analyses.

```
[1] viridis_0.5.1  viridisLite_0.3.0 SpatialEpi_1.2.3
[4] spdep_1.1-2 sf_0.7-4 spData_0.3.0
[7] INLA_18.07.12  sp_1.3-1 Matrix_1.2-17
[10] cowplot_0.9.4  VIM_4.8.0data.table_1.12.2
[13] colorspace_1.4-1  arsenal_3.1.0  mice_3.5.0
[16] lattice_0.20-38gganimate_1.0.3inspectdf_0.0.1
[19] here_0.1 lubridate_1.7.4epitools_0.5-10
[22] naniar_0.4.2janitor_1.2.0  knitr_1.23
[25] forcats_0.4.0  stringr_1.4.0  dplyr_0.8.1
[28] purrr_0.3.2 readr_1.3.1 tidyr_0.8.3
[31] tibble_2.1.1ggplot2_3.1.1  tidyverse_1.2.1
[34] plyr_1.8.4  readxl_1.3.1
```

Table S4. 3 Summary of the registry observations included/excluded based on the missing information and imputation.

	Total number	Cases with missing postal code excluded in the urban/non-urban classification)	Missing age (excluded from the age-standardized estimates)	Postal code areas not included in the census (excluded from the age-standardized estimates)
All cancer cases	7,055	200	15	8
After postal code imputation (included in calculating the age-standardization)	7,031			
C33-C34 Trachea, bronchus, and lung cases	648	17	0	2
After postal code imputation (included in calculating the age-standardized estimates)	646			
	Total number	**Missing municipality/village (excluded in the urban/non-urban classification)**	**Missing age (excluded from the age-standardized estimates)**	
Deaths	13,567	11	2	
After municipality/village imputation (included in calculating the age-standardization)	13,565			

Table S4. 4 Number and percentage of cancer cases (2007-2014) and deaths (2007-2015) by year and urban/non-urban areas in the district of Limassol, Cyprus.

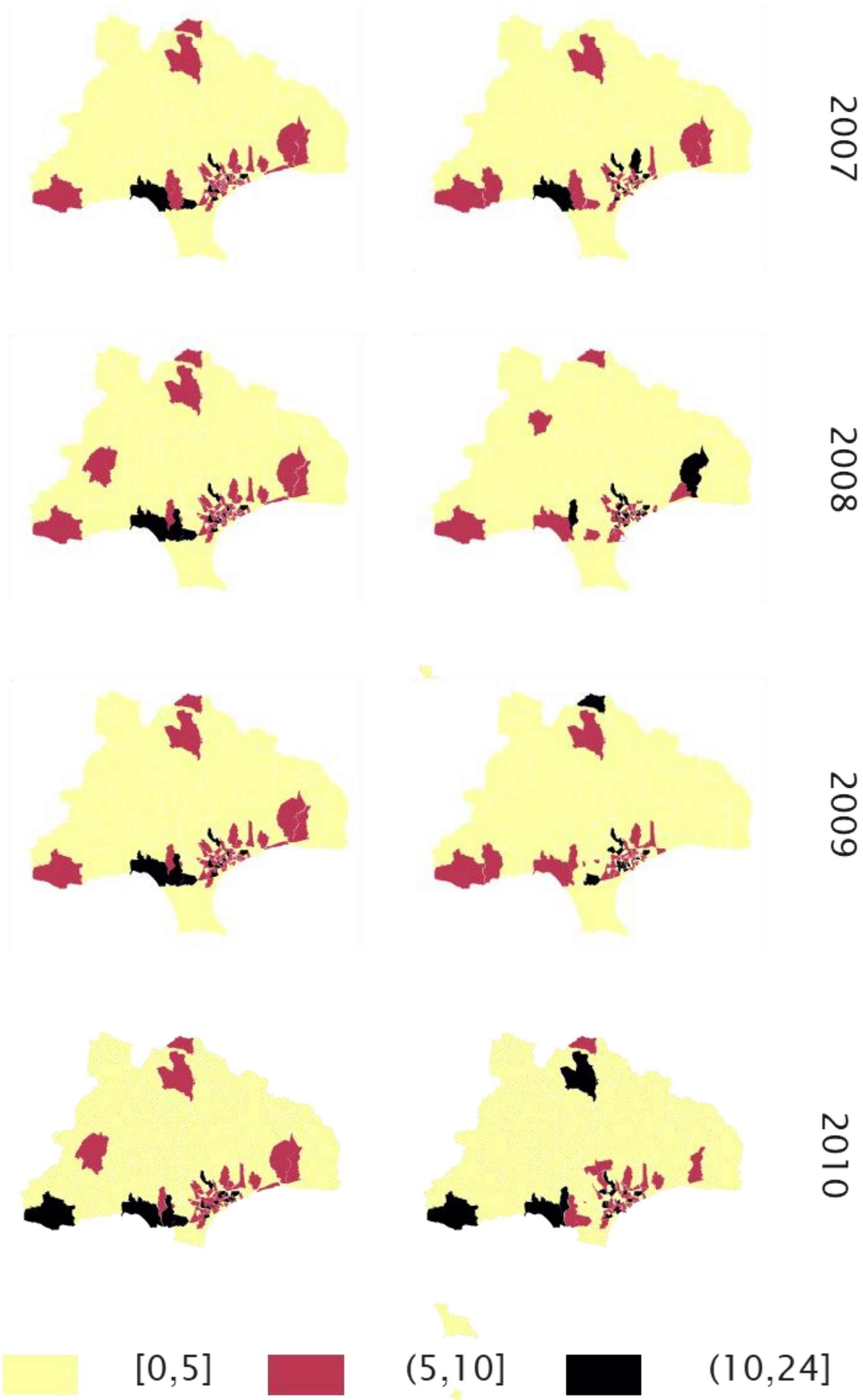
All cancer			Trachea, bronchus, and lung cancer			Deaths	
verall =7,055)	Urban	Non-Urban	Overall (n=648)	Urban	Non-Urban	Overall (n=13 567)	Urban
(10.9%)	598 (79.4%)	155 (20.6%)	62 (9.6%)	47 (79.7%)	12 (20.3%)	1.532 (11.3%)	1,150 (75.1%)
(11.9%)	675 (82.4%)	144 (17.6%)	67 (10.3%)	60 (90.9%)	6 (9.1%)	1.466 (10.8%)	1,136 (77.5%)
(11.7%)	649 (80.2%)	160 (19.8%)	68 (10.5%)	56 (82.4%)	12 (17.6%)	1.421 (10.5%)	1,098 (77.3%)
(12.6%)	673 (79.2%)	177 (20.8%)	86 (13.3%)	67 (82.7%)	14 (17.3%)	1.397 (10.3%)	1,045 (74.8%)
(12.9%)	705 (80.6%)	170 (19.4%)	89 (13.7%)	68 (79.1%)	18 (20.9%)	1.448 (10.7%)	1,079 (74.5%)
(13.1%)	711 (79.2%)	187 (20.8%)	81 (12.5)	63 (79.7%)	16 (20.3%)	1.569 (11.6%)	1,186 (75.6%)
(12.7%)	709 (81.0%)	166 (19.0%)	100 (15.4%)	76 (76.8%)	23 (23.2%)	1.445 (10.7%)	1,087 (75.2%)
3 (14.2%)	776 (79.5%)	200 (20.5%)	95 (14.6%)	78 (83.9%)	15 (16.1%)	1.599 (11.8%)	1,197 (74.9%)
						1,690 (12.5%)	1,286 (76.1%)
	5,496 (80.2%)	1,359 (19.8%)		515 (81.6%)	116 (18.4%)		10,264 (75.7%

Table S4. 5 Summary of the number of cancer cases (all and trachea, bronchus and lung cancer) and deaths, and crude cancer incidence and mortality rates in the district of Limassol, Cyprus, by year since 2007 (until 2014 for the cancer estimates and until 2015 for the death).

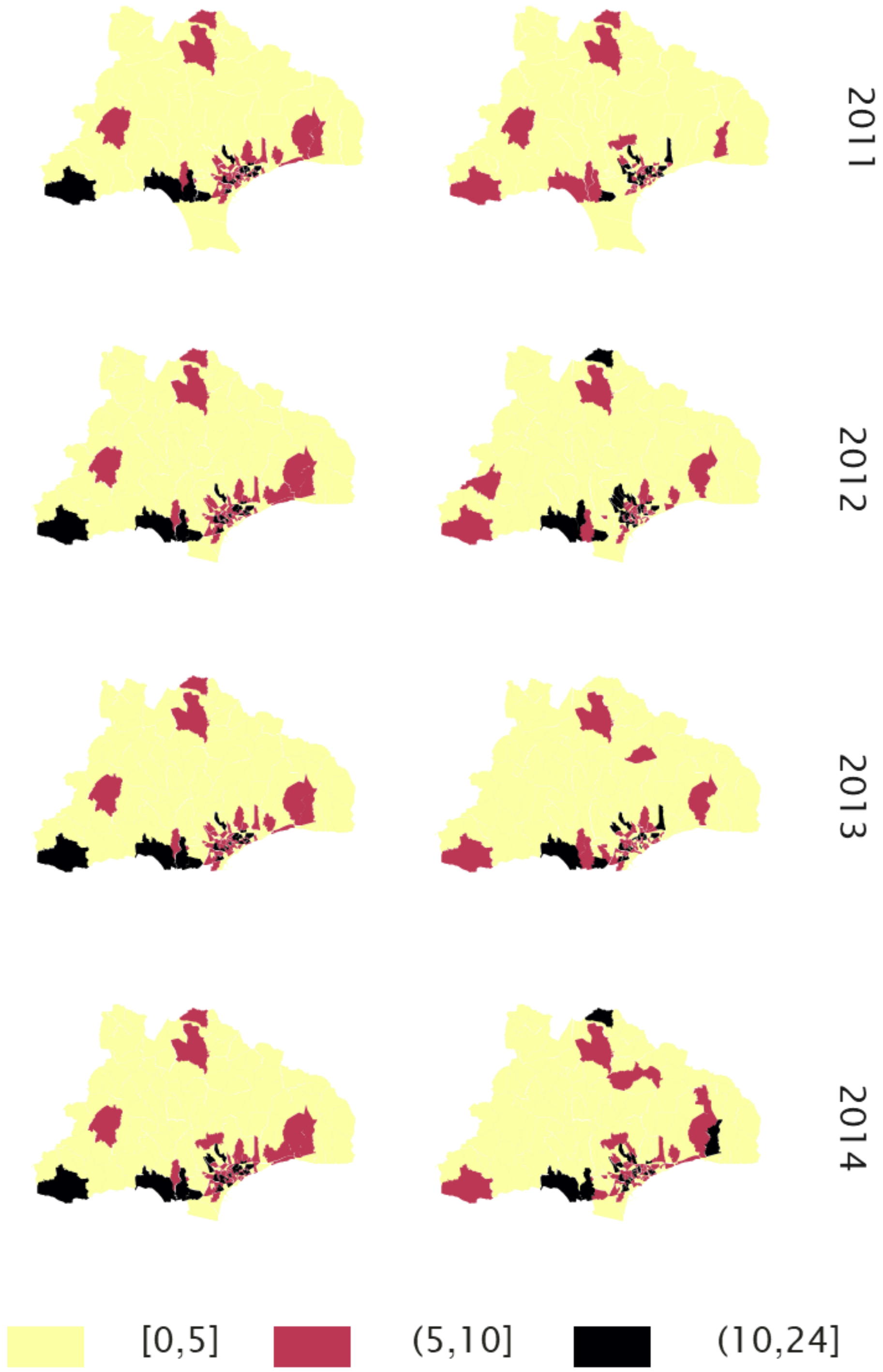
	All cancer		Trachea, bronchus, and lung cancer		End-year population at risk		Deaths		Mid-year population at risk
ear	Total number	Crude incidence per 100,000	Total number	Crude incidence per 100,000			Total number of deaths	Crude mortality per 1,000	
007	772	352.5	62	28.3	218,997		1,532	7.1	216,176
008	839	373.9	67	29.9	224,397		1,466	6.6	221,243
009	826	358.8	68	29.5	230,197		1,421	6.3	226,825
010	888	377.1	86	36.5	235,497		1,397	6.0	232,104
011	907	375.9	89	36.9	241,297		1,448	6.1	237,658
012	926	382.8	81	33.5	241,897		1,569	6.5	241,338
013	894	373.0	100	41.7	239,697		1,445	6.0	240,787
014	1,003	423.9	95	40.2	236,597		1,599	6.7	238,329
015							1,690	7.2	235,544

Supplementary figures

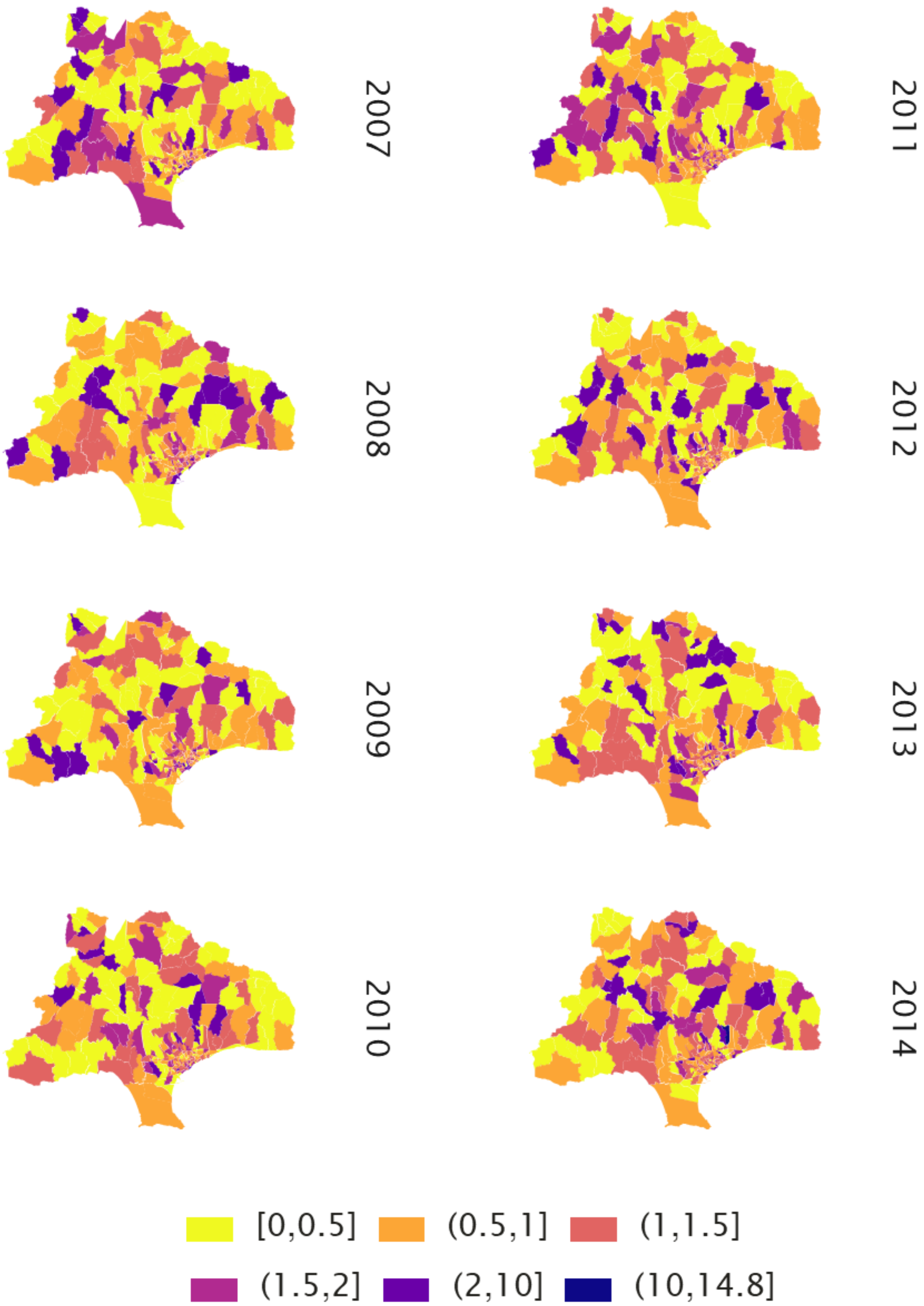
A [Observed and expected cancer cases, by postal code, in the district of Limassol, 2007-2014.]



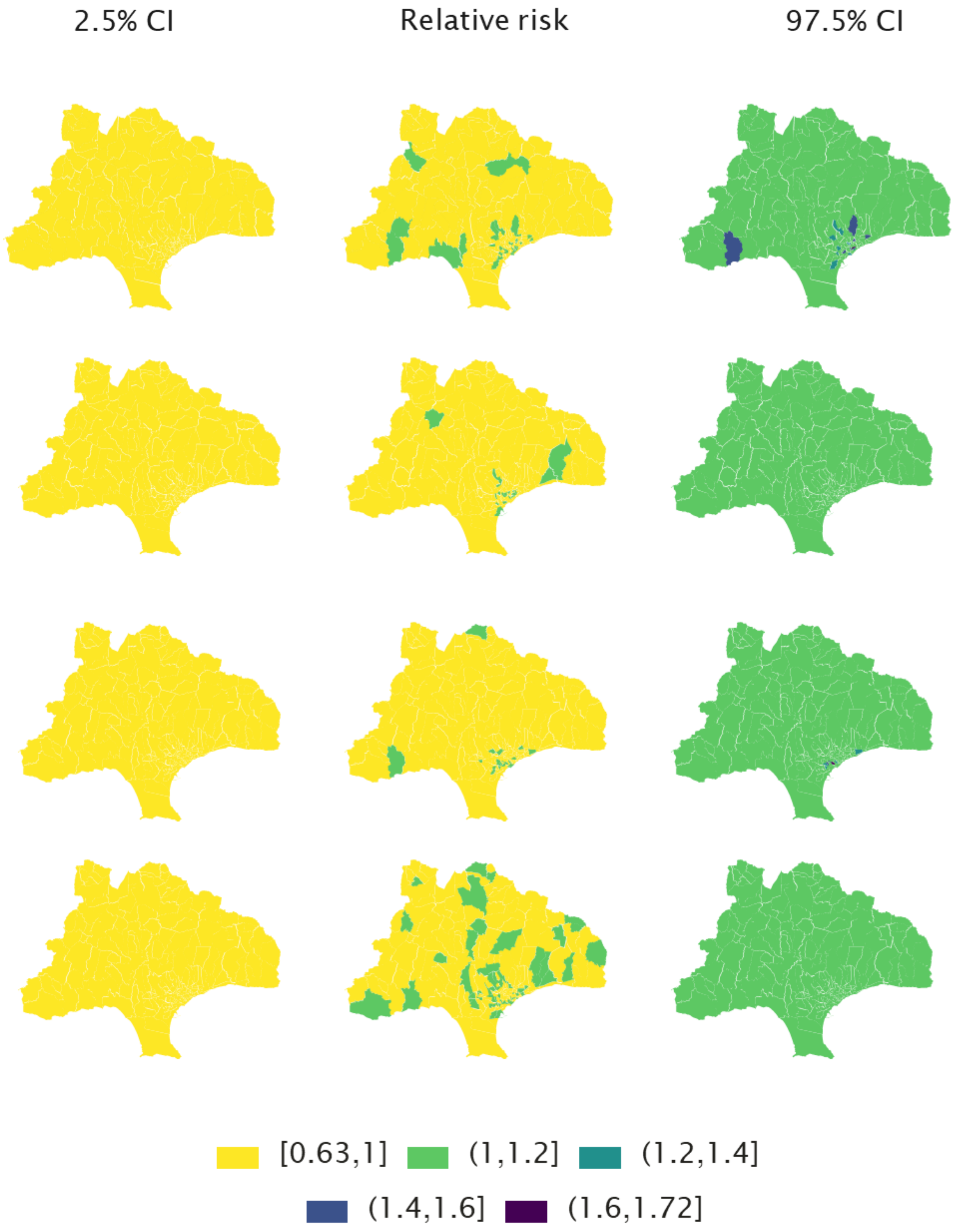
A [Observed and expected cancer cases, by postal code, in the district of Limassol, 2007-2014.] (cont.)



B [All cancer SIR, by postal code, in the district of Limassol, 2007-2014.]



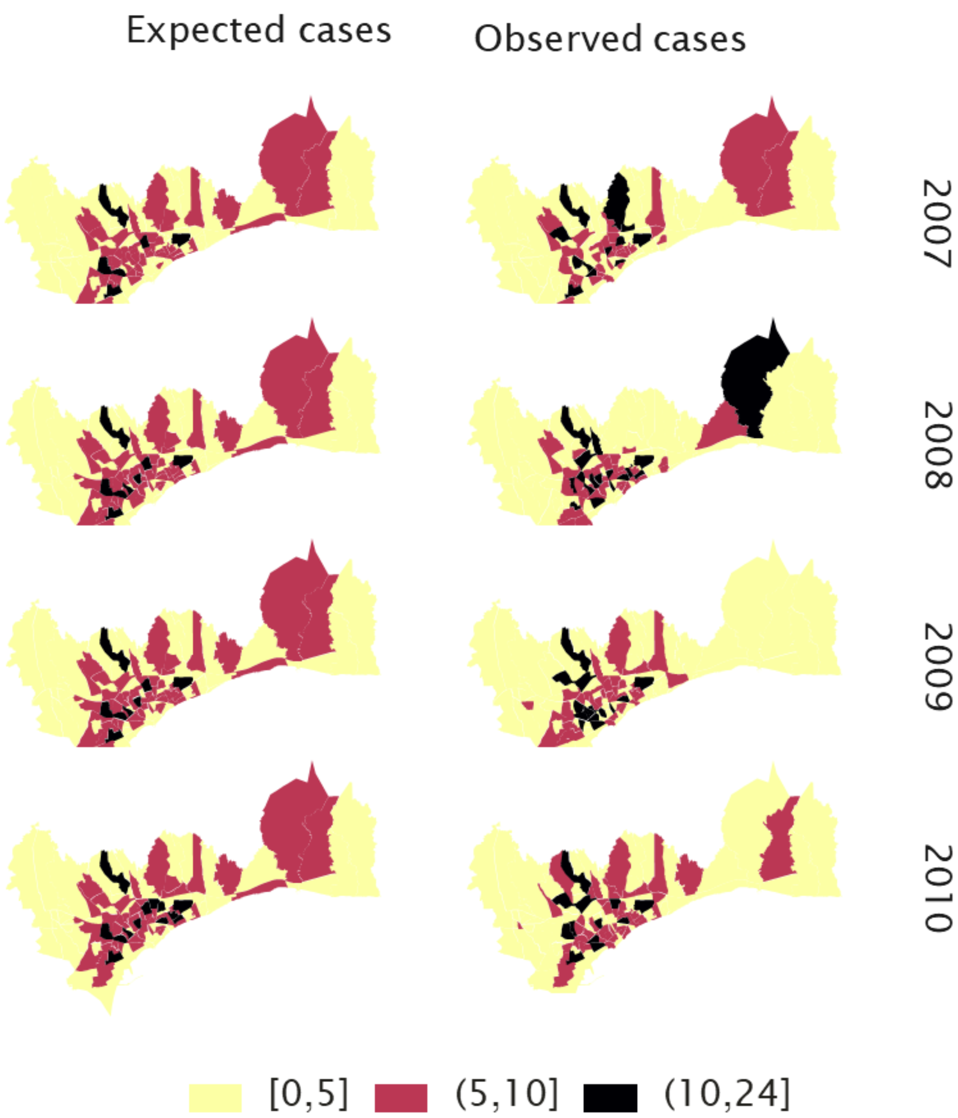
C [Smoothed relative risk of all-cancer incidence and 95% credible intervals, by postal code, in the district of Limassol, 2007-2014.]



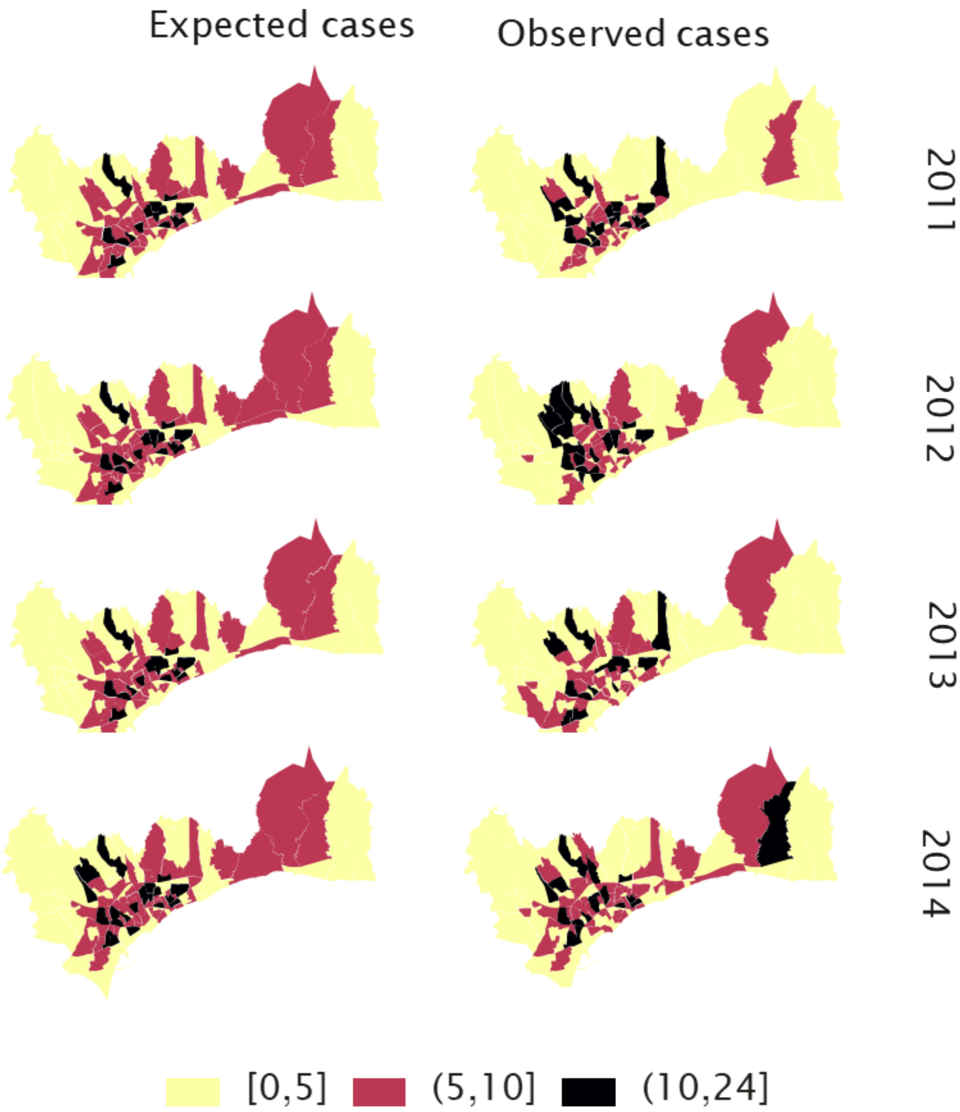
C [Smoothed relative risk of all-cancer incidence and 95% credible intervals, by postal code, in the district of Limassol, 2007-2014.] (cont.)

Figure S4. 1 Maps of the observed and expected cancer cases and SIR (A, B), smoothed relative risk of all-cancer incidence and 95% credible intervals (C), by postal code, in the district of Limassol, 2007-2014.

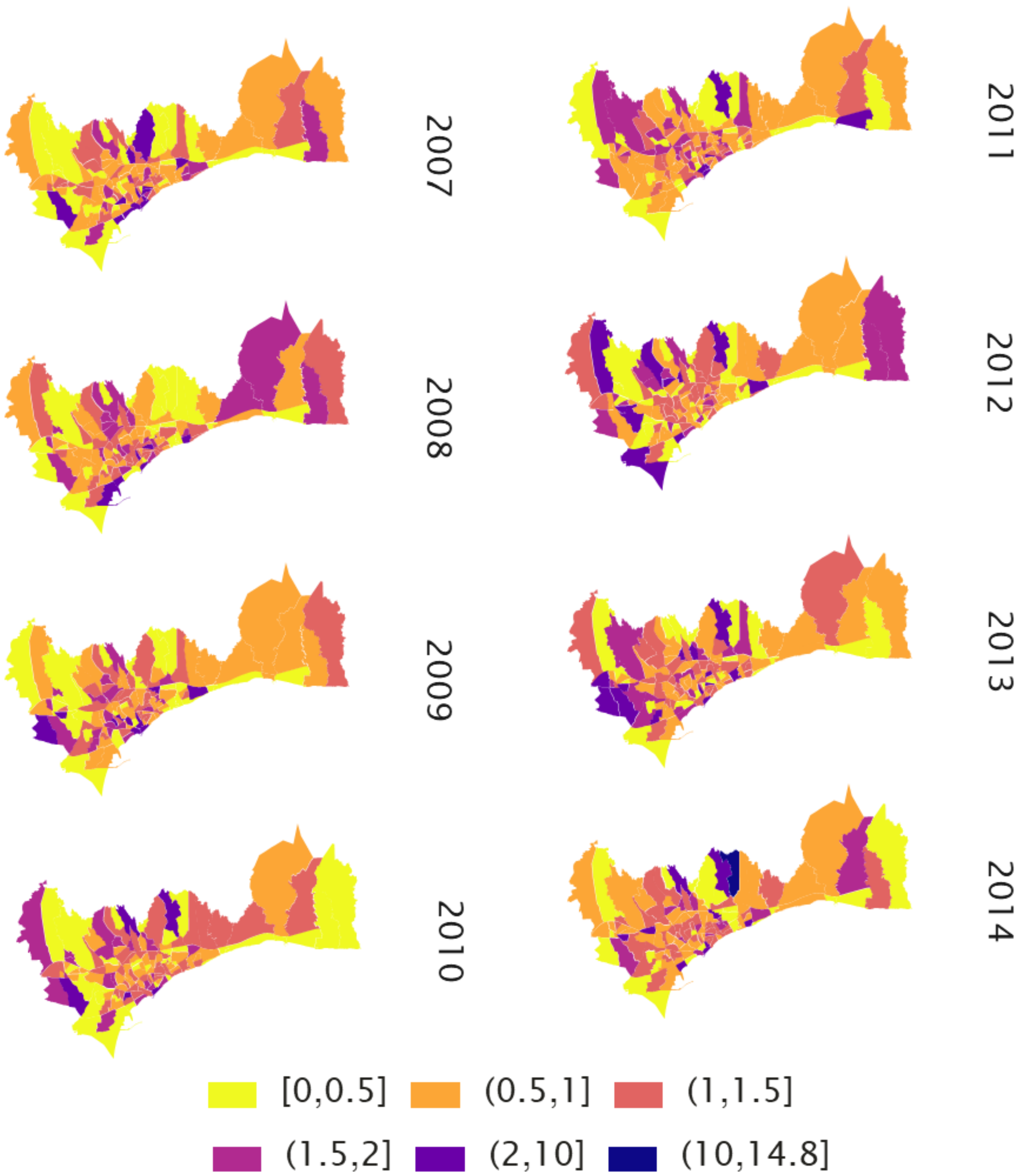
A [Observed and expected cancer cases by postal code, in the urban part of the district of Limassol, 2007-2014.]



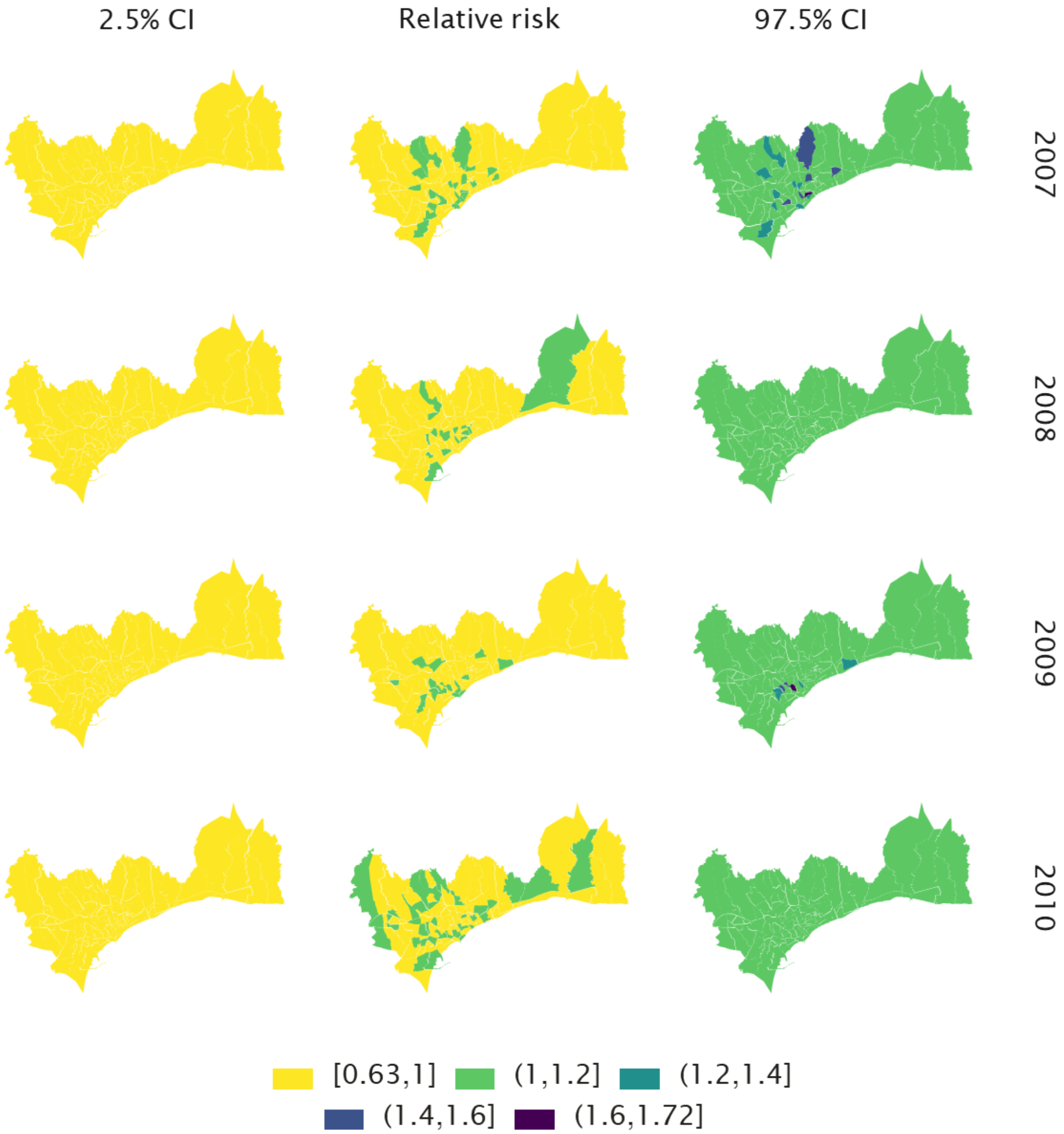
A [Observed and expected cancer cases by postal code, in the urban part of the district of Limassol, 2007-2014.] (cont.)



B [All cancer SIR by postal code, in the urban part of the district of Limassol, 2007-2014.]



C [Smoothed relative risk of all-cancer incidence and 95% credible intervals, by postal code, in the urban part of the district of Limassol, 2007-2014.]



C [Smoothed relative risk of all-cancer incidence and 95% credible intervals, by postal code, in the urban part of the district of Limassol, 2007-2014.] (cont.)

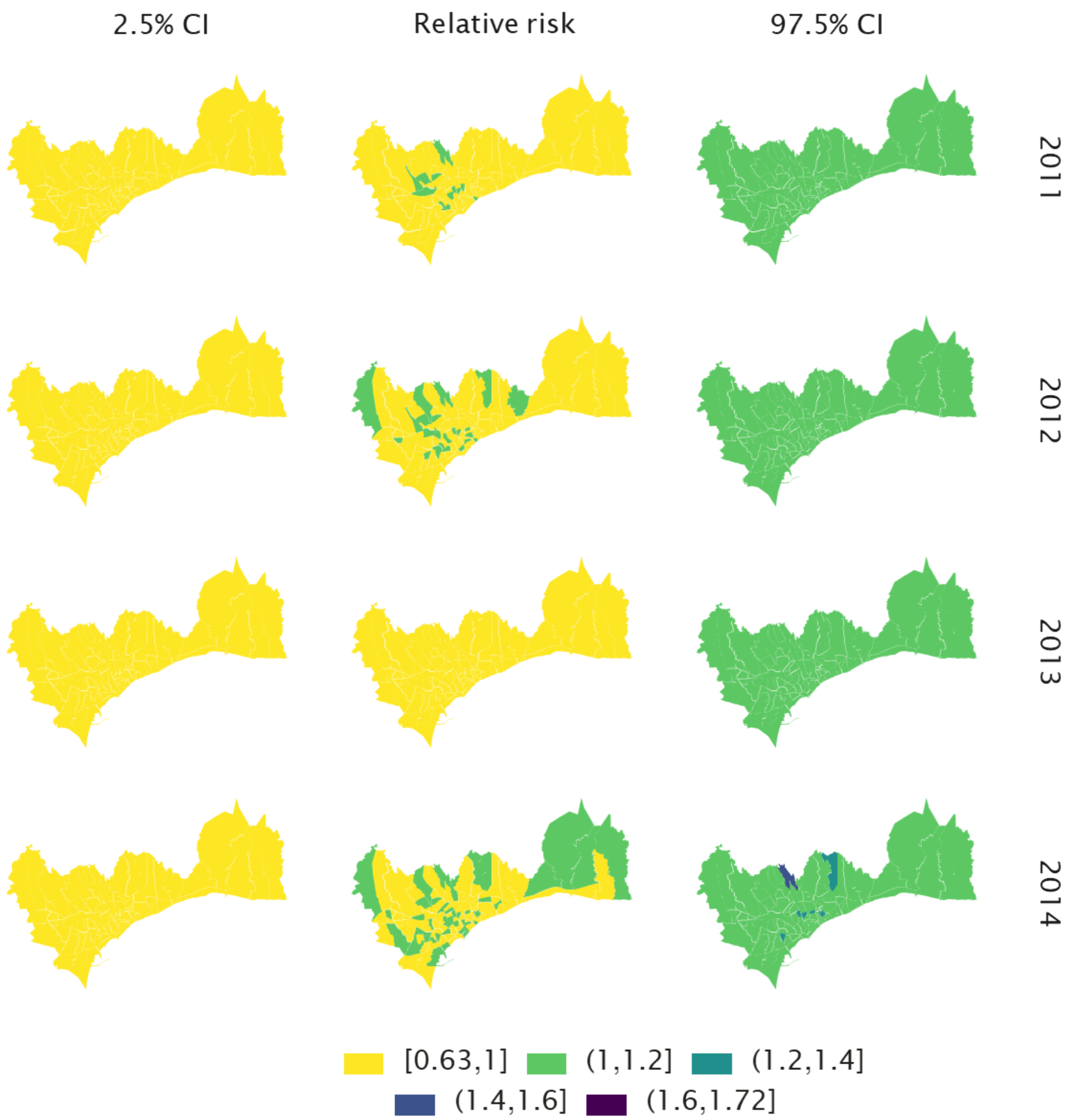
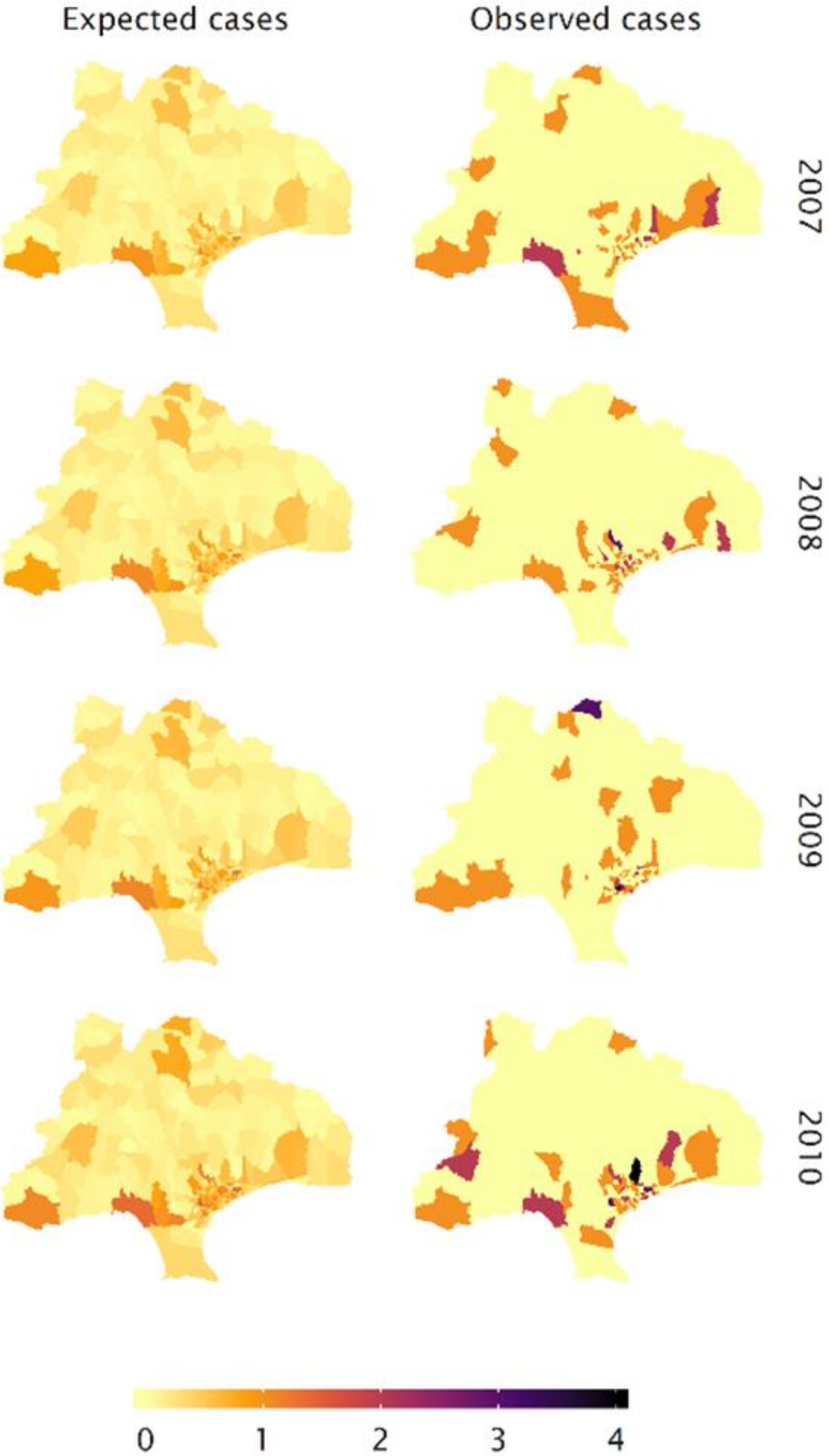
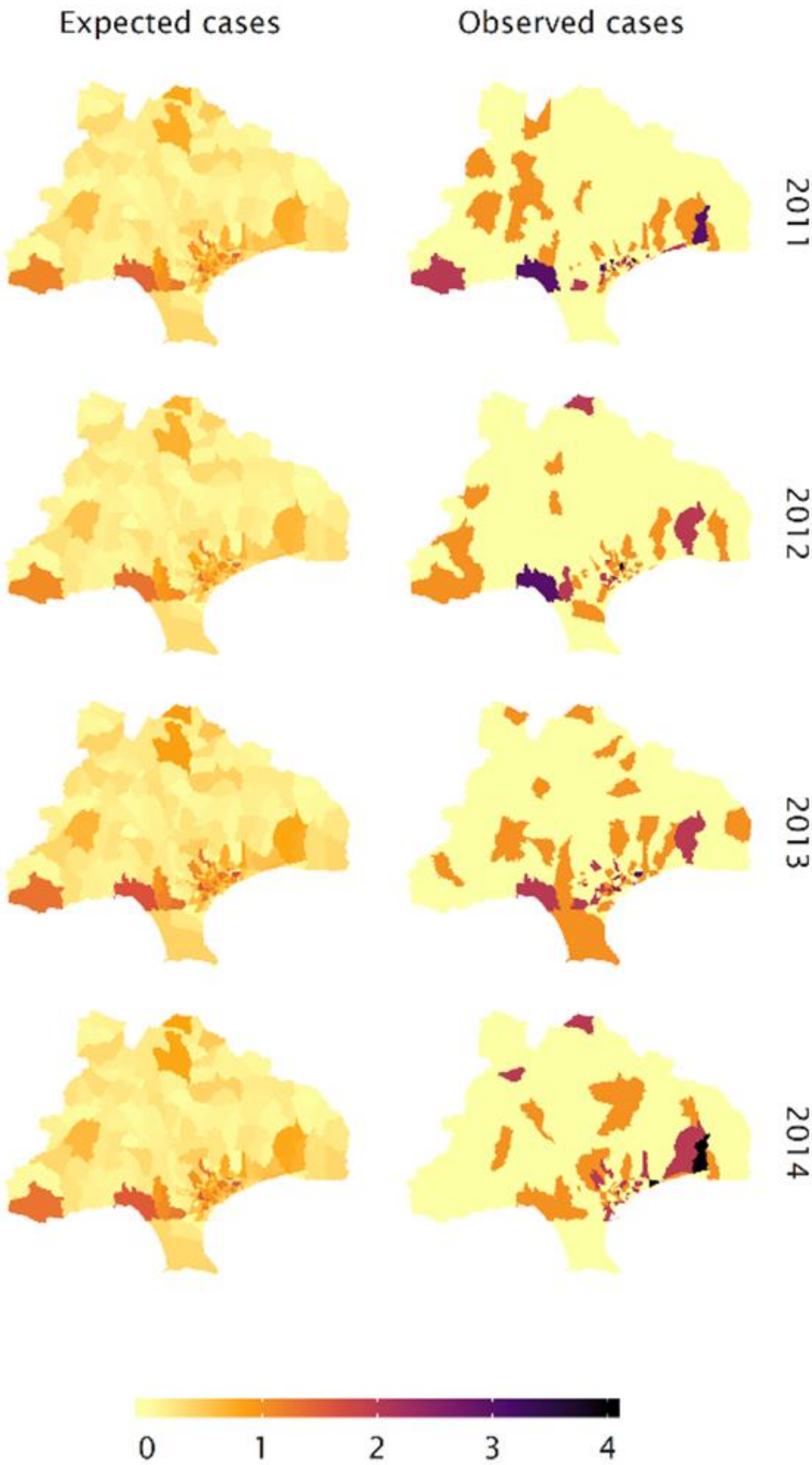


Figure S4. 2 Maps of the observed and expected cancer cases and SIR (left), smoothed relative risk of all-cancer incidence and 95% credible intervals (right), by postal code, in the urban part of the district of Limassol, 2007-2014.

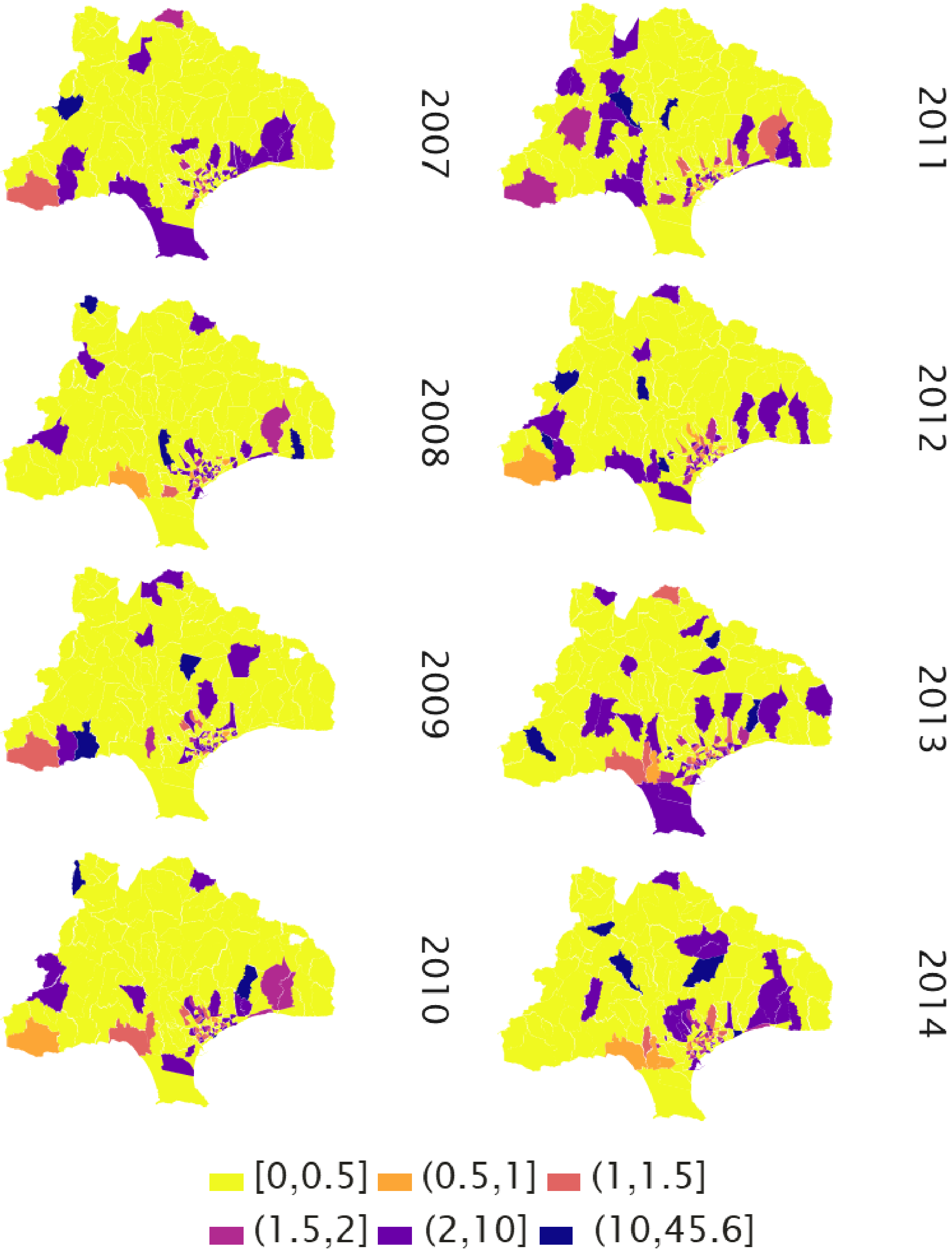
A [Observed and expected trachea, bronchus and lung-cancer cases, by postal code, in the district of Limassol, 2007-2014.]



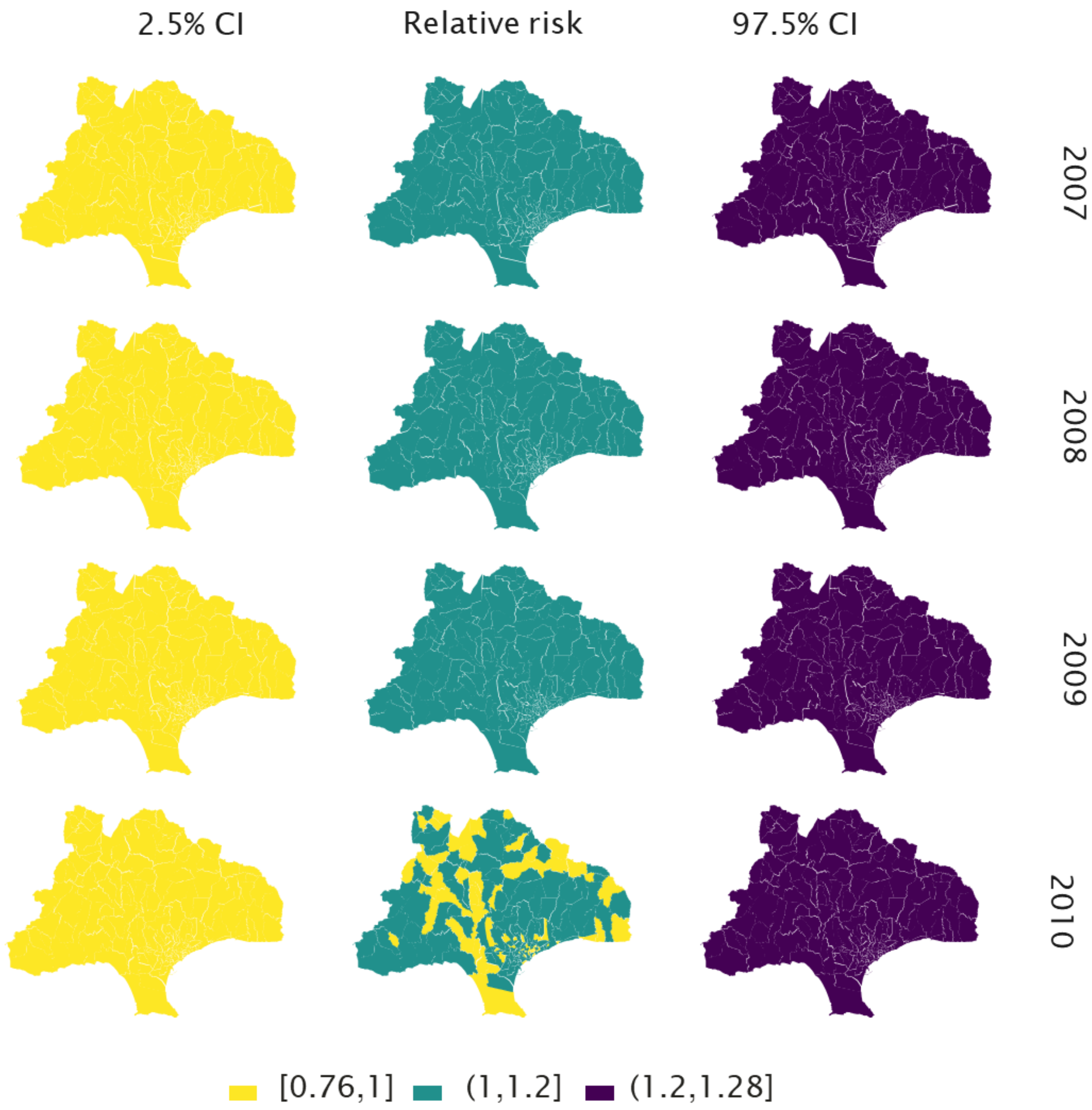
A [Observed and expected trachea, bronchus and lung-cancer cases, by postal code, in the district of Limassol, 2007-2014.] (cont.)



B [Trachea, bronchus and lung-cancer SIR, by postal code, in the district of Limassol, 2007-2014.]



C [Smoothed relative risk of trachea, bronchus and lung-cancer incidence and 95% credible intervals, by postal code, in the district of Limassol, 2007-2014.]



C [Smoothed relative risk of trachea, bronchus and lung-cancer incidence and 95% credible intervals, by postal code, in the district of Limassol, 2007-2014.] (cont)

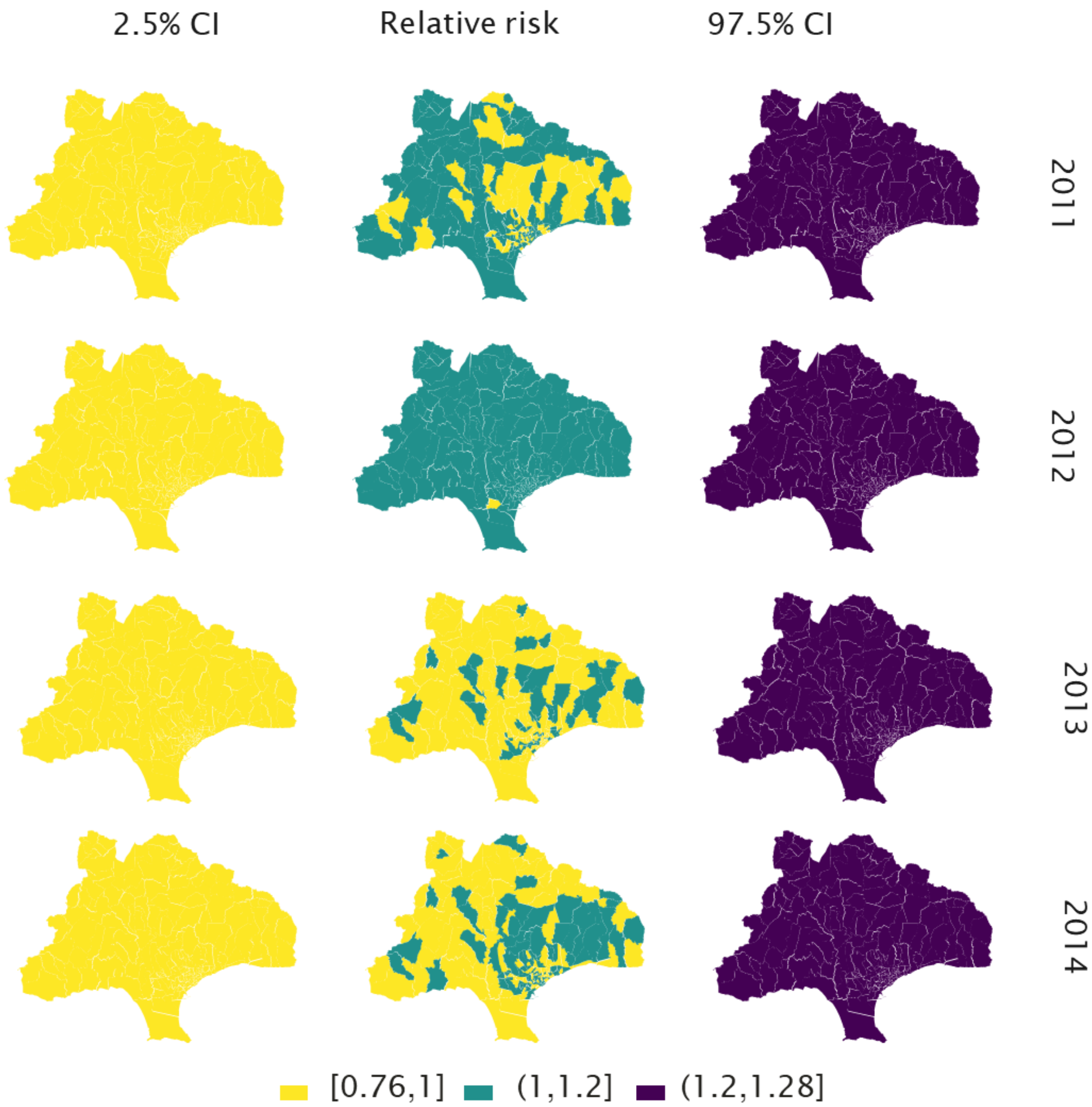
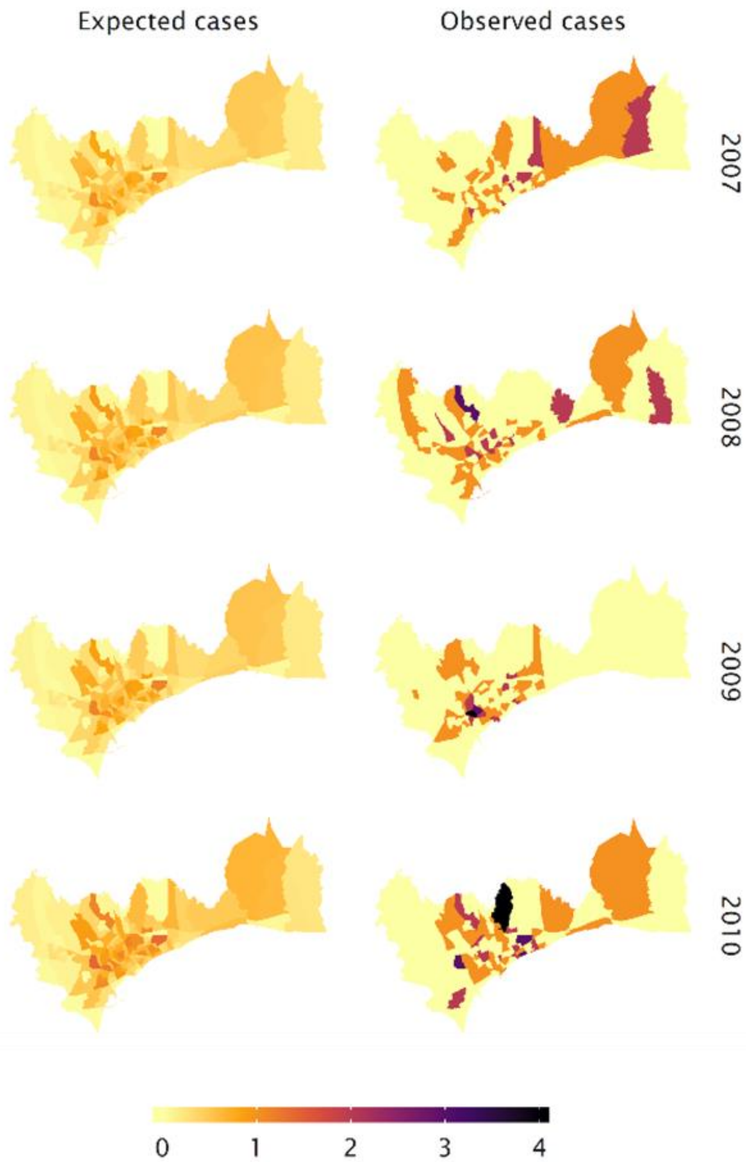
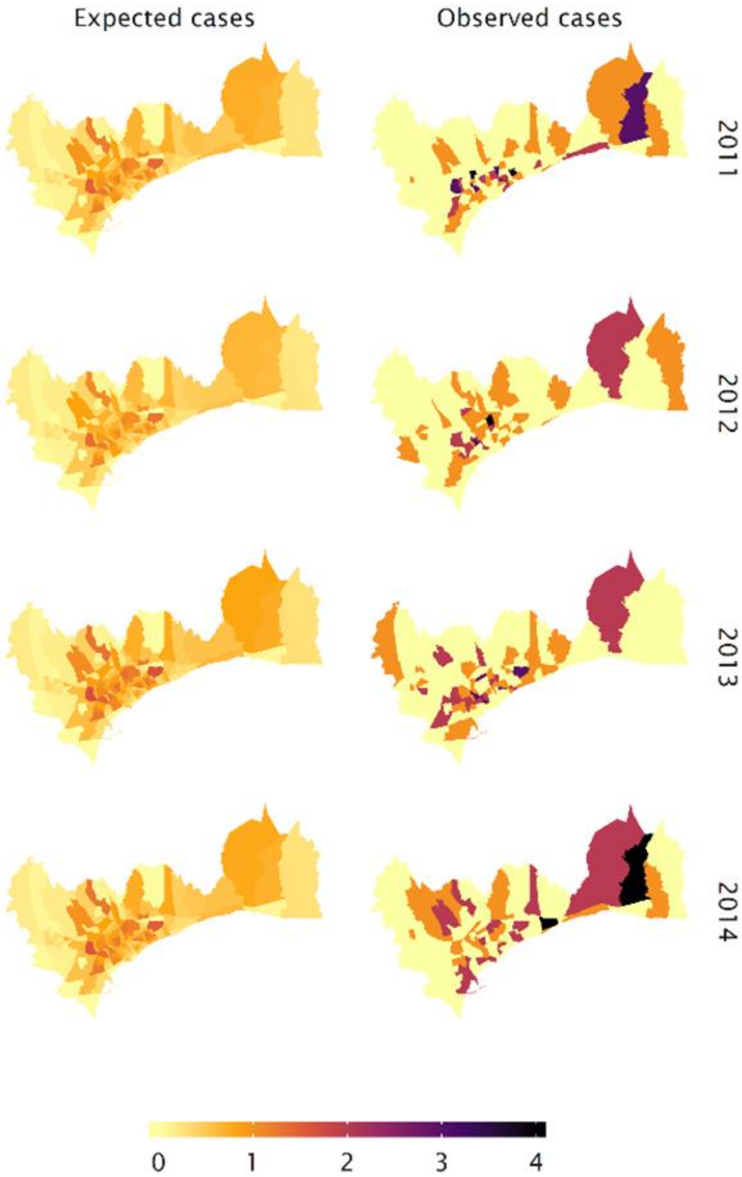


Figure S4. 3 Maps of the observed and expected cancer cases and SIR (left), smoothed relative risk of trachea, bronchus and lung cancer incidence and 95% credible intervals (right), by postal code, in the district of Limassol, 2007-2014.

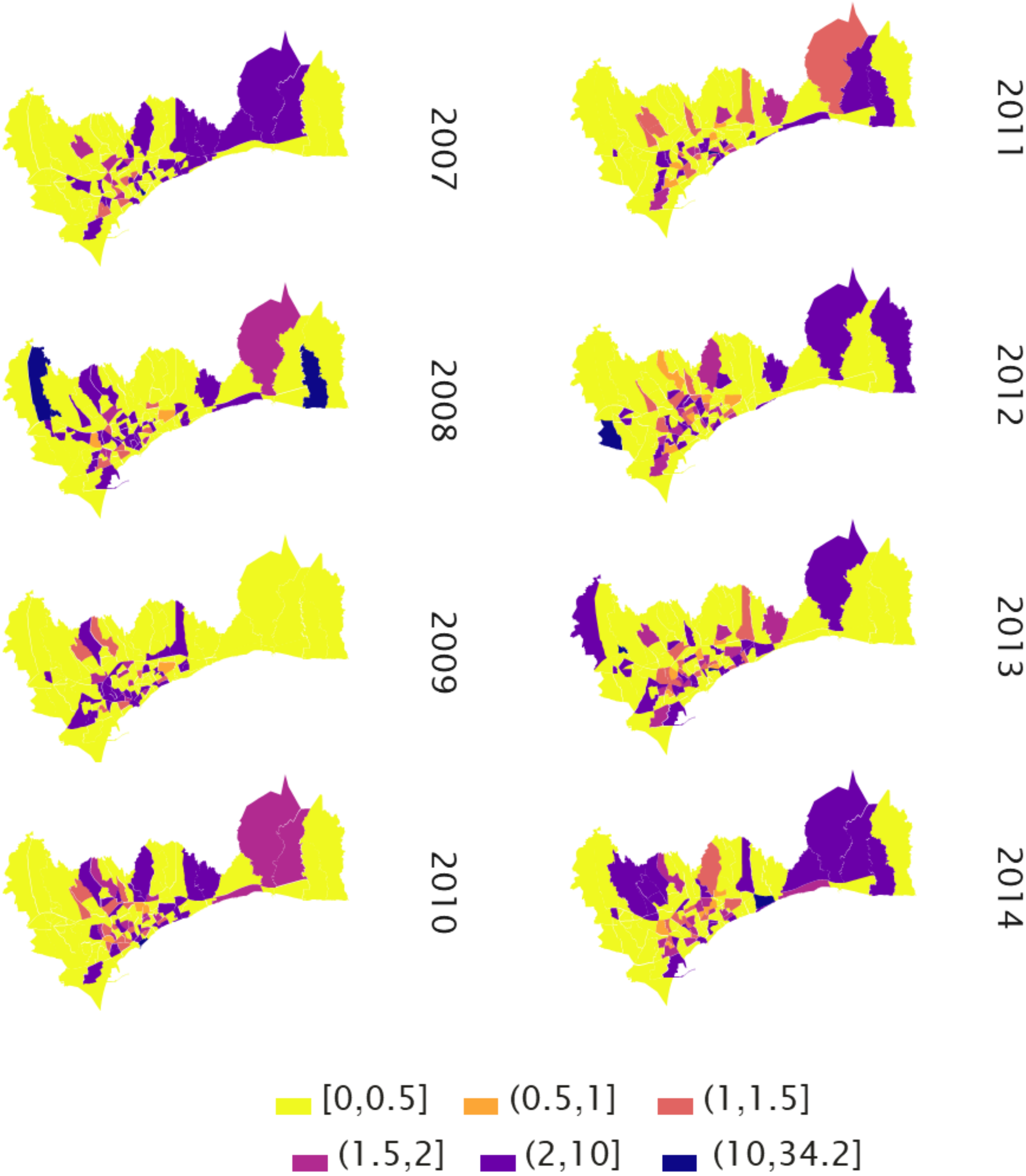
A [Observed and expected trachea, bronchus and lung-cancer cases, by postal code, in the urban part of the district of Limassol, 2007-2014.]



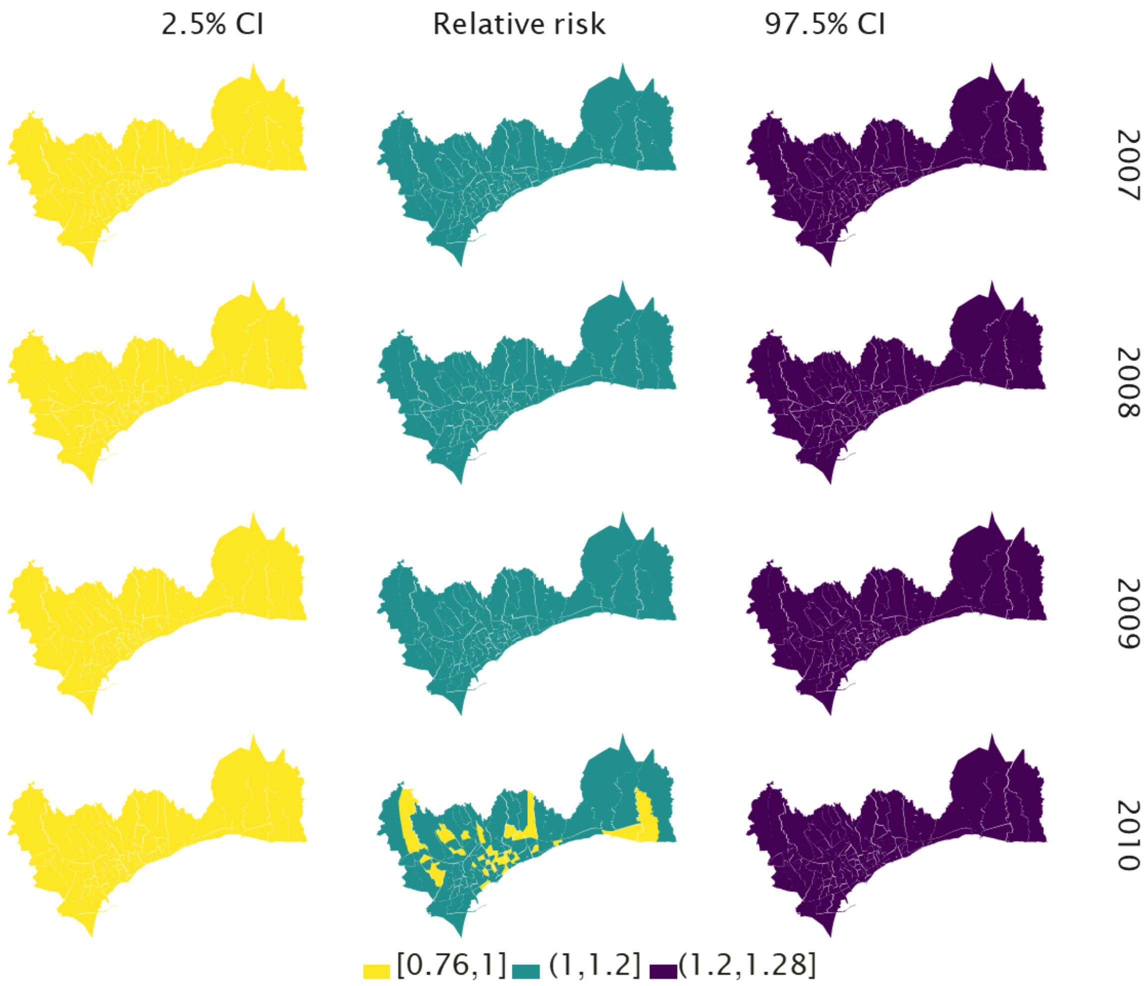
A [Observed and expected trachea, bronchus and lung-cancer cases, by postal code, in the urban part of the district of Limassol, 2007-2014.] (cont.)



B [Trachea, bronchus and lung-cancer SIR, by postal code, in the urban part of the district of Limassol, 2007-2014.]



C [Smoothed relative risk of trachea, bronchus and lung-cancer incidence and 95% credible intervals, by postal code, in the urban part of the district of Limassol, 2007-2014.]



C [Smoothed relative risk of trachea, bronchus and lung-cancer incidence and 95% credible intervals, by postal code, in the urban part of the district of Limassol, 2007-2014.] (cont.)

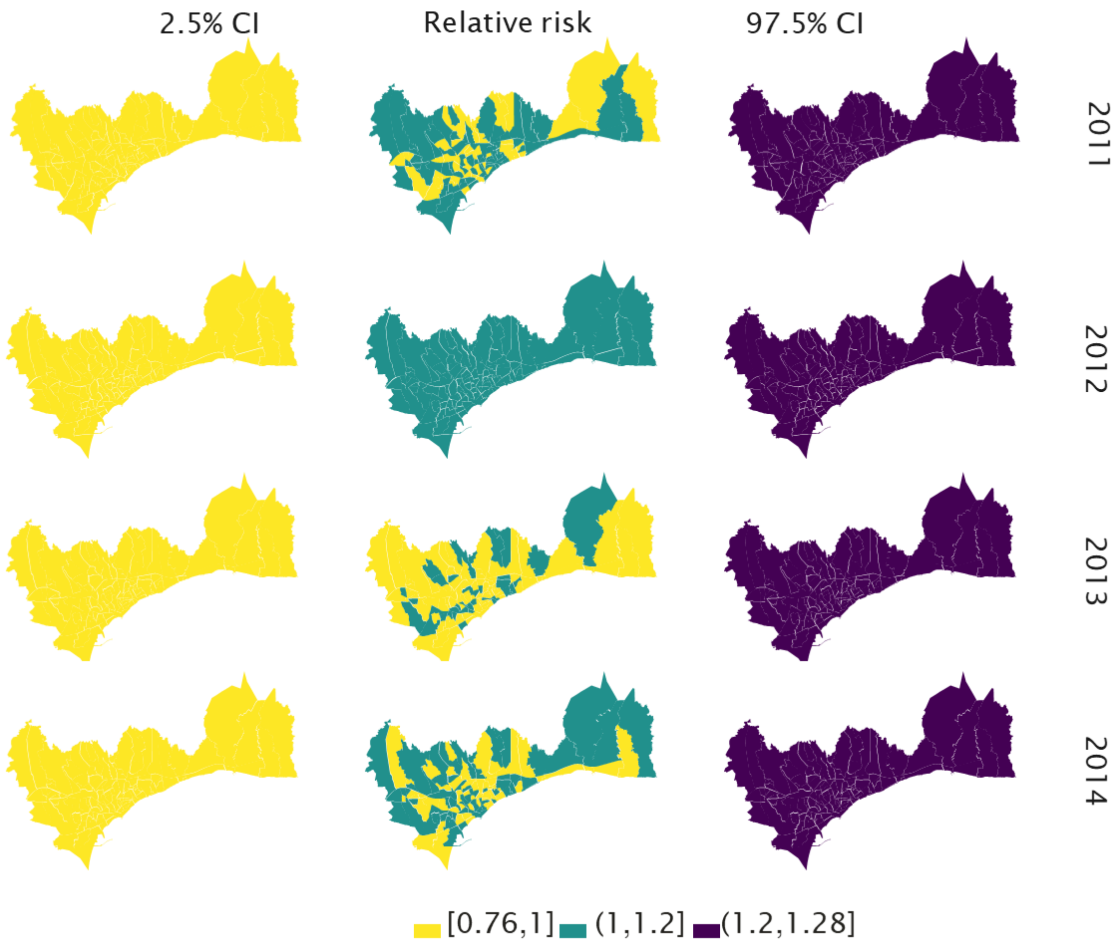
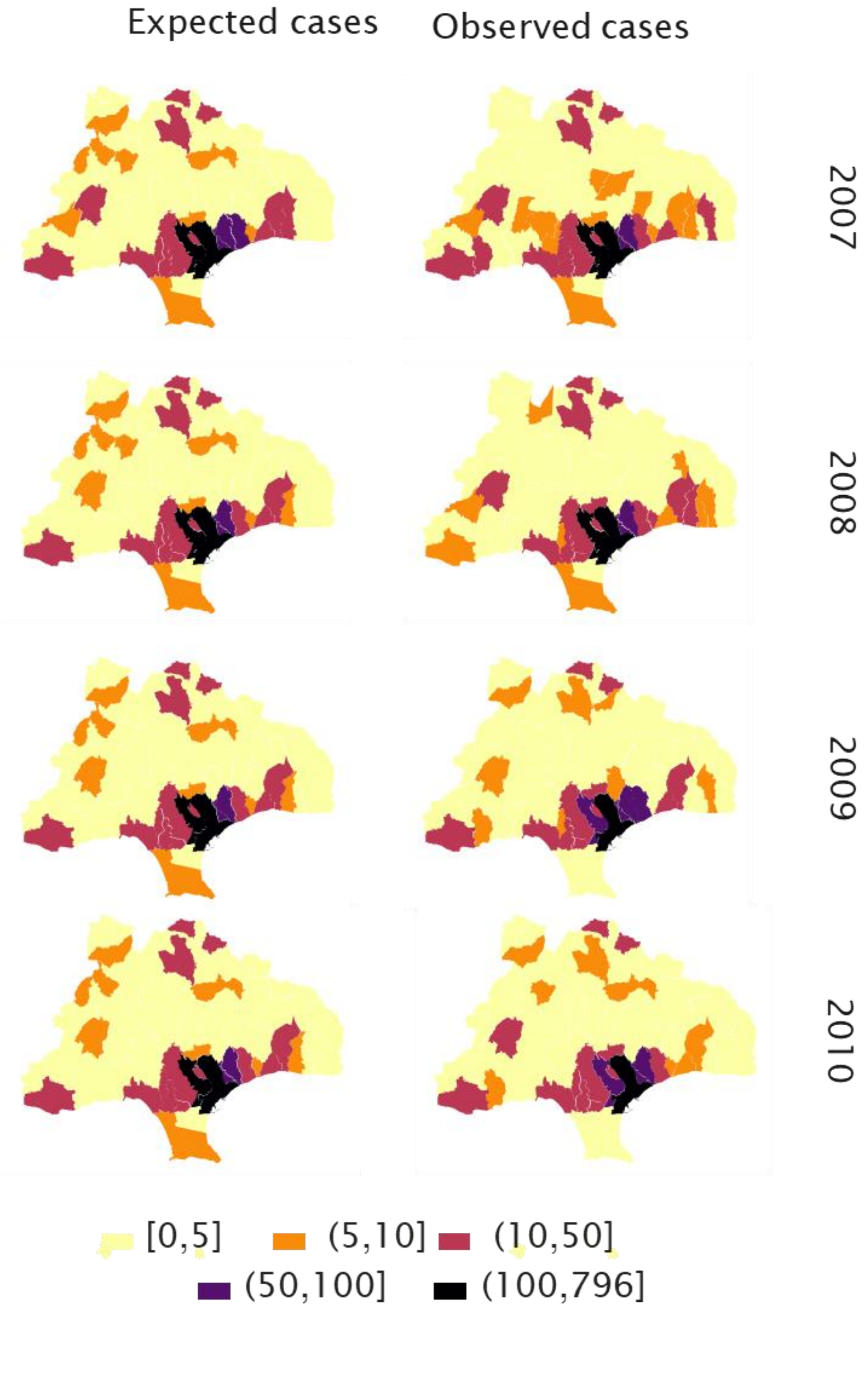
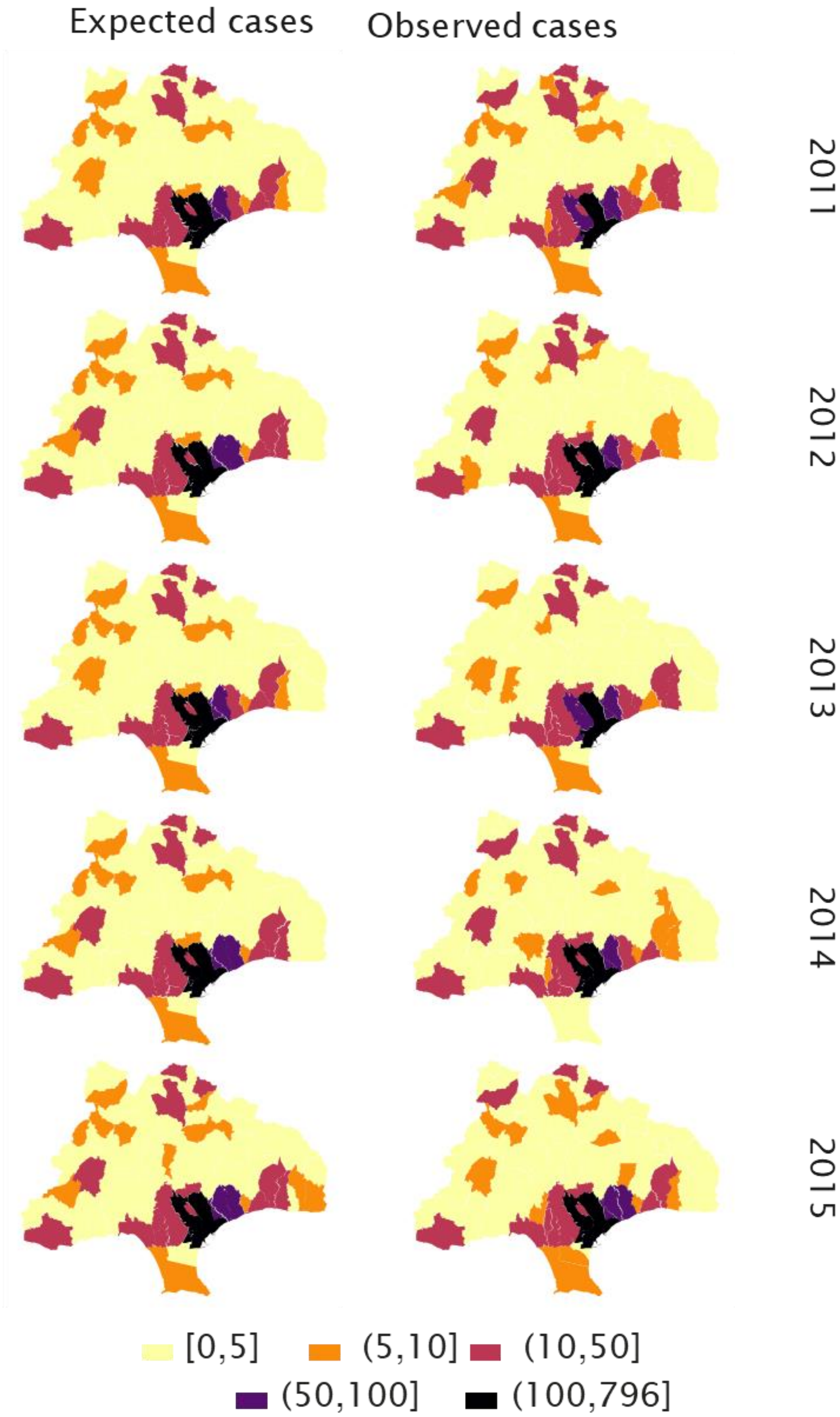


Figure S4. 4 Maps of the observed and expected cancer cases and SIR (left), smoothed relative risk of trachea, bronchus and lung-cancer incidence and 95% credible intervals (right), by postal code, in the urban part of the district of Limassol, 2007-2014.

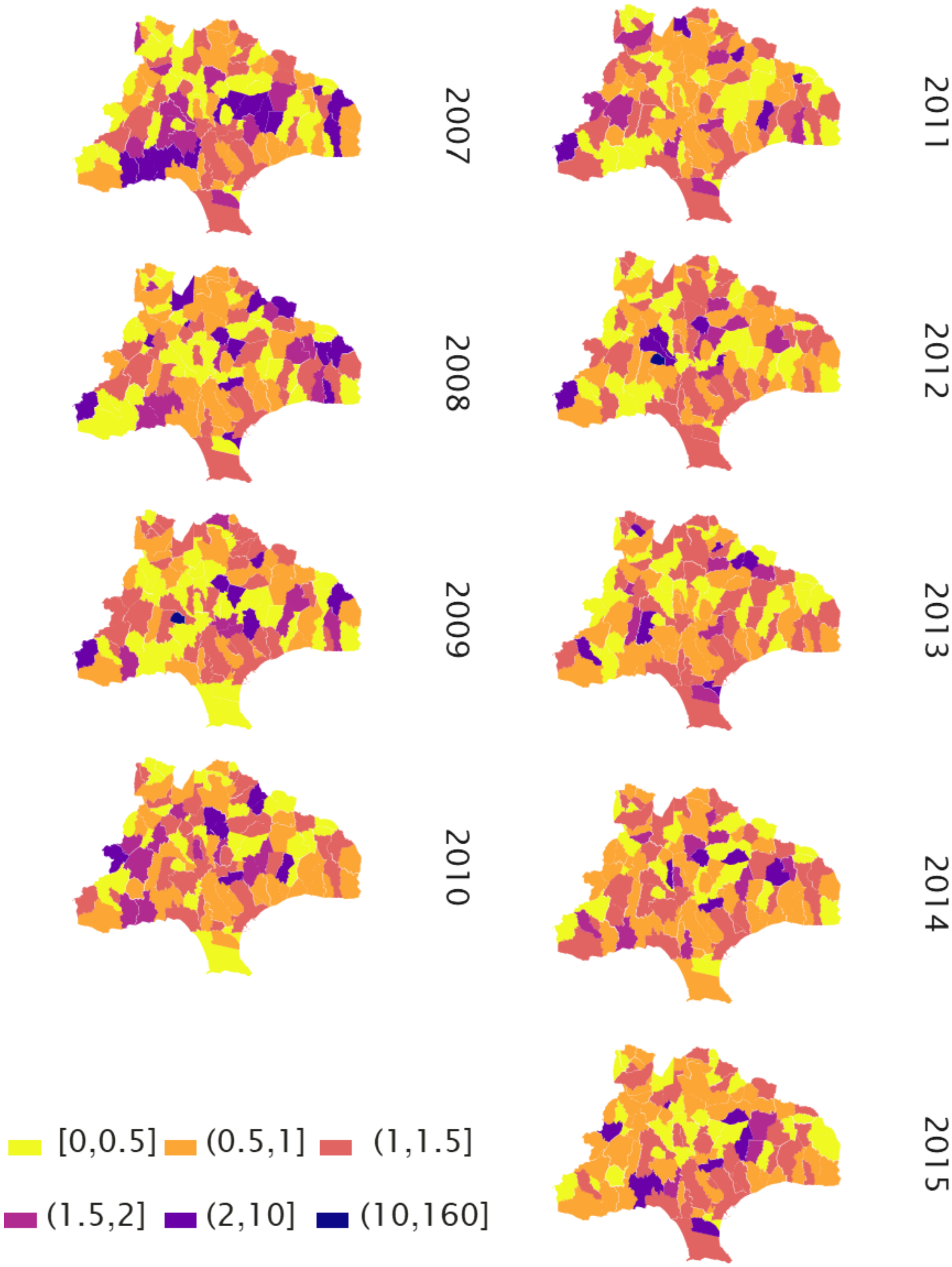
A [Observed and expected deaths, by municipality/village, in the district of Limassol, 2007-2014.]



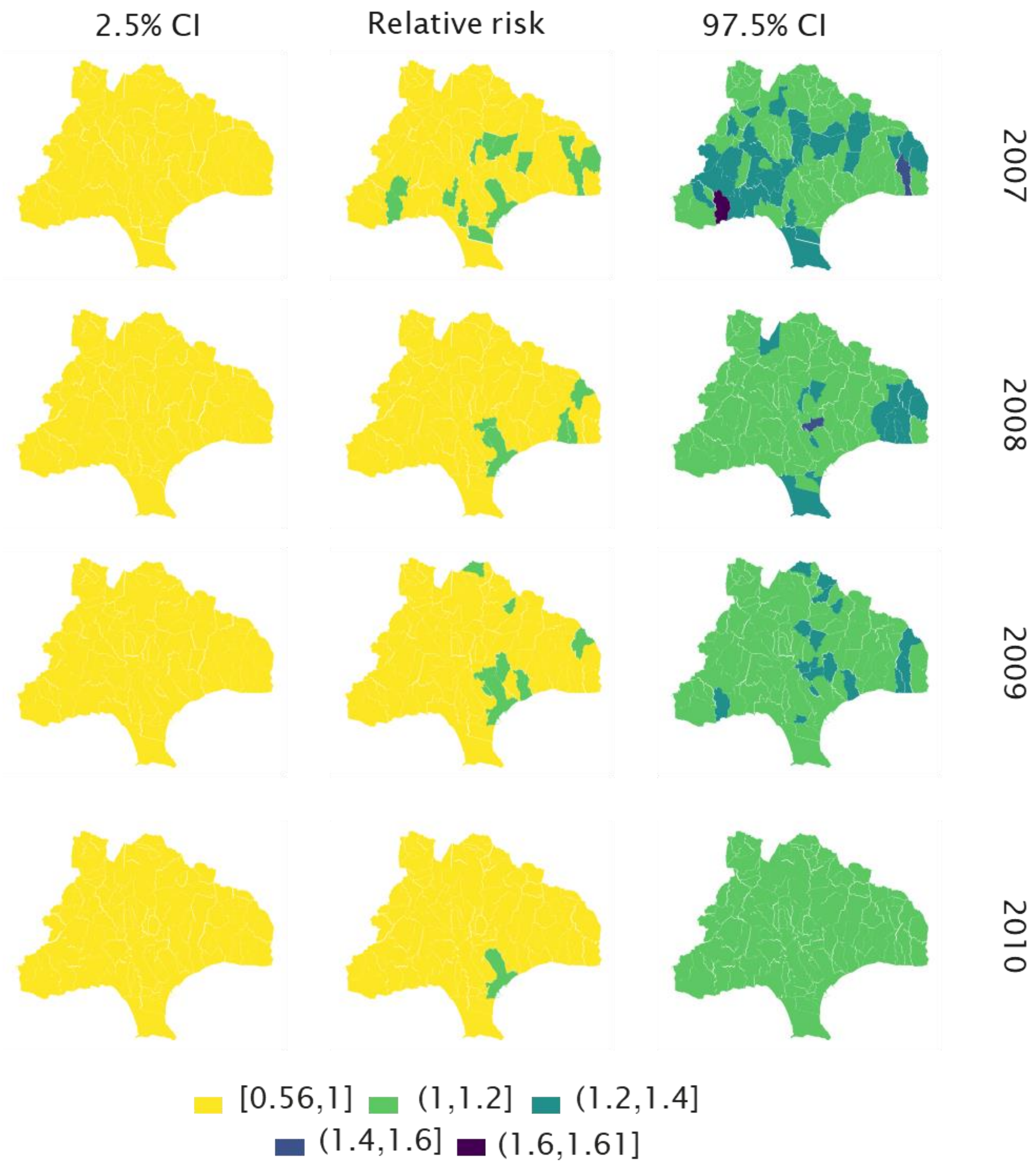
A [Observed and expected deaths, by municipality/village, in the district of Limassol, 2007-2014.]



B [All cause SMR, by municipality/village, in the district of Limassol, 2007-2014.]



C [Smoothed relative risk of death and 95% credible intervals, by municipality/village, in the district of Limassol, 2007-2014.]



C [Smoothed relative risk of death and 95% credible intervals, by municipality/village, in the district of Limassol, 2007-2014.] (cont.)

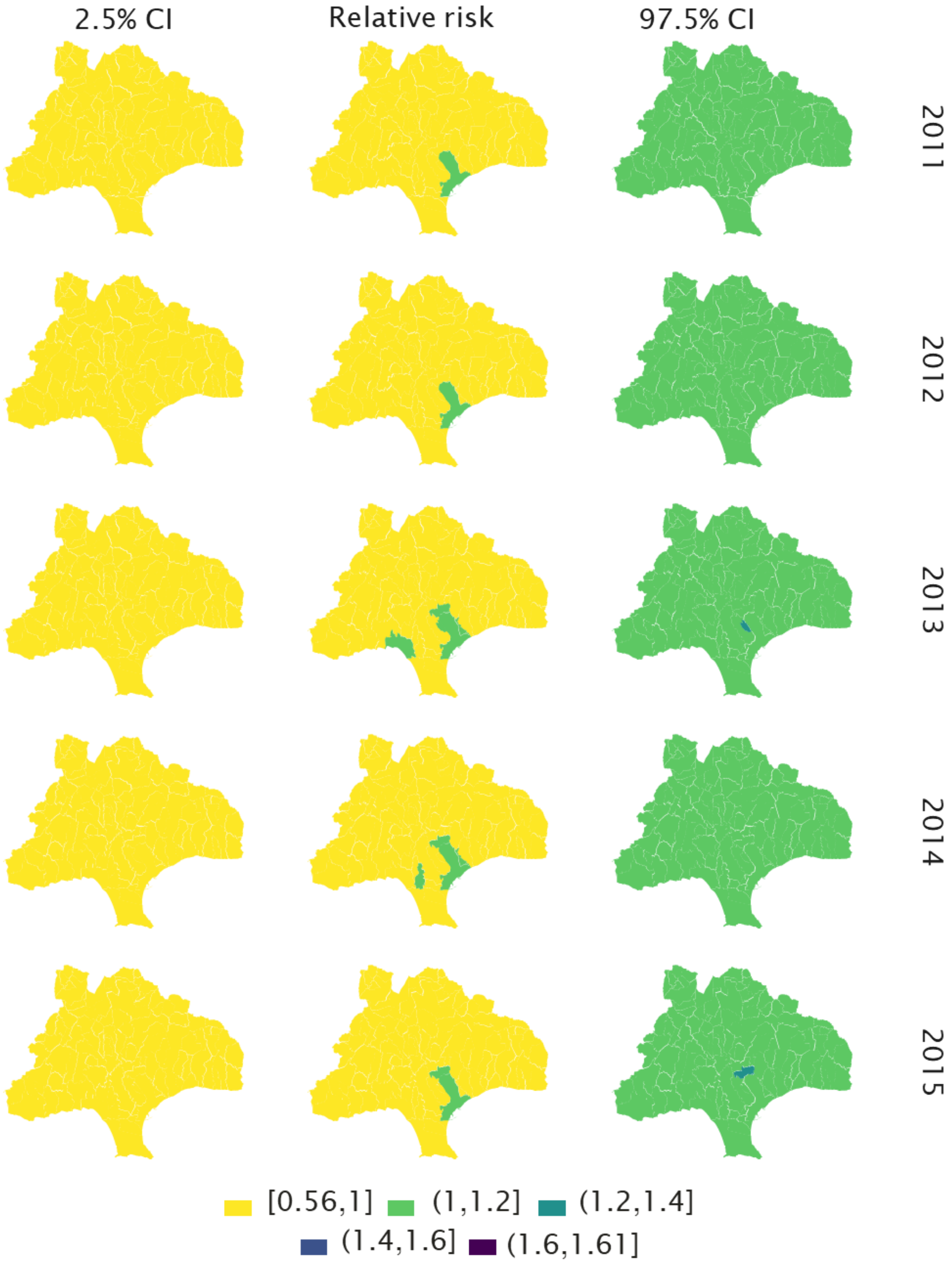
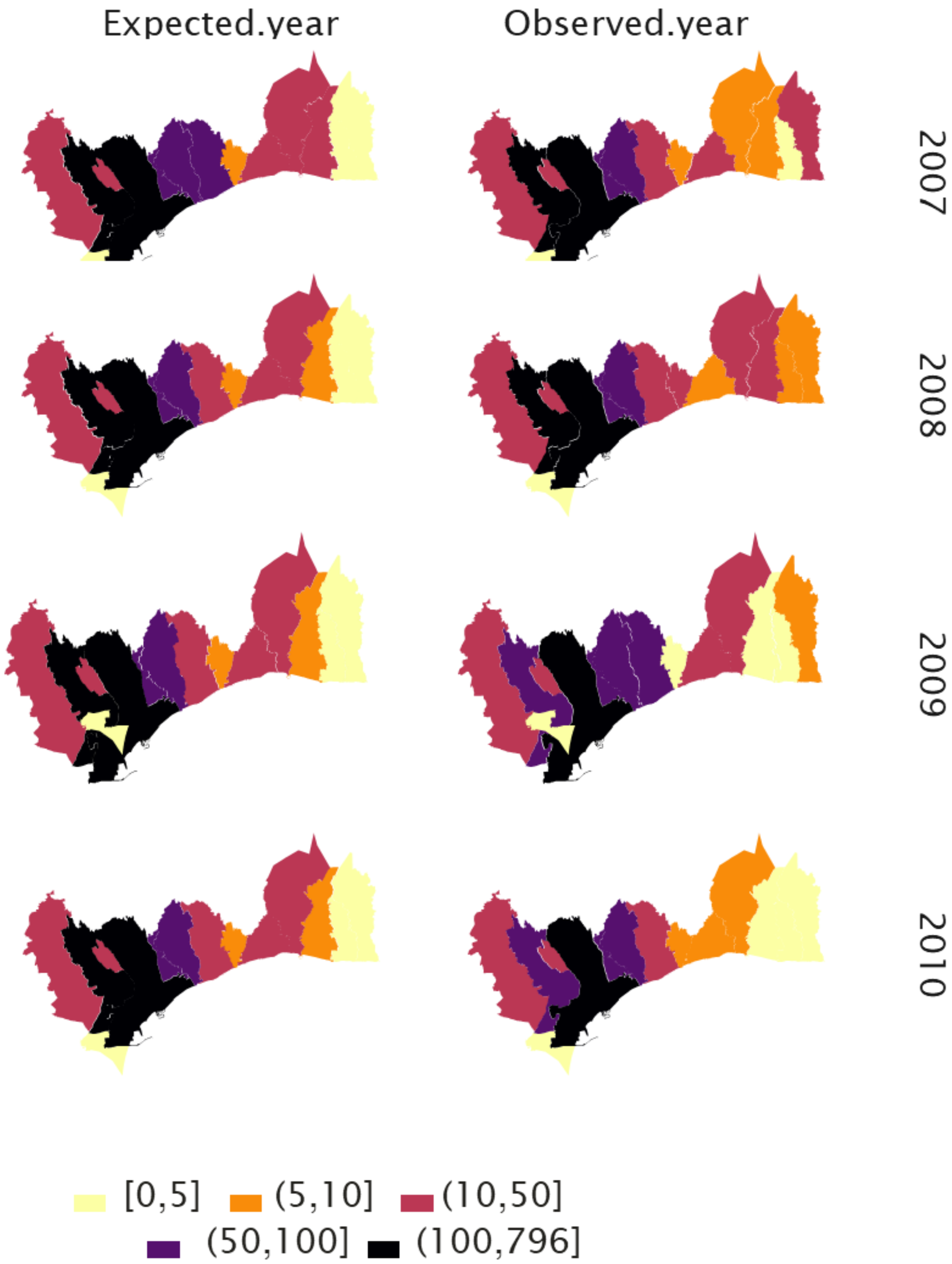
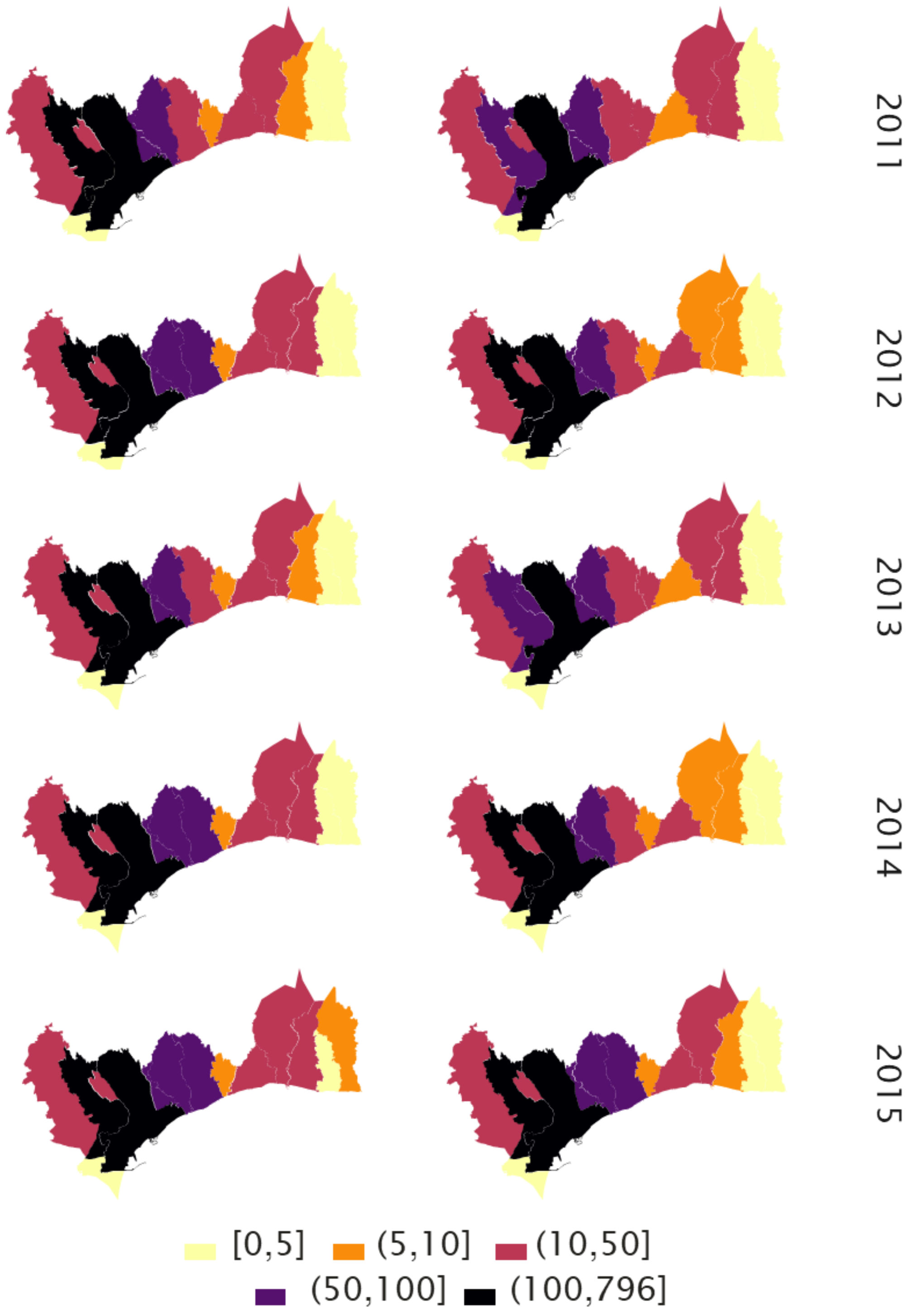


Figure S4. 5 Maps of the observed and expected deaths and SMR (left), smoothed relative risk of mortality and 95% credible intervals (right), by municipality/village, in the district of Limassol, 2007-2015.

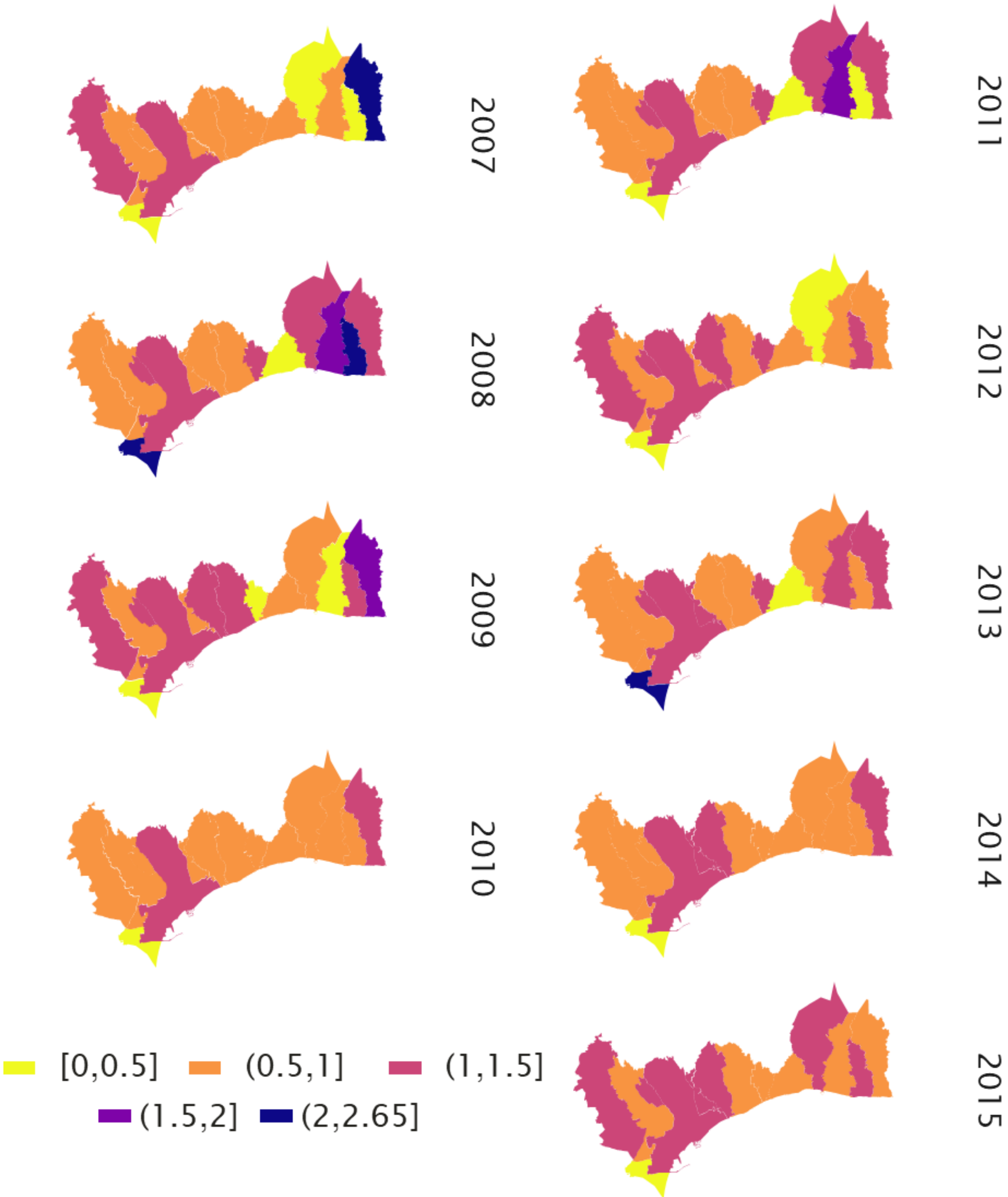
A [Observed and expected deaths, by municipality/village, in the urban areas of the district of Limassol, 2007-2014.]



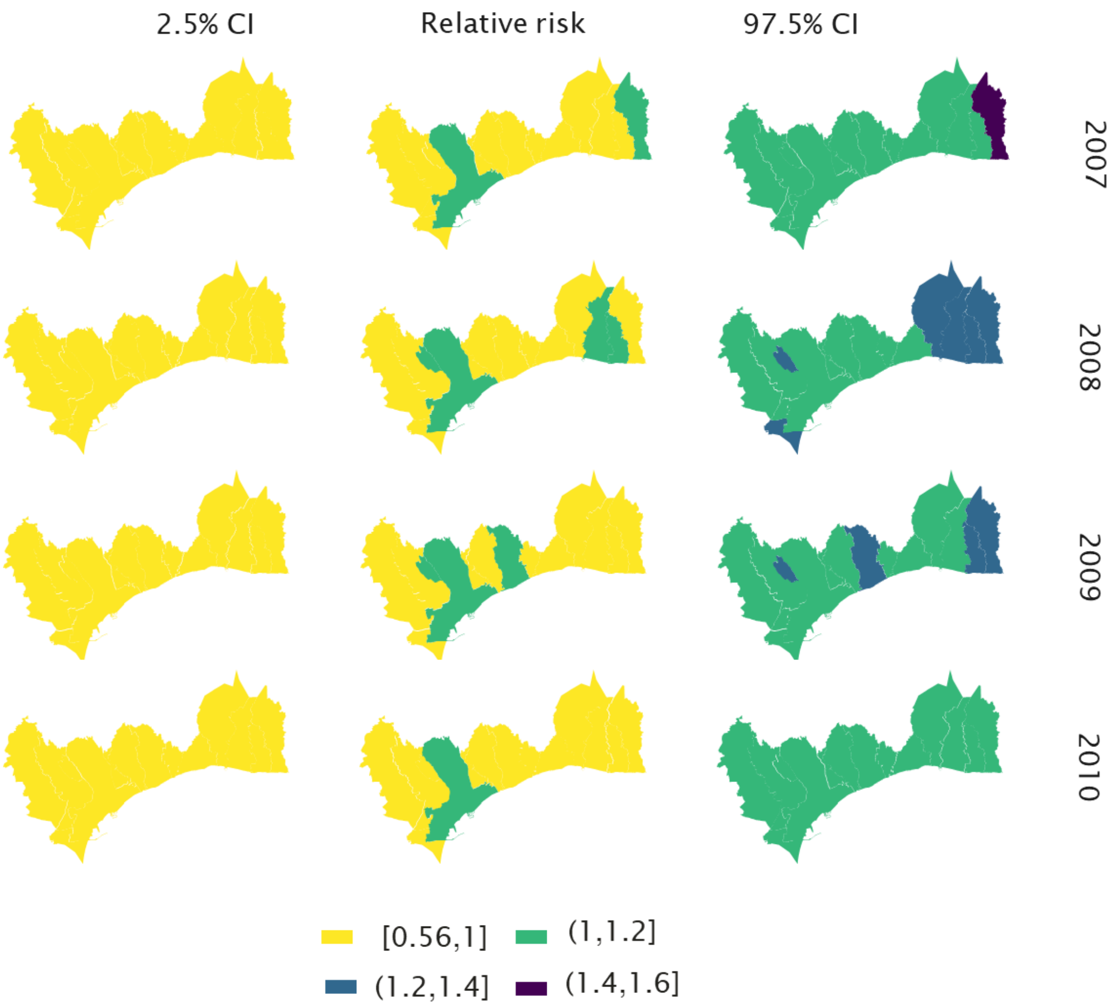
A [Observed and expected deaths, by municipality/village, in the urban areas of the district of Limassol, 2007-2014.] (cont.)



B [All cause SMR, by municipality/village, in the urban areas of the district of Limassol, 2007-2014.]



C [Smoothed relative risk of death and 95% credible intervals, by municipality/village, in the urban areas of the district of Limassol, 2007-2014.]



C [Smoothed relative risk of death and 95% credible intervals, by municipality/village, in the urban areas of the district of Limassol, 2007-2014.] (cont.)

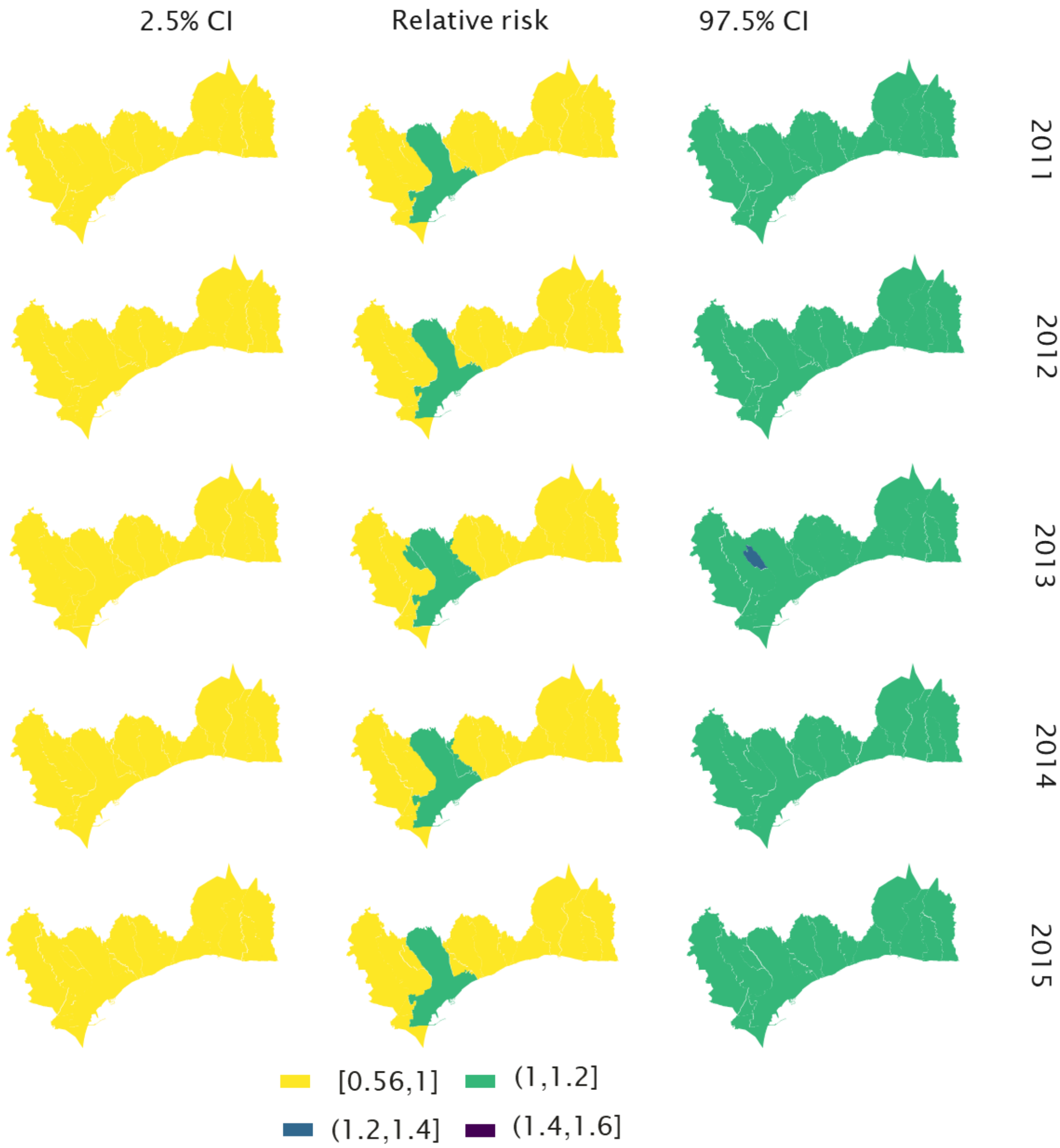


Figure S4. 6 Maps of the observed and expected deaths and SMR (left), smoothed relative risk of mortality and 95% credible intervals (right), by municipality/village, in the district of Limassol, 2007-2015.

Supplementary information

Estimation of the population at risk per year by postal code and municipality/village

Census data were available by postal code and age group, as well as by municipality/community by age group. The following age groups used are the following 0-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64 65-69 70-74 75-80, and >80 years old.

Census includes population estimates until October 1, 2011. Given that the cancer registry data are aggregated by year, the number of cases refers to 12 months, therefore the population (used in the denominator of the incidence calculation) should also refer to 12 months. Using as a baseline the population on October and the population estimates for the whole year (end-year) or the mid-year population (used for the mortality rates) were calculated by area (either postal code area, or by municipality/village ("geo code" area), and for the district, as needed). Using the estimates of the most recent demographic report[2] the district end- and mid-year population were used or calculated and then applied to estimate the population at the smaller areas for each non-census year. The process is described bellow for the calculation of the end-year postal code population and for the mid-year population by municipality/village ('geo coded areas").

<u>Population at risk by postal code area for non-census years</u>

To calculate the population at risk by year and by postal code area or municipality/village, we used as reference the population of the 2011 census and the following process:

- Total end-year population per postal code area or municipality/village for the non-census years

[2] Demographic report: http://www.cystat.gov.cy/mof/cystat/statistics.nsf/populationcondition_21main_en/populationcondition_21main_en?OpenForm&sub=1&sel=1 (accessed: 16 June, 2019).

- Using the enumerated population of the 2011 census
  - Estimation of the proportion of the district population that belongs to the postal code area

$$\text{Postal code or municipality/village population proportion} = \frac{\text{Postal code enumerated population}}{\text{District enumerated population}} \quad (1)$$

- Using the total district population estimate for the non-census year
  - Estimation of the total postal code or municipality/village population

$$Postalcode \vee municipality/village\ end - yearpopulation = Postalcodepopulationproportion(1) * Districtpopulationestimatefor the non - censusyear \ \mathbf{(2)}$$

- Total end-year population per age group per postal code area or municipality/village for the non-census years
  - Using the enumerated population of the 2011 census
    - Estimation of the proportion of the total postal code or municipality/village population that belongs to each age group

$$Agegrouppopulationproportionatthepostalcode \vee municipality/village = \frac{Agegroupenumeratedpopulation}{Postalcodeenumeratedpopulation} \ \mathbf{(3)}$$

- Using the total postal code population for the non-census year (as estimated in the previous step (2))
  - Estimation of the age group population at the postal code

$$Agegroupend - yearpopulationatpostalcodearea = Agegrouppopulationproportionatthepostalcode(3) * Postalcodeend - yearpopulation(2)$$

<u>Mid-year population distribution by municipality/village for non-census years</u>

Mid-year population estimates are available for the total population. Assuming that the proportion of the district population at the middle of the year is the same as the end of the year, we estimated the district mid-year population. Then, using the population at the census 2011 as a reference, the mid-year population per municipality/village (4-digit geo code) was calculated using the change per year.

- Total mid-year population per municipality/village for the non-census years
  - Using the enumerated population of the 2011 census
    - Estimation of the proportion of the district population that belongs to the municipality/village

$$Municipality/village\ populationproportion = \frac{Municipality/villageenumeratedpopulation}{Districtenumeratedpopulation}\ \mathbf{(4)}$$

- Using the total mid-year district population estimate for the non-census year
  - Estimation of the total municipality/village population

$$Municipality/village\ mid - yearpopulation = Municipality/village\ populationproportion(4) * Districtmid - yearpopulationestimateforthenon - censusyear\ \mathbf{(5)}$$

- Total mid-year population per age group per municipality/village for the non-census years
  - Using the enumerated population of the 2011 census
    - Estimation of the proportion of the total municipality/village population that belongs to each age group

$$Agegrouppopulationproportionatthe\ municipality/village = \frac{Agegroupenumeratedpopulation}{Municipality/villageenumeratedpopulation}\ \mathbf{(6)}$$

  - Using the total municipality/village population for the non-census year (as estimated in the previous step (5))
    - Estimation of the age group population at the postal code

$$Agegroupmid - yearpopulationat\ municipality/village = Agegrouppopulationproportionatthe\ municipality/village\ (6) * Municipality/villa\ yearpopulation(5)$$

The crude and age-adjusted rates (incidence and mortality) will be estimated using the district as a reference.

Limitations:

- Possible sudden changes in small area population cannot be taken into consideration as they are not accounted for in the estimates.
- The population used as reference to derive the proportions refers to the enumerated population and it has not been adjusted using the post-enumeration survey (some comments can be found in the table).

RECORD Statement

RECORD checklist* of items that need to be reported in studies of routinely collected data. The items that are unique to the STROBE statement (e.g. those referring to study design of observational studies) have been deleted from the table for brevity.

	Item No.		RECORD items	Location in manuscript where items are reported
Title and abstract				
	1	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.		
		RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.		Title
		RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.		Not applicable
Introduction				
Background rationale	2	Explain the scientific background and rationale for the investigation being reported		Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses		Introduction
Methods				
Study Design	4	Present key elements of study design early in the paper		Not applicable
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		Not applicable
Participants	6	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.		Methods and flow chart in the supplementary information

		RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.	Not applicable
		RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Not applicable
Variables	7	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Not applicable
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement).	
		Describe comparability of assessment methods if there is more than one group	Not applicable
Bias	9	Describe any efforts to address potential sources of bias	Not applicable (limitations are discussed)
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Methods
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods
		(b) Describe any methods used to examine subgroups and interactions	Not applicable (analysis by age group is of descriptive nature)
		(c) Explain how missing data were addressed	Methods
		(e) Describe any sensitivity analyses	Methods
Data access and cleaning methods		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Not applicable

		RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Methods
Linkage		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Not applicable
Results			
Participants	13	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Results
		(b) Give reasons for non-participation at each stage.	Methods
		(c) Consider use of a flow diagram	Table included in the supplementary material
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders	Results
		(b) Indicate the number of participants with missing data for each variable of interest	Methods and results
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results section (counfounder adjustment not applicable)
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not relevant
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Not relevant
Discussion			

Key results	18	Summarise key results with reference to study objectives	Discussion
Limitations	19	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	DIscussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Not applicable
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Not applicable
Accessibility of protocol, raw data, and programming code		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee.The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement.*PLoS Medicine* 2015; in press.

Published manuscripts included in the dissertation

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☆

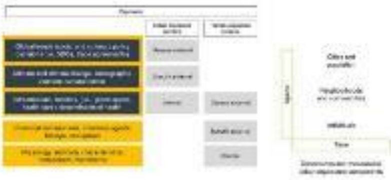
Xanthi D. Andrianou, Konstantinos C. Makris *

Cyprus International Institute for Environmental and Public Health, Cyprus University of Technology, Limassol, Cyprus

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 3 May 2018

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.

* Corresponding author at: Cyprus International Institute for Environmental and Public Health, Cyprus University of Technology, Irenes 95, Limassol 3041, Cyprus.
E-mail address: konstantinos.makris@cut.ac.cy (K.C. Makris).

https://doi.org/10.1016/j.scitotenv.2018.04.329

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 multi-dimensional 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 multi-dimensionality 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 spatio-temporally 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

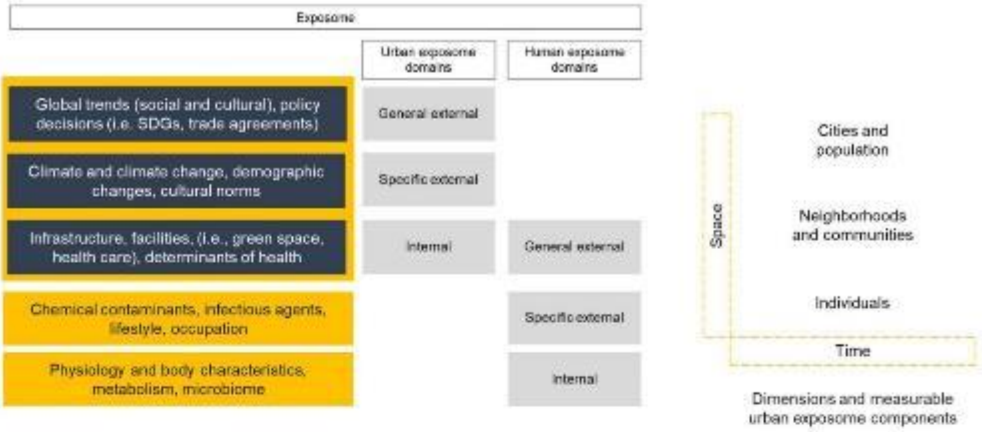


Fig. 1. The continuum of urban exposome - human exposome. Neighborhoods and individuals, cities and populations are the measurable components of the urban-, and human-exposomes, integrating assessments at the local (urban)- and personal-level.

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

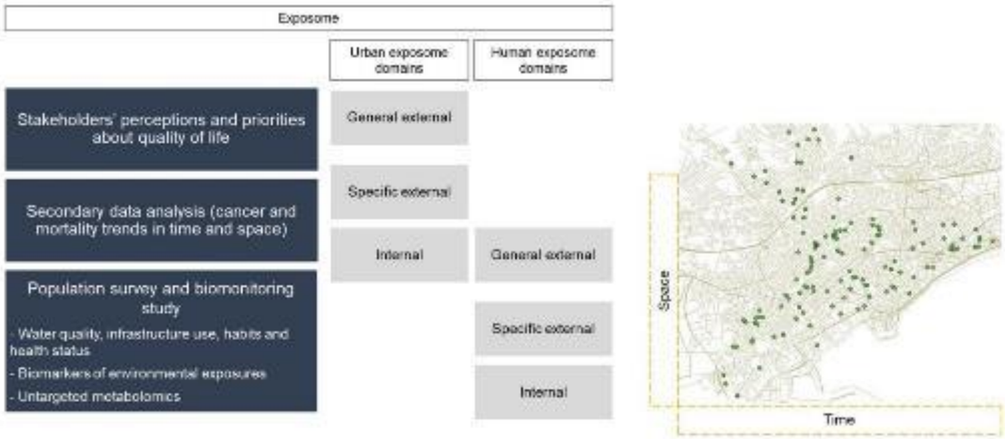


Fig. 2. Schematic depiction of the application of the urban exposome concept for the municipality of Limassol, Cyprus. The map shows the distribution of the houses visited within the limits of the Limassol Municipality for the population survey and the biomonitoring study.

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.

References

About EXPOsOMICS|EXPOSOME [WWW Document], 2016. http://www.exposomicsproject.eu, Accessed date: 3 August 2016.

Andrianou, X.D., Charisiadis, P., Andra, S.S., Makris, K.C., 2014. Spatial and seasonal variability of urinary trihalomethanes concentrations in urban settings. Environ. Res. 135:289–295. https://doi.org/10.1016/j.envres.2014.06.015.

Cities in Europe - The New OECD-EC Definition [WWW Document], 2012. http://ec.europa.eu/regional_policy/en/information/publications/regional-focus/2012/cities-in-europe-the-new-oecd-ec-definition, Accessed date: 13 February 2017.

Dai, D., Prussin, A.J., Marr, L.C., Vikesland, P.J., Edwards, M.A., Pruden, A., 2017. Factors shaping the human exposome in the built environment: opportunities for engineering control. Environ. Sci. Technol. 51:7759–7774. https://doi.org/10.1021/acs.est.7b01097.

Escher, B.I., Hackermüller, J., Polte, T., Scholz, S., Aigner, A., Altenburger, R., Böhme, A., Bopp, S.K., Brack, W., Busch, W., Chadeau-Hyam, M., Covaci, A., Eisenträger, A., Galligan, J.J., Garcia-Reyero, N., Hartung, T., Hein, M., Herberth, G., Jahnke, A., Kleinjans, J., Klüver, N., Krauss, M., Lamoree, M., Lehmann, I., Luckenbach, T., Miller, G.W., Müller, A., Phillips, D.H., Reemtsma, T., Rolle-Kampczyk, U., Schüürmann, G., Schwikowski, B., Tan, Y.-M., Trump, S., Walter-Rohde, S., Wambaugh, J.F., 2016. From the exposome to mechanistic understanding of chemical-induced adverse effects. Environ. Int. https://doi.org/10.1016/j.envint.2016.11.029.

European Cities – The EU-OECD Functional Urban Area Definition - Statistics Explained [WWW Document], 2016. http://ec.europa.eu/eurostat/statistics-explained/index.php?title=Archive:European_cities_%E2%80%93_the_EU-OECD_functional_urban_area_definition.

Goal 11: United Nations Partnerships for SDGs Platform [WWW Document], 2016. https://sustainabledevelopment.un.org/partnerships/goal11/, Accessed date: 12 August 2016.

Goal 3: Sustainable Development Knowledge Platform [WWW Document], 2016. https://sustainabledevelopment.un.org/sdg3, Accessed date: 12 August 2016.

Ishitsuka, K., Nakayama, S.F., Kishi, R., Mori, C., Yamagata, Z., Ohya, Y., Kawamoto, T., Kamijima, M., 2017. Japan Environment and Children's Study: backgrounds, activities, and future directions in global perspectives. Environ. Health Prev. Med. 22 (61). https://doi.org/10.1186/s12199-017-0667-y.

Environment, Japan, Children's Study/Ministry of the Environment Government of Japan [WWW Document], 2018. http://www.env.go.jp/chemi/ceh/en/, Accessed date: 26 March 2018.

Landrigan, P.J., Fuller, R., Acosta, N.J.R., Adeyi, O., Arnold, R., Basu, N. (Nil), Baldé, A.B., Bertollini, R., Bose-O'Reilly, S., Boufford, J.I., Breysse, P.N., Chiles, T., Mahidol, C., Coll-Seck, A.M., Cropper, M.L., Fobil, J., Fuster, V., Greenstone, M., Haines, A., Hanrahan, D., Hunter, D., Khare, M., Krupnick, A., Lanphear, B., Lohani, B., Martin, K., Mathiasen, K.V., McTeer, M.A., Murray, C.J.L., Ndahimananjara, J.D., Perera, F., Potočnik, J., Preker, A.S., Ramesh, J., Rockström, J., Salinas, C., Samson, L.D., Sandilya, K., Sly, P.D., Smith, K.R., Steiner, A., Stewart, R.B., Suk, W.A., van Schayck, O.C.P., Yadama, G.N., Yumkella, K., Zhong, M., 2017. The Lancet Commission on pollution and health. Lancet 0. https://doi.org/10.1016/S0140-6736(17)32345-0.

National Research Council, 2012. Exposure Science in the 21st Century: A Vision and a Strategy. https://doi.org/10.17226/13507.

Pineo, H., Glonti, K., Rutter, H., Zimmermann, N., Wilkinson, P., Davies, M., 2017. Characteristics and use of urban health indicator tools by municipal built environment policy and decision-makers: a systematic review protocol. Syst. Rev. 6 (2). https://doi.org/10.1186/s13643-017-0406-x.

Population Census 2011, 2014. WWW Document. Stat. Serv. Repub. Cyprus. URL. http://www.mof.gov.cy/mof/cystat/statistics.nsf/census-2011_cystat_en/census-2011_cystat_en?OpenDocument, Accessed date: 9 September 2014.

Probst-Hensch, N., 2017. Happiness and its molecular fingerprints. Int. Rev. Econ. 64:197–211. https://doi.org/10.1007/s12232-017-0268-4.

Project Overview - HEALS [WWW Document], HEALS URL. http://www.heals-eu.eu/index.php/project/, Accessed date: 4 August 2016.

Rothenberg, R., Stauber, C., Weaver, S., Dai, D., Prasad, A., Kano, M., 2015. Urban health indicators and indices—current status. BMC Public Health 15 (494). https://doi.org/10.1186/s12889-015-1827-x.

UN-HABITAT. Our Mission [WWW Document], 2016. http://mirror.unhabitat.org/categories.asp?catid=10, Accessed date: 7 October 2016.

United Nations Human Settlements Programme, World Health Organization, Kobe Centre, 2016. Global Report on Urban Health Equitable, Healthier Cities for Sustainable Development. WHO Kobe Centre, Kobe, Japan.

Vineis, P., Chadeau-Hyam, M., Gmuender, H., Gulliver, J., Herceg, Z., Kleinjans, J., Kogevinas, M., Kyrtopoulos, S., Nieuwenhuijsen, M., Phillips, D., Probst-Hensch, N., Scalbert, A., Vermeulen, R., Wild, C.P., 2017. The exposome in practice: design of the EXPOsOMICS project. Int. J. Hyg. Environ. Health https://doi.org/10.1016/j.ijheh.2016.08.001.

Vlahov, D., Galea, S., 2002. Urbanization, urbanicity, and health. J. Urban Health 79:S1–S12. https://doi.org/10.1093/jurban/79.suppl_1.S1.

Vrijheid, M., Slama, R., Robinson, O., Chatzi, L., Coen, M., van den Hazel, P., Thomsen, C., Wright, J., Athersuch, T.J., Avellana, N., Basagaña, X., Brochot, C., Bucchini, L., Bustamante, M., Carracedo, A., Casas, M., Estivill, X., Fairley, L., van Gent, D., Gonzalez, J.R., Granum, B., Gražulevičienė, R., Gutzkow, K.B., Julvez, J., Keun, H.C., Kogevinas, M., McEachan, R.R.C., Meltzer, H.M., Sabidó, E., Schwarze, P.E., Siroux, V., Sunyer, J., Want, E.J., Zeman, F., Nieuwenhuijsen, M.J., 2014. The human early-life exposome (HELIX): project rationale and design. Environ. Health Perspect. 122:535–544. https://doi.org/10.1289/ehp.1307204.

WHO|Healthy Cities (Ed.), 2016. WWW Document. WHO URL. http://www.euro.who.int/en/health-topics/environment-and-health/urban-health/activities/healthy-cities, Accessed date: 10 December 2016.

WHO|Urban population growth (Ed.), 2016. WWW Document. WHO URL. http://www.who.int/gho/urban_health/situation_trends/urban_population_growth_text/en/, Accessed date: 15 September 2016.

Wild, C.P., 2012. The exposome: from concept to utility. Int. J. Epidemiol. 41:24–32. https://doi.org/10.1093/ije/dyr236.

World Health Organization, United Nations Human Settlements Programme, 2010. Hidden Cities: Unmasking and Overcoming Health Inequities in Urban Settings. World Health Organization; UN-HABITAT, Kobe, Japan.

Application of the urban exposome framework using drinking water and quality of life indicators: a proof-of-concept study in Limassol, Cyprus

Xanthi D. Andrianou[1], Chava van der Lek[1,2], Pantelis Charisiadis[1], Solomon Ioannou[1], Kalliopi N. Fotopoulou[1], Zoe Papapanagiotou[3], George Botsaris[3], Carijn Beumer[2] and Konstantinos C. Makris[1]

[1] Cyprus International Institute for Environmental and Public Health, Cyprus University of Technology, Limassol, Cyprus
[2] Department of Health, Ethics and Society, Faculty of Health, Maastricht University, Maastricht, Netherlands
[3] Department of Agricultural Sciences, Biotechnology and Food Sciences, Cyprus University of Technology, Limassol, Cyprus

ABSTRACT

Background: Cities face rapid changes leading to increasing inequalities and emerging public health issues that require cost-effective interventions. The urban exposome concept refers to the continuous monitoring of urban environmental and health indicators using the city and smaller intra-city areas as measurement units in an interdisciplinary approach that combines qualitative and quantitative methods from social sciences, to epidemiology and exposure assessment.

Methods: In this proof of concept study, drinking water and quality of life indicators were described as part of the development of the urban exposome of Limassol (Cyprus) and were combined with agnostic environment-wide association analysis. This study was conducted as a two-part project with a qualitative part assessing the perceptions of city stakeholders, and quantitative part using a cross-sectional study design (an urban population study). We mapped the water quality parameters and participants' opinions on city life (i.e., neighborhood life, health care, and green space access) using quarters (small administrative areas) as the reference unit of the city. In an exploratory, agnostic, environment-wide association study analysis, we used all variables (questionnaire responses and water quality metrics) to describe correlations between them.

Results: Overall, urban drinking-water quality using conventional indicators of chemical (disinfection byproducts-trihalomethanes (THM)) and microbial (coliforms, *E. coli*, and Enterococci) quality did not raise particular concerns. The general health and chronic health status of the urban participants were significantly (false discovery rate corrected p-value < 0.1) associated with different health conditions such as hypertension and asthma, as well as having financial issues in access to dental care. Additionally, correlations between THM exposures and participant behavioral characteristics (e.g., household cleaning, drinking water habits) were documented.

Conclusion: This proof-of-concept study showed the potential of using integrative approaches to develop urban exposomic profiles and identifying within-city

Submitted 10 December 2018
Accepted 26 March 2019
Published 24 May 2019

Corresponding author
Konstantinos C. Makris, konstantinos.makris@cut.ac.cy

Academic editor
Nora Nock

Additional Information and Declarations can be found on page 24

DOI 10.7717/peerj.6851

How to cite this article Andrianou XD, van der Lek C, Charisiadis P, Ioannou S, Fotopoulou KN, Papapanagiotou Z, Botsaris G, Beumer C, Makris KC. 2019. Application of the urban exposome framework using drinking water and quality of life indicators: a proof-of-concept study in Limassol, Cyprus. PeerJ 7:e6851 DOI 10.7717/peerj.6851

differences in environmental and health indicators. The characterization of the urban exposome of Limassol will be expanded via the inclusion of biomonitoring tools and untargeted metabolomics.

Subjects Epidemiology, Public Health, Spatial and Geographic Information Science
Keywords Exposome, Urban health, Small area, Epidemiology

INTRODUCTION

The definition of the exposome in 2005 by Dr. Wild introduced a paradigm in environmental and population health research, which promotes studies that either encompass simultaneous assessment of multiple exposures of the general population or focus on specific time windows of susceptibility (e.g., pregnancy), to capture the totality of environmental/lifestyle/behavioral exposures (*Wild, 2005*; *Robinson et al., 2015*; *Andra et al., 2015*; *Cui et al., 2016*). The definition of the exposome along with the advances in methodologies for high throughput analysis in shorter time has also redefined the study paradigm in environmental health (*Buck Louis, Smarr & Patel, 2017*). Thus, decoding the exposome will not benefit only environmental health, but it will lead to better understanding of disease development and progression and it will allow for comprehensive monitoring of environment-disease associations.

The exposome as a paradigm has fostered innovation in exposure assessment. It allows for intra- and inter-disciplinary approaches in public health to become more widespread than they are now, as it is indicated by the number of "exposomes" that have been defined to address different totalities and with different units of reference (*National Research Council, 2012*; *Escher et al., 2016*; *Dai et al., 2017*).

Cities are dynamic and complex systems that become the future focus of public health systems, because they currently host more than half of the global population and generate >80% of the global GDP (*Urban Development Overview, 2018*; *Zhang, 2011*). Using terminology similar to the one used for the human exposome, the urban exposome extends the utility of the human exposome, and it is defined as the totality of indicators (quantitative or qualitative) that shape the quality of life and health of urban populations (*Andrianou & Makris, 2018*). Monitoring of these indicators that can be either external or internal city parameters, is not merely the sum of individual human exposures, but places cities and their smaller areas in the center of an urban-oriented study framework, previously defined as the urban exposome framework (*Andrianou & Makris, 2018*). Following the urban exposome approach, the quality of life in urban centers is concurrently assessed together with other indicators, such as water quality, or prevalence/incidence of communicable, and non-communicable diseases using interdisciplinary methodology. This framework expands previous study approaches where the urban exposome is defined as the sum of exposures in cities (*Probst-Hensch, 2017*; *Robinson et al., 2018*), and proposes a more interdisciplinary and holistic approach to assess health determinants of the general population.

To present the first application of the urban exposome framework, we used drinking-water quality metrics and quality of life indicators. As more people nowadays live in cities, providing easy access to safe and affordable water, as well as eliminating possible within-city health and societal disparities becomes more challenging. Besides the technical provisions to maintain water of good quality, the uninterrupted availability of water becomes an issue due to climate change manifestations, especially in areas that are already or expected to be hit harder by extended droughts and other related meteorological phenomena. Europe, overall, is expected to face increases both in the extent of geographical areas affected by droughts and in the duration of such climatic events (*Samaniego et al., 2018*). In particular, cities located in Southeast Europe and the Mediterranean region are predicted to face challenges in maintaining water availability and adequate water quality in the future (*Samaniego et al., 2018*). Therefore, cities and their smaller areas (i.e., neighborhoods, or other small administrative areas) are warranted to address water-related issues, such as water demand, safety, security, and quality issues, while tackling societal inequalities and health disparities. In this context, the concept and the study framework of the urban exposome can be introduced to help scientists and policy makers in the systematic spatio-temporal surveillance and monitoring of a city's heterogeneous health profile.

The urban exposome study framework has a hypothesis-generating scope and goes beyond the classical one exposure-one outcome approach urban studies. Therefore, our aim was to present a proof-of-concept study using the urban exposome framework to monitor urban health dynamics. The study setting was Limassol, Cyprus. The urban center of Limassol ("city of Limassol") is defined as a medium-sized city (~200,000 inhabitants according to the 2011 Population Census of Cyprus) (*Ministry of Finance of the Republic of Cyprus, 2014*; *Eurostat, 2017*) and it consists of the municipality of Limassol and neighboring municipalities. The city of Limassol currently faces rapid economic development with half of the urban population of the city residing within the municipality of Limassol (~110,000 inhabitants).

The specific objective of this analysis was to describe chemical and microbiological parameters of drinking water quality, coupled with quality of life indicators as measured in the municipality of Limassol, in summer 2017. In this approach we used quarters which are the smallest within-municipality administrative areas, as the unit of reference. To complete the urban exposome of Limassol to the extent possible, additional analysis of routine surveillance data is necessary but it goes beyond the scope of the present analysis.

MATERIALS AND METHODS

Application of the urban exposome in the municipality of Limassol, Cyprus

We have previously described the urban exposome as all indicators that need to be continuously monitored for the assessment of city health (*Andrianou & Makris, 2018*). Within the framework of the urban exposome, external to the city parameters that cannot be influenced by the city itself can be either general (e.g., global trends and policy decisions) or more specific (e.g., climate change impacts, demographic changes, culture). It follows that internal parameters are those that are integral to the city, such as

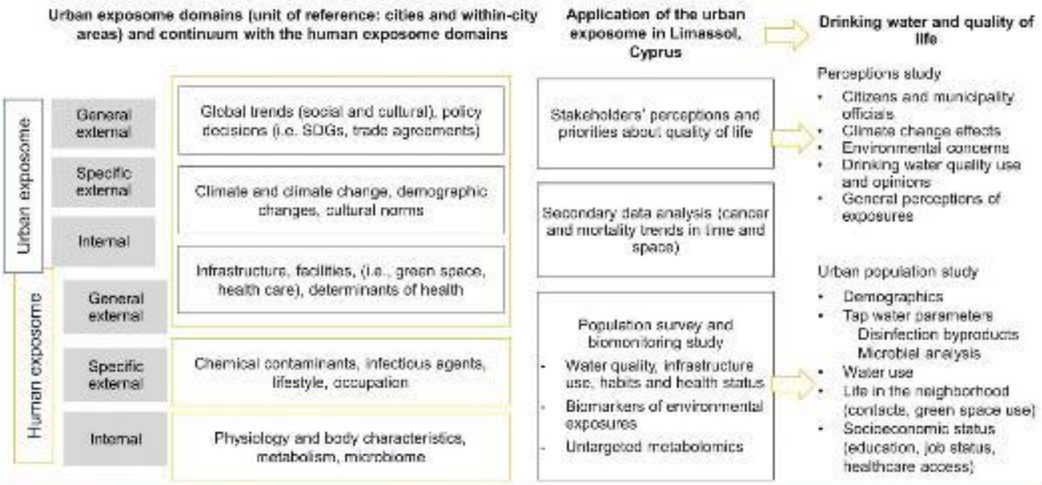


Figure 1 Urban exposome—human exposome continuum, and the practical application of the urban exposome framework in the urban setting of Limassol city. The parts of the urban exposome specifically discussed in the current analysis include a perceptions study and an urban population study, which includes parameters measured in drinking-water to assess the water quality coupled with questionnaire responses about individual lifestyle, behavioral, and personal health indicators. Full-size DOI: 10.7717/peerj.6851/fig-1

infrastructure, built/neighborhood environment and determinants of population health (e.g., socioeconomic factors). Either external or internal to the city, the parameters described before can influence and be influenced by each other both horizontally (within each domain) and/or vertically (between domains). A study was conducted in the summer of 2017 to describe the water and quality of life aspects of the urban exposome of Limassol, following an integrative and interdisciplinary approach (Fig. 1). This approach included the following parts:

- A perceptions survey with a mixed-methods approach to evaluate the perceptions of stakeholders (i.e., citizens and municipality officials) about the quality of life and certain environmental risks (e.g., chemical and microbial risks in drinking-water) in the city.
- A cross sectional urban population study with a short questionnaire and collection of tap water samples from households distributed in the quarters of the municipality of Limassol to evaluate water quality indicators and citizens' attitudes about the environment, quality of life in the city and self-reported health status.

In this analysis, we focus on the general external urban exposome through the perceptions study and the internal exposome domain through the inclusion of drinking water chemical/microbiological indicators, responses on neighborhood's quality of life and participant characteristics (Fig. 1). Using the human exposome framework as a reference, this study also explored the human exposome domains, that is, the general external domain (perceptions study), the specific external domain (drinking water and quality of life indicators) and the internal domain (participant characteristics) (Fig. 1).

Perceptions study

For the perceptions study, the urban community-based participatory research methodology was applied to actively engage the municipality of Limassol and citizens (identified as community stakeholders) about urban health issues (*Rojas & Neutra, 2008*). The stakeholders' perceptions were assessed using a mixed methods approach. Face-to-face interviews were conducted, and short questionnaires were administered to the municipality officials (i.e., technical officers from the municipality of Limassol and neighboring municipalities). The questions asked during the face-to-face interviews and the questionnaire for the municipality officers focused on the identification of trends shaping the city of Limassol, assessment of the climate change manifestations and their impact, scoring of environmental health concerns, an assessment of what was believed to be the citizens' major health threats with regards to urban life, and perspectives about future opportunities to improve health in the city. For the citizens' perceptions, an online anonymous questionnaire initially distributed via email among staff at the Cyprus University of Technology campus that is in the municipality of Limassol, and then to the general public via mailing lists maintained at the Cyprus International Institute for Environmental and Public Health for the dissemination of newsletters, and social media (Facebook). This online questionnaire included various questions on climate change perceptions, environmental concerns in general, health perceptions, and perceptions about drinking-water quality.

Urban population study

A cross-sectional population study was set up in the municipality of Limassol, Cyprus. Participants ($n = 132$) were recruited after being informed about the study through phone calls made in collaboration with the municipality of Limassol, in the summer of 2017 from all quarters of the municipality, following the 2011 Census population distribution (Table S1). For this study, we also collected urine samples which will be used in the biomonitoring part (measurement of chemical exposures in urine) of the assessment of the urban exposome (not included in this analysis). Thus, sample size estimations were based on the assumption that a total of 120 participants randomly selected from the whole municipality would allow us to evaluate the baseline levels of environmental exposures, as according to previous biomonitoring studies a sample of at least 120 randomly selected participants is adequate to capture the 95th percentile of the population levels (*Becker et al., 2013*). Quarters that are small in area and population, with one participant, were merged with neighboring ones and three quarters located along the beachfront, each having one participant were also merged together (Fig. S1). To ensure high spatial coverage, only one participant was recruited per street.

Tap water samples were collected from all participating households and in situ measurements of free chlorine were taken during house visits. The drinking water indicators that were assessed were trihalomethanes (THM) along with the free chlorine, from the category of the chemical parameters, and total coliforms, *E. coli*, *Enterococcus* spp., *Pseudomonas aeruginosa*, and total viable counts (TVC) at 22 and 37 °C, from the category of the microbial parameters. These indicators (besides free chlorine) are also routinely monitored in the European Union (*EU Council, 1998*). All participants were asked to complete a questionnaire that included, among others, questions about life in their neighborhoods, self-reported health status, and drinking water habits. The questionnaire was adapted by the validated urban health and the European Health Survey questionnaires (*Republic of Cyprus, Ministry of Finance, 2014*; *European Urban Health Indications System Part 2, 2012*; *Pope et al., 2016*). From this questionnaire the quality of life indicators (e.g., access to health care services, life in the neighborhood and use of green spaces) were assessed.

The study was approved by the National Bioethics Committee of Cyprus (decision number: 2017/23). All participants read and signed the informed consent documents before data collection. The STROBE statement is available in the Supplementary Material (*von Elm et al., 2007*).

Water sampling and analysis

The main faucet used for satisfying the water needs of the participating household was selected for drinking-water sampling. The tap water faucet was externally cleaned with ethanol prior to sample collection, and the water was then left to flow freely for ~30 s. Tap water samples for THM analysis were collected in falcon containers with oxidation preservative mixture, while the tap water samples used in the microbial analysis were collected in sterile polypropylene vials. The THM analysis was conducted according to the previously published methods by *Charisiadis et al. (2015)*. All four THM species were measured in the collected tap water samples from the participating households: chloroform (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform (TBM). The limits of detection (LOD) were 0.13 μg/L for TCM and DBCM, and 0.11 μg/L for BDCM and TBM.

Microbial analysis was conducted after the water was cultured onto selective media for the detection and enumeration of total coliforms, *E. coli*, *Enterococcus* spp., *P. aeruginosa*, and TVC at 22 and 37 °C. The methods used for the microbial analysis are presented the Supplementary Methods document.

All water samples were collected from the main faucet of the household used to satisfy their potable needs and it was directly connected to the municipality's water supply.

Residual chlorine was measured with a portable photometer (MaxiDirect; Lovibond, Amesbury, England) in water directly collected from the tap using the DPD (N,N-diethyl-p-phenylenediamine) method.

Statistical analysis for the urban population study

Descriptive analysis of the questionnaire responses

Descriptive statistics (i.e., means and standard deviation (sd) for the continuous variables, and frequencies and percentage by category for the categorical variables) were calculated for the responses to the questionnaire. The descriptives were grouped by category of question (i.e., demographics and other background characteristics, drinking water habits and cleaning activities, lifestyle and behavioral indicators, healthcare services access, health status, life in the neighborhood) for the complete study population (n = 132).

Descriptive analysis of the water quality indicators

Descriptive statistics for the drinking-water THM and microbial counts were separately presented for the samples collected directly from the tap when no filter was attached (n = 119) from those 13 samples that were collected with a filter present. When THM values were below the LOD (n = 4 for TCM and n = 1 for TBM), they were imputed to LOD/2. The sum of all THM species (total THM) and the sum of the brominated species (BrTHM; i.e., BDCM, DBCM, and TBM) were calculated. For the statistical analysis of the microbial water quality we considered the presence or absence of colonies for *E. coli* and *Enterococcus* spp. instead of the absolute count number (EU Council, 1998). For the coliforms, *P. aeruginosa*, and TVC at 22 and 37 °C presence or absence were also considered. Specifically, for TVC at 22 and 37 °C a smaller number of samples was analyzed (n = 95) due to external contamination. For the THM concentrations the descriptives included: mean, sd, median, and percentiles, that is, 25th, 75th percentiles, and the range, that is, min and max, while for the microbial analysis the frequency of samples with at least one colony-forming unit (CFU) (and the percentage) was calculated. Water samples collected from households (n = 13) having permanently connected point of use filters in the main faucet were excluded from the main statistical analysis.

The results of the THM and microbial analyses were presented separately for the total THM, the *E. coli* and the *Enterococci* spp., as they are considered of higher priority compared to the single THM species and the other microbial indicators (e.g., coliforms).

Mapping of the water and the quality of life indicators

To evaluate how indicators pertaining to the water and quality of life are distributed in different quarters of Limassol, we mapped a selection of urban indicators by quarter. For the water quality indicators, the median levels of total THM, free chlorine, BrTHM per quarter were mapped, as well as, the percentage of samples with detectable levels of coliforms and TVC. From the urban questionnaire data, all indicators were mapped. However, for brevity, we present in the maps and discuss selected indicators per category for the following: (i) issues on access to health care services due to delays and financial constraints, (ii) life in the neighborhood, and (iii) two indicators from the category on access to green spaces to illustrate potential differences between quarters.

Exploratory environment-wide association study

We performed an exploratory environment-wide association study (EWAS) to agnostically synthesize knowledge and concurrently investigate possible associations of the measured water quality indicators and questionnaire-based socioeconomic, lifestyle, and behavioral factors. This exercise helped us demonstrate how an EWAS approach can be incorporated in analyses that are based upon the urban exposome framework.
The outcomes used in the EWAS analysis were three self-reported health status outcomes:

(i) general health status, (ii) diagnosed with any chronic disease, and (iii) diagnosed with any disease in the past year ("any disease the past year," that is, asthma, diabetes, allergies, hypertension, cardiovascular or respiratory illnesses, depression, cancer, musculoskeletal problems) (*Patel, Bhattacharya & Butte, 2010*). The EWAS analysis included a correlation matrix between all variables, regression analysis, and a multi-omics based approach to describe correlations between all the variables measured accounting for specific health outcomes.

The variables included in the EWAS approach were divided in the following "blocks/groups" to reflect different parameters of the human exposome, since the analysis was performed at the individual level:

- Block/group 1 (specific external domain): water THM levels, free chlorine
- Block/group 2 (specific external and internal domain): drinking water habits (e.g., number of glasses of water consumed by source)
- Block/group 3 (specific external and internal domain): household cleaning activities (e.g., dishwashing, mopping, bathroom cleaning)
- Block/group 4 (general external domain): neighborhood quality of life (variables of "highest consensus": heath care access, life in the neighborhood and green urban spaces)
- Block/group 5 (internal domain): participant characteristics (e.g., age, sex, BMI)
- Block/group 6 (internal domain): self-reported diseases in the past year (e.g., asthma, diabetes, allergies, hypertension, cardiovascular or respiratory illnesses, depression, cancer, or musculoskeletal problems).

In all categorical variables the "I don't know/I don't want to answer" responses were re-coded to "missing." Then, scores were added per category (presented in Table S2) and used in statistical analysis when categorical variables could not be used (e.g., correlations).

In the preliminary correlation analysis, all variables (including the three outcomes) were used as continuous and the Spearman correlation coefficient was calculated without any transformations. The results were visualized with a correlation plot. Then, regression models were fitted. The variable for the general health status was used as continuous in linear regression whereas responses for self-reported chronic disease and any disease the past year were used as binary variables in logistic regression. The regression models were repeated after adjusting for age and sex. The continuous predictors were scaled and centered in all regression models. The p-values of all model parameters that were used for inference (i.e., excluding the intercept for the univariable models and excluding the intercept, age, and sex coefficients from the adjusted models) were summarized and corrected for Benjamini–Hoechberg false discovery rate (FDR). Only parameters with an FDR-corrected p-value < 0.10 separately applied to the univariate (n = 129 tests) and the adjusted models (n = 123 tests) were considered statistically significant.

In the last part of the EWAS analysis, we followed an approach used in multi-omics studies where the variables are grouped and partial least squared discriminatory analysis (block PLS-DA) is conducted to identify possible correlations between the variables of the different blocks accounting for an outcome (*Rohart et al., 2017*). In this analysis, the predictor variables were used as continuous and all outcomes were used as categorical. The correlations between the predictor variables in blocks were presented in circular plots (circo plots) where positive and negative Pearson pairwise connections are shown in the circle and lines indicate the levels of each variable within each outcome category.

All analyses (regressions and block PLS DA) were performed for the three outcomes using all the blocks/groups as predictors except for the analysis for the outcome "any disease the past year." This variable was created as the summary of the variables of block/group 6 (self-reported diseases the past year). Thus, in this analysis, the separate diseases of block/group 6 were not included due to their association with the outcome of "any disease the past year."

All analyses were conducted in R 3.5.1 with RStudio 1.1.423 (*RStudio Team, 2015*; *R Core Team, 2017*). Input data, the output, scripts, and the questionnaires are available in the Supplementary Material. The packages used in the analysis are listed in Table S3.

RESULTS

Perceptions study results

Approximately, 10 municipality technical officers were approached for interviews and to fill in the municipality questionnaire. In total, five interviews were conducted, and six questionnaires were administered. The importance of climate change and its effects was pointed out by all municipality officers during the face-to-face interviews and within the questionnaire responses. In rating the environmental concerns (one for very low and five for very high concern), water quality had the lowest score with increasing order of scoring for soil contamination < waste < general chemical exposures < noise < air pollution.

In total, 181 participants responded to the online questionnaire that was addressed to citizens and 134 (74%) filled in the complete questionnaire. A total of 91 of the respondents reported living in Limassol (35% males and 65% females) with a mean age of 35 years old (range:18–77 years old). The majority (81%) was born on Cyprus, and 13% were born in another EU country, the rest (6%) were born in a non-EU country. As expected from the distribution of the questionnaire among the staff of the university, most of the respondents (84%) were highly educated holding at least a Bachelor's degree. Approximately half of the respondents were married (46%) with children (47%).

Residents of urban Limassol ($n = 91$) were mostly concerned about being severely exposed to air pollution and noise (Table 1). Water quality ranked low while air pollution and noise ranked high in the "severely exposed" category among all environmental exposures. Approximately 30% of the respondents reported that they were not exposed to water pollution or soil contamination, but at the same time an equally high proportion of respondents reported "don't know," suggesting inadequate knowledge about the drinking-water or soil quality in their city. With regards to water quality, 81% reported worrying about chemical exposures, and 41% reported they were exposed to chemicals daily.

Among all urban respondents, only ~30% reported the consumption of tap water, while 32% reported treating the water before consumption (filtering or cooking), and 39% mentioned not drinking the tap water at all. Also, the "highest in importance" concerns of

Table 1 Perceptions about environmental exposures among the respondents from the city of Limassol (*n* = 91).

	Severely exposed	Somewhat exposed	Not exposed	Don't know
Noise (traffic, airplanes, factories, neighbours, animals, restaurants/bars/clubs)	38 (42%)	48 (53%)	5 (5%)	0 (0%)
Air pollution (fine dust, grime, fume, ozone)	40 (44%)	40 (44%)	10 (11%)	1 (1%)
Bad smells (industry, agriculture, waste)	15 (17%)	35 (38%)	39 (43%)	2 (2%)
Water pollution (microbes/chemicals in drinking water)	8 (9%)	22 (24%)	31 (34%)	30 (33%)
Soil contamination (eg., chemical waste dump)	5 (5%)	15 (17%)	32 (35%)	39 (43%)

Table 2 Background characteristics of for the urban population study conducted in Limassol, Cyprus.

	Overall (*n* = 132)
Age (mean (sd))	45.6 (13.2)
Sex (%)	
Females	82 (62.1)
Males	50 (37.9)
BMI (mean (sd))	26.25 (5.06)
Marital status (%)	
Cohabitating	8 (6.1)
Divorced	15 (11.4)
Married	82 (62.1)
Single	26 (19.7)
Widowed	1 (0.8)
Education (%)	
Primary school	2 (1.5)
Gymnasium	2 (1.5)
High School/Technical School	28 (21.4)
Non-university tertiary education	16 (12.2)
Post-secondary education	6 (4.6)
Bachelor's degree (BSc/BA)	45 (34.4)
Master's degree or doctorate (MSc/MA, PhD)	32 (24.5)

the citizens about tap water quality were those associated with either chemicals (47%), or microbes (37%) and much less concern was expressed about the taste (10%).

Population study results

Background information and opinions

In total, 132 residents of the Limassol municipality answered the questionnaire and agreed to water collection from their households' main tap. The distribution of the study participants by quarter and the population can be found in Table S1. The mean age was 45.6 years and the majority were females (62.1%). Most of the participants were born in Cyprus (*n* = 114 (86.4%)) living there for all their lives (Table 2; Table S4).

Most of the study participants reported being in very good or good health condition (46% and 43%, respectively). However, 21% reported having a chronic disease and 57% reported at least one of the following health conditions during the past year: asthma,

Table 3 Health status indicators assessed through the questionnaire among the 132 participants of the urban population study (Limassol, Cyprus).

	Overall (n = 132)
General health assessment (%)	
Very good	61 (46.2)
Good	57 (43.2)
So and so	12 (9.1)
Bad	1 (0.8)
Very bad	1 (0.8)
Chronic disease (%)	
Do not know	5 (3.8)
I don't want to answer	3 (2.3)
No	97 (73.5)
Yes	27 (20.5)
Any disease in the past year (%)	
No	57 (43.2)
Yes	75 (56.8)

cardiovascular diseases, hypertension, diabetes, liver conditions, cancer, depression, or musculoskeletal problems (Table 3). In regard to access to health care, the main questions were about delays due to lack of transportation or long waiting lists (Table S5). Lack of transportation did not seem to be a major constraint to access health care centers among those that opted to answer; however, long waiting lists were reported by 11%. To the question about financial constraints for health care access, delays in dental care were most frequently mentioned (14%). Most participants (64%) reported living close to green spaces, but a total of 63% also reported that these green spaces were not well-maintained and there was a consensus for not using them. A summary of the responses about health care access, lifestyle, the quality of life in the neighborhood and other urban topics can be found in Table S5.

Water quality indicators assessment of drinking water habits

The main chemical water quality indicators assessed were THM. Only 2% of the households' tap water exceeded the THM parametric value (100 μg/L). Results conforming with the parametric values were also obtained for the microbial indicators monitored, that is, *E.coli* and *Enterococci* spp. All samples were within the parametric values (zero CFU per 100 mL), except for one household where Enterococci colonies were detected. Total coliforms were detected in 28 of the 132 households and *P. aeruginosa* counts were detected in five out of the 132 households (Tables 4 and 5).

The drinking-water consumption habits reported by the urban participants similarly reflected what was already observed in the perceptions study (presented earlier) where only 30% reported consuming tap water and most participants reported a preference for other sources (Table 6). The majority reported using tap water in general, however bottled water use was noted by most respondents. The more frequently reported single drinking water source was bottled water (30%) followed by tap water (22%). A comparable proportion of

Table 4 Chemical drinking water parameters analyzed in water samples collected in Limassol, Cyprus (2017) for $n = 119$ samples collected from faucets without point of use filter and for $n = 13$ samples collected from faucets with a point of use filter that could not be removed.

Samples collected from faucets without filter

	n	Mean	Standard deviation	Median	25th percentile	75th percentile	Min	Max
Regulated chemical parameters								
Total THMs (μg/L)	119	30.5	32.22	15.2	6.99	50.83	3.17	210.5
Non-regulated chemical parameters								
Free chlorine (mg/L)	119	0.2	0.16	0.2	0.05	0.32	ND	0.7
TCM (μg/L)	119	2.1	2.24	1	0.47	3.16	0.07	13.3
BDCM (μg/L)	119	4.9	5.45	2	0.95	7.32	0.91	30.9
DBCM (μg/L)	119	9.1	11.18	2.4	1.18	15.52	1.07	66.2
TBM (μg/L)	119	14.4	14.63	7.7	3.94	22.6	0.06	100.3
BrTHMs (μg/L)	119	28.4	30.24	13.5	6.22	46.94	3.10	197.3

Samples collected from faucets with filter

	n	Mean	Standard deviation	Median	25th percentile	75th percentile	Min	Max
Regulated chemical parameters								
Total THMs (μg/L)	13	9.6	9.0	5.0	4.0	9.9	3.2	28.4
Non-regulated chemical parameters								
Free chlorine (mg/L)	13	0.1	0.1	0.1	0.0	0.1	ND	0.3
TCM (μg/L)	13	0.9	1.0	0.5	0.5	0.7	0.2	3.8
BDCM (μg/L)	13	1.7	1.7	1.0	0.9	1.1	0.9	5.8
DBCM (μg/L)	13	2.1	2.4	1.2	1.1	1.5	1.0	9.5
TBM (μg/L)	13	4.9	6.7	2.2	1.2	5.2	1.0	25.4
BrTHMs (μg/L)	13	8.7	8.5	4.7	3.5	9.4	2.9	28.0

the participants reported the combined use of tap water and bottled water (Table 6). More than half of the study partipants reporting consuming less than one glass of water per day from the tap (median number of glasses consumed from tap was one glass/day) (Table 6).

Mapping of urban indicators of water and quality of life

The measured water quality indicators in each household were aggregated and mapped by quarter. For the chemical water parameters, the mapped median total THM and the brominated species (BrTHM) by quarter showed similar patterns (Fig. 2). As the BrTHM are a subset of the total THM, their median values by quarter were lower. The highest median THM values were observed in the quarters located between the beachfront and the northern quarter of Agia Fylaxi (near the center of the city). Mapping of free chlorine levels followed an opposite pattern to THM, that is, higher levels of free chlorine in the seaside quarters and slightly higher in the northern quarter (being closer to the main water treatment plant). The maximum median value of total THM was 63 μg/L and it was observed in the center of Limassol (quarter of Agios Georgios). In this quarter, the median free chlorine levels were below detection. The range of the median total THMs by quarter was 6–63 μg/L for the small quarters in the beachfront and behind the city port and the

Table 5 Microbial drinking water parameters analyzed in water samples collected in Limassol, Cyprus (2017) for $n = 119$ samples collected from faucets without point of use filter and for $n = 13$ samples collected from faucets with a point of use filter that could not be removed.

Samples collected from faucets without filter	*n*	Samples with at least one CFU *n* (%)
Regulated microbial parameters		
E. coli (cfu per 100 mL)	119	0 (0)
Enterococcus spp. (cfu per 100 mL)	119	1 (0.8)
Non-regulated microbial parameters		
Coliforms (per 100 mL)	119	27 (22.7)
Pseudomonas aeruginosa (per 100 mL)	119	5 (4.2)
TVC at 22 °C (per one mL)	86	12 (14)
TVC at 37 °C (per one mL)	86	30 (34.9)
Samples collected from faucets with filter	*n*	**Samples with at least one CFU *n* (%)**
Regulated microbial parameters		
E. coli (cfu per 100 mL)	13	0 (0)
Enterococcus spp. (cfu per 100 mL)	13	0 (0)
Non-regulated microbial parameters		
Coliforms (per 100 mL)	13	1 (7.7)
Pseudomonas aeruginosa (per 100 mL)	13	0 (0)
TVC at 22C (per one mL)	7	1 (14.3)
TVC at 37C (per one mL)	7	3 (42.9)

quarter of Agios Georgios. The variability of the median free chlorine levels was smaller, ranging from below detection to 0.4 mg/L in the quarters of Agia Zoni and Agia Trias (in the center and by the seafront, respectively). A map with the quarter names of municipality of Limassol is available in Supplementary Information (Fig. S1).

With regards to the microbial parameters, as mentioned in the previous section, only one sample had detectable colonies of *Enterococcus* spp. while *E. coli* was not detected at all. Thus, we mapped only the percentage of samples found to be positive for coliforms or had detectable heterotrophic bacteria (TVC at 22 and 37 °C) (Fig. 3). In a one quarter, two of the three samples analyzed were positive for coliforms and, therefore, it had the highest percentage of samples with colonies. This quarter was geographically located in the zone with the highest median chlorine levels (0.3 mg/L) (Figs. 2 and 3).

Description and mapping of access to health care services, life in the neighborhood and use of green spaces

With regards to access to health care, most participants reported having issues with two major parameters, that is, long waiting lists and financial constraints to access dental care. From the respective maps (Fig. 4), participants living in the quarters of Katholiki, Agia Trias, Omonoia, and Agios Nektarios did not report any issues pertaining to access to

Table 6 Self-reported choices of water sources by the study participants ($n = 132$) of the urban population study in Limassol, Cyprus.

Water sources				n (%)
Bottled water				40 (30.5)
Tap water				29 (22.1)
Water from vending machines				4 (3.1)
Spring water				3 (2.3)
Tap water and bottled water				37 (28.2)
Bottled water and spring water				3 (2.3)
Bottled water and water from vending machines				2 (1.5)
Tap water and other				2 (1.5)
Tap water and water from vending machines				2 (1.5)
Tap water and spring water				1 (0.8)
Any three sources (tap water, bottled, water from vending machines, spring water or other)				5 (3.8)
Number of glasses (about 250 mL) per day by source	**n**	**Mean**	**SD**	**Median**
Tap water	130	2.52	3.6	0
Bottled water	130	3.83	4.2	2.2
Water from vending machines	130	0.54	2	0
Spring water	130	0.33	1.3	0
Other source	130	0.51	2.9	0

health care. Whereas, other quarters such as Agios Ioannis/Arnaoutogeitonia, Agia Zoni, and Agios Nikolaos were more consistently in the "mid-range" with 20% participants reporting issues for both indicators. With regards to the question about having someone in the neighborhood to ask for help in emergencies, overall, only 25/132 participants opted for the answers "I don't know" and "I disagree completely or probably" (Fig. 5). However, responses of strong agreement ("I completely agree" vs all the other options from "I probably agree" to "I completely disagree") varied a lot across the quarters. For example, in Agios Spyridonas only 20% agreed that there is always someone to help them while in Agios Nikolaos 80% (Fig. 5). With regards to proximity and use of green space, most participants from all quarters reported that they agree living near to green space but they do not use it for activities (Fig. 6). This is evident in quarters by the seafront and the largest quarter of Agia Fylaxi/Panagia Evangelistria which is peripheral to the city the center and closer to less densely populated areas.

Exploring environment-wide associations within the municipality of Limassol

A correlation plot between all variables used in the EWAS analysis (listed in Table S2) did not show any specific or unexpected patterns of correlation among the urban variables (Fig. 7). Notable correlations were observed among different variables of the same block/group. All THM compounds in drinking-water correlated well with each other and they were negatively correlated with free chlorine levels. Additionally, strong correlation was observed among the household cleaning variables (mopping, dishwashing and bathroom cleaning). The variables of the "cleaning" block/group

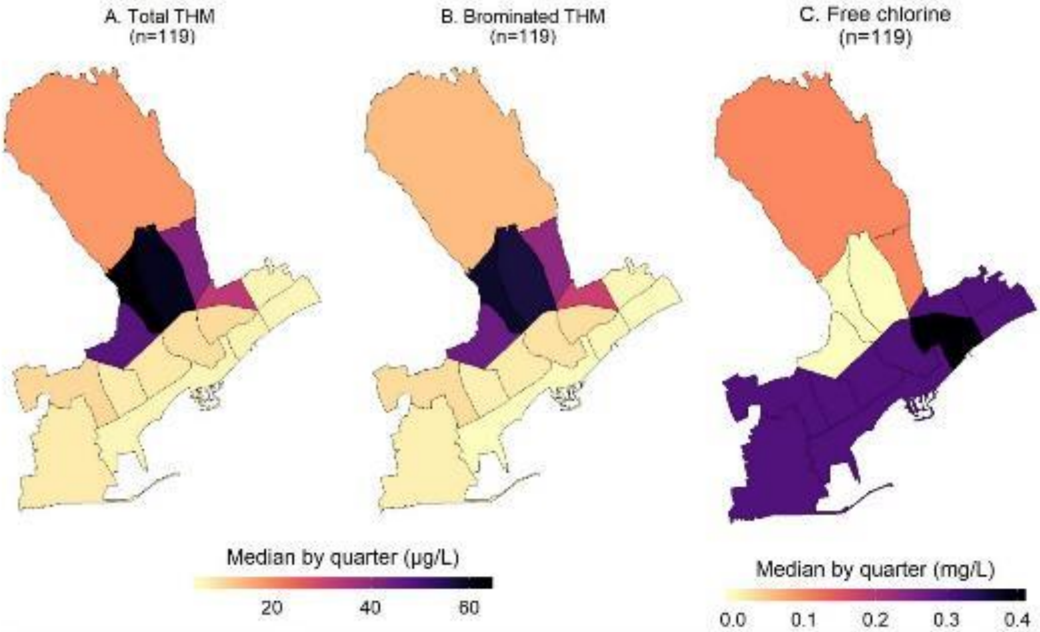


Figure 2 Maps of the median water total THM (A), BrTHM (B), and free chlorine (C) levels by quarter within the municipality of Limassol, Cyprus (2017).
Full size DOI: 10.7717/peerj.6851/fig-2

(block/group 3) correlated also with certain health conditions, such as musculoskeletal problems (neck problems).

In the regression part of the EWAS analysis, a total of 129 predictors were summarized from the simple models and 123 predictors were used in the models adjusted for age and sex. These predictors include both parameters measured in water, that is, THM, and questionnaire responses (summarized in Table S2). In the models adjusted for age and sex, four parameters had an FDR-corrected p-value < 0.1, that is, financial issues in access to dental care, depression, hypertension, and asthma. Having encountered financial issues in access to dental care (n = 18, (14.1%) participants) and depression (n = 3, (2.8%) participants) were statistically significant negative predictors for better general health status, while higher odds of having a chronic disease were associated with hypertension and asthma (n = 19, (16.2%) and n = 10, (8.5%) participants, respectively). In the univariate regression, in addition to the parameters that were significant in the adjusted models, musculoskeletal problems (i.e., neck and back problem) were associated with higher odds of having a chronic disease but not with the outcome of general health status. The parameters ranked by the FDR adjusted p-value can be found in Table S6.

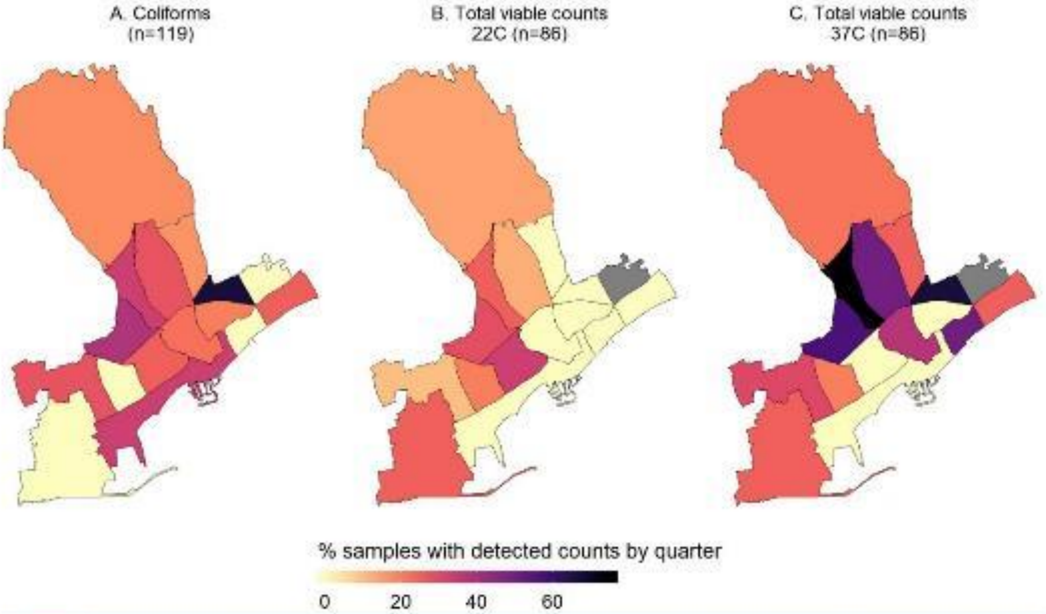


Figure 3 **Maps of the percentage of samples with detectable counts of the monitored microbial parameters, i.e. Coliforms (A), and total viable counts at 22 (B) and 37C (C), by quarter within the municipality of Limassol, Cyprus (2017).** Full-size DOI: 10.7717/peerj.6851/fig-3

The results of the second EWAS analysis and the correlation between the variables used in the PLS-DA models were summarized in the circular plots (circo plots) of Fig. 8. Again, all three outcomes were used; however, the model for the chronic disease did not converge and thus the plot is not presented. For the other two outcomes the associations between the variables were not the same, as expected due to the difference in the outcomes between the two models. The THM variables correlated with each other and with the household cleaning activities (i.e., dishwashing, mopping, bathroom cleaning) as it was also shown in the simple correlation plots. The correlations were less in number when the outcome was "any disease the past year" compared to the correlations visualized in the circo plot of the "general health" as an outcome. Additionally, different levels of the predictor variables were noted depending on the outcome, as it can be seen by the lines on the outside perimeter of the circular plot. These lines, however, were not used for interpretation due to the study's exploratory nature to avoid any misleading inferences.

DISCUSSION

In this proof of concept study of the urban exposome, we used an interdisciplinary approach to identify trends in perceptions about environmental exposures and how they

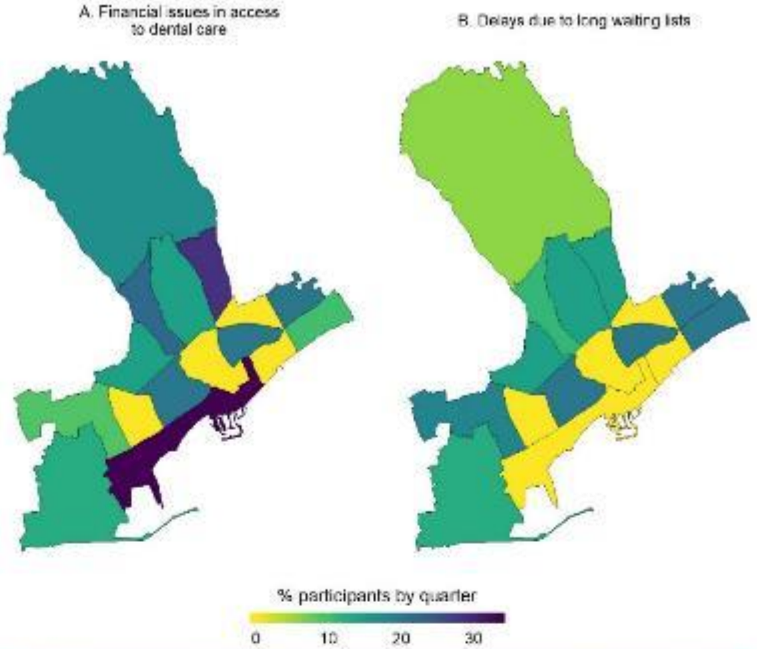


Figure 4 Percentage of study participants reporting constraints in access to health care, i.e. financial issue in access to dental care (A) and delays due to long waiting lists (B), by quarter of the Limassol municipality, Cyprus (2017). Full-size DOI: 10.7717/peerj.6851/fig-4

correlated with the spatially-resolved drinking-water quality trends of chemical and microbial indicators for the municipality of Limassol during the hot season (summer). Quality of life indicators (e.g., access to green spaces, the life in the neighborhood and reasons for delay or financial constraint in access to health care) were mapped at the level of the quarter (smallest administrative unit). No clear disparities at the quarter level were observed for all neighborhood-based queries, but financial constraints, especially for dental care were noted. Additionally, we generated global linkages and correlations between the health status of urban participants and their environmental/lifestyle/behavioral exposures at the individual level. A total of 129 parameters from 36 variables either directly measured in water (water quality) or derived from the survey (quality of life in the city) were integrated using an exploratory, agnostic, exposome-based EWAS approach. The general health and chronic health status of the urban participants were significantly associated in regression analysis with different health outcomes (e.g., hypertension, asthma) and quality of life indicators (e.g., financial issues in access to dental care). Circular correlation plots were derived from 36 urban exposome variables which were divided in six groups and accounted for self-reported health indicators

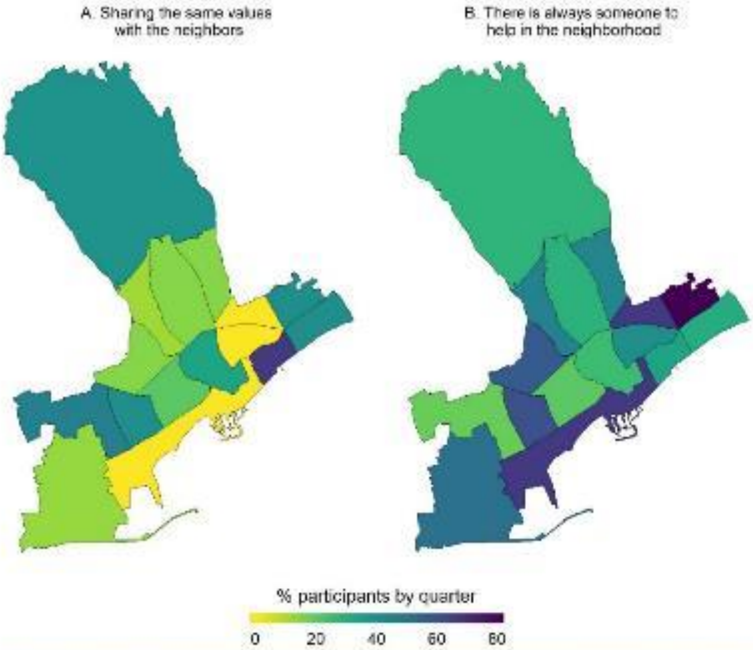


Figure 5 Percentage of study participants agreeing with different statements about life in the neighborhood, i.e. on sharing the same values with the neighbors (A), and whether there is someone to help in the neighborhood (B), by quarter of the Limassol municipality, Cyprus (2017).
Full-size DOI: 10.7717/peerj.6851/fig-5

(general health and having any diseases the past year). This study is an application of the urban exposome framework and the first to generate a snapshot of the actual urban exposome of Limassol, Cyprus, with a focus on water and quality of life indicators.

Urbanization, migration and other drivers of societal changes in urban settings are shaping population health and quality of life in cities leading to interventions such as the large scale neighborhood renewal programs that aim to improve living conditions and quality of life in cities (*Kramer et al., 2017*). The impact of such neighborhood-based programs could be enhanced with the comprehensive assessment of environmental, economic, societal, and other health parameters in the city. Within the context of improving urban life, novel paradigms such as the exposome can be adapted to provide a more interdisciplinary approach in tackling urban problems. The urban exposome can be viewed simply as the totality of environmental exposures occurring in cities (*Probst-Hensch, 2017*; *Robinson et al., 2018*). However, this definition is rather centered on individuals and it does not include wider determinants of urban health. For example, a recent study described the human exposome in city-based cohorts and focused on specific exposure-effect associations in one or multiple cohorts being pooled together

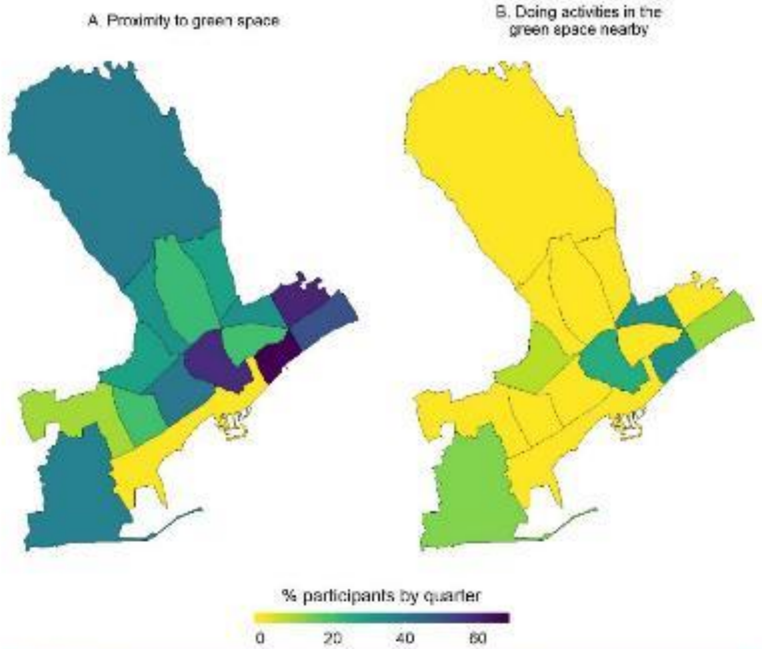


Figure 6 Maps by quarter of the percentage of study participants within the quarters of Limassol municipality, Cyprus (2017) agreeing that they live in close proximity to green space (A) and they do activities in the green space nearby (B). Full-size DOI: 10.7717/peerj.6851/fig-6

(*Robinson et al., 2018*). In this study, we propose a novel approach using the urban exposome as a study framework to describe systematically how broader urban characteristics can be evaluated with an interdisciplinary methodology. Thus, we have placed the city and its smaller areas as the measurable units in the center of this exposome approach. Moreover, we have used the perceptions and the urban population study as two sources of information that can be summarized to provide a snapshot of the urban exposome of Limassol focused on water and quality of life.

The case of water pollution and the provision of safe and clean water to urban dwellers presents one of the most challenging elements to be incorporated within the urban exposome framework. This might be due to the complex systems that drive water quality and water choices given also the aging water infrastructure in urban settings. These challenges are also evident in the literature and in studies of water quality indicators but their links with the exposome are scarce. To our knowledge, the literature in exposome approaches to evaluate water quality is limited and it has not focused on the urban environment or the general population. For example, using an environment-wide association study methodology, the pregnancy exposome study on the INMA-Sabadell

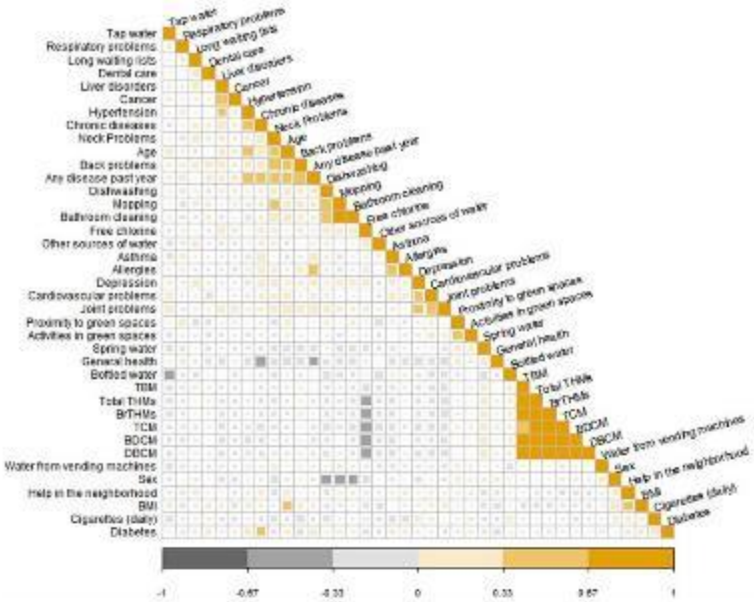


Figure 7 **Correlation plot (Spearman correlation coefficient) for all the variables used in the environment-wide association exploratory analysis.**
Full-size DOI: 10.7717/peerj.6851/fig-7

Birth Cohort in Spain looked into modeled at the individual level water disinfection byproducts (THM), among a wider set of other exposures ranging from urinary markers of chemical exposures to air pollution and noise (*Robinson et al., 2015*). They showed that the three THM "classes" studied (total and brominated THM, and chloroform) were strongly correlated with each other, but not with the other environmental exposures (*Robinson et al., 2015*). *Albouy-Llaty et al. (2016)* explored the association between endocrine disruptors (atrazine metabolites and nitrate/atrazine mixture) in drinking water and preterm birth accounting for socioeconomic factors (deprivation index) in the Poitou-Charentes region of France (*Albouy-Llaty et al., 2016*). The exposure to atrazine and the nitrate/atrazine mixture at the individual level was inferred from routine community monitoring of water quality; preterm birth was found to be associated with the deprivation index at the level of the neighborhood but not with the exposure to atrazine metabolites. Exposure to atrazine (measured through the metabolite 2-hydroxyatrazine) was not found to be a significant risk factor for preterm birth when accounting for the socioeconomic status of the area (*Albouy-Llaty et al., 2016*).

This is the first application of the urban exposome framework that took place in a medium-sized European city, Limassol, Cyprus. We used an agnostic approach following the urban exposome framework and we described water quality indicators at the level of

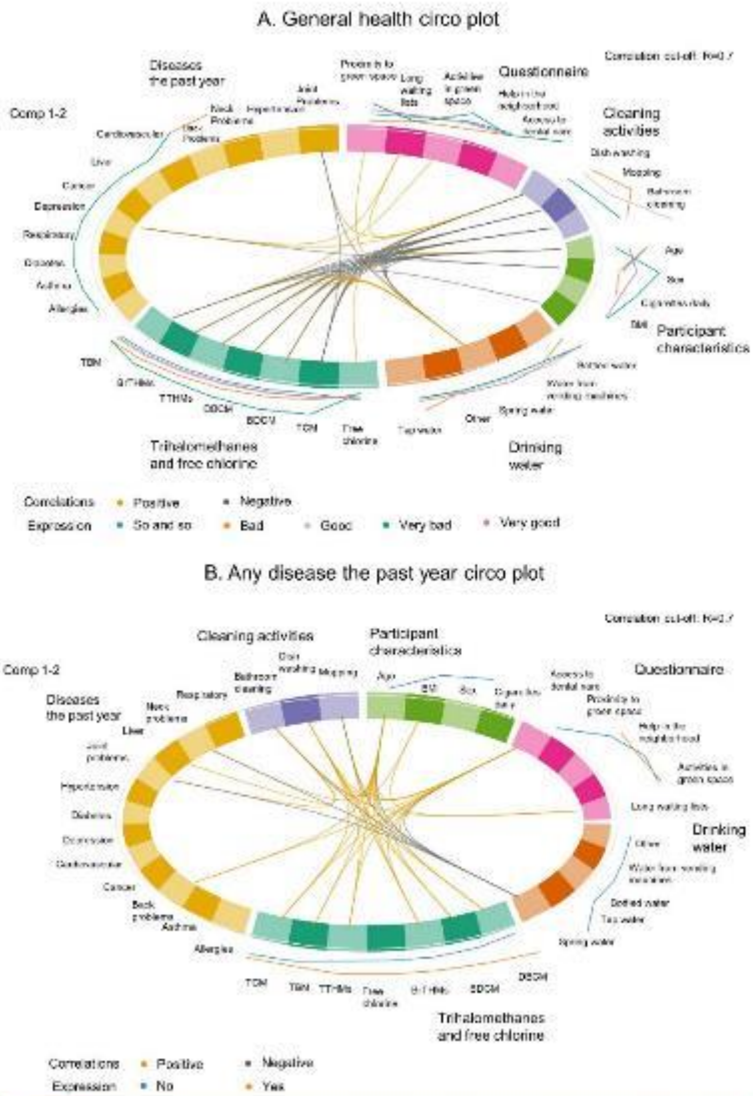


Figure 8 Circular plots of the correlations between the variables used in the environmental-wide analysis by block/group of variables accounting for general health (A) and any disease the past year (B).
Full-size DOI: 10.7717/peerj.6851/fig-8

quarter (the smallest administrative area within a municipality), accounting for urban, general population characteristics and additionally including the opinions/perceptions of residents and municipality technical stakeholders. The analysis included a suite of water quality aspects (chemical and microbial) which belong to the internal domain of the urban exposome and the specific external domain of the human exposome, and stakeholders' opinions about environmental issues (specific external urban exposome and general external human exposome). Moreover, quality of life was assessed through citizens' answers about access to healthcare and green spaces, and it was included along with lifestyle/behavior, and demographics in the EWAS analysis. This analysis is part of developing the urban exposome profile of Limassol and provides a snapshot of the state of the city, which will be combined with analysis of routinely collected data.

As mentioned before, our study aimed to provide a methodological approach in a relatively small city. Therefore, the generated associations of different participant characteristics and quality of life indicators with general health or with having a chronic disease in the EWAS study should be interpreted with caution due to the lack of adequate statistical power. In our case, the EWAS analysis is limited by the data at hand but, it is more of exploratory nature, as it is a part of this proof of concept study. Previous EWAS-exposome studies have been broader, with larger sample sizes, and, thus, more power (*Patel & Manrai, 2014*).

One observation that stood out in the correlation analysis is the negative association of water THM with cleaning activities. Previous studies have shown positive correlations between cleaning activities and urinary THM levels, and not between water THM levels and cleaning activities (*Charisiadis et al., 2014*). However, our observation, taking into consideration previous work on the exposure assessment to disinfection byproducts (*Güngler et al., 2018*), indicates the complexity of exposure assessment using environmental measurements as proxies of exposure, especially in EWAS studies. The inclusion of the perceptions study in developing the urban exposome profile of Limassol, with the use of a qualitative and quantitative approach allowed important community concerns about their urban life to surface. Air pollution was ranked as the most significant concern among the study respondents. Besides the general interest of air pollution and its health effects, Cyprus experiences frequent dust storms (*World Health Organization, 2018*; *Achilleos et al., 2014*). These events have probably triggered a specific concern among the population making air pollution the most frequently reported environmental concern in our study. Overall, the results presented here, should be interpreted with caution because of limitations in the study design (i.e., the cross-sectional design) and the small sample size or possible sampling bias (especially in the perceptions study).

This proof-of-concept study aimed to showcase the utility of the urban exposome framework in a urban study setting extending the continuum of the human exposome concept, thus, providing the methodological background for future studies. We were able to demonstrate the use of different tools in an integrative and interdisciplinary approach to capture the baseline urban exposome of Limassol municipality in this case. The same approach can be generalized. For example, if applied to other urban dwellings with bigger sample, it will allow us to scale up the application of such integrative and multidisciplinary protocols and will allow for the wider transfer and generalizability of the results. Future studies should also incorporate a more comprehensive assessment of urban quality of life (*Serag El Din et al., 2013*). In this analysis, the indicators of quality of life were limited to life in the neighborhood or the use of green space and the questionnaires were based on indicators previously assessed in larger urban studies which had not included Cypriot cities (*European Urban Health Indications System Part 2, 2012*; *Pope et al., 2016*). Additional information about social life is available from this study population and it will be incorporated the urban exposome of Limassol. Next steps will incorporate the analysis of routinely collected data of the registries and human biomonitoring analyses in a more complete characterization of the urban exposome in Limassol city. Moreover, given the "stakeholders" assessment of environmental problems, we have moved on with air quality measurements throughout the municipality, which were conducted in the spring of 2018 while we explore how the routinely collected data from the one governmental station for air quality measurements can be also included. This study shows how the goal of developing the urban exposome framework can be achieved by using all the available information in a real-time assessment of urban health and provide a tool for decision-making to stakeholders.

Our analysis did not raise any specific concerns about the quality of tap drinking water at the urban quarter scale of Limassol city using both chemical and microbial indicators. It was shown however, that residents do not trust, in general, the tap water and opt for using bottled water or water from other sources such as the "vending machine" water (groundwater from mountainous wells) which is very common practice in Cyprus. The cost of tap water is lower compared to bottled or "vending machine" water, and thus not using tap water may pose additional burden to household budgets, as it has been shown in other studies (*Massoud et al., 2013*). Mapping the cost of water by quarter would likely be informative about the existence or not of differences within Limassol in the economic burden of water consumption. Urban green space was particularly noted for being close to participants' households; however, limited use of such green spaces (e.g., parks) was reported. Both aspects of access to health care and the use of green spaces within Limassol, were studied for the first time. Our approach could form the basis for future targeted and more integrative urban studies on these topics.

In general, our first results on the application of the urban exposome are promising and in need for verification and expansion. First and foremost, given the different habits of the citizens, exposome studies need to be more inclusive in the assessment of different water sources. Besides the inclusion of standard water testing parameters, future studies should address participant perceptions which are linked to behaviors, and, thus, exposures. Developing the health profile of a city in urban exposome terms and integrating different approaches comes with several limitations. Spatio-temporal considerations should be accounted for in the dynamic nature of urban exposome profiling. Although enough to estimate the background levels of population exposures to chemicals, the relatively small sample size might have not allowed us to capture spatial differences of the indicators measured within the smaller city administrative units. Additionally, the lack of biomonitoring data on water-related exposures (i.e., to disinfection byproducts in urine) have hindered the full deployment of EWAS tool capabilities. However, the availability of urine biospecimen for this survey will allow us to use biomonitoring and untargeted metabolomics tools in a follow-up manuscript.

CONCLUSIONS

Developing sustainable city health profiles with the aid of the urban exposome framework is a novel approach, yet, far from being simple or reductionistic in approach. It demands a comprehensive characterization of relevant indicators ranging from drinking water quality to health perceptions and opinions collected from the general population and technical stakeholders, etc. The urban exposome framework and its application will pave the way for developing the next innovative solutions and public health interventions for the city. This proof of concept case study of the urban exposome in Limassol, Cyprus demonstrates the feasibility of using novel exposome approaches in studying the city and its smaller within-city areas (quarters) as the units of reference. Within this context, the absolute water quality indicators, city residents,' and other stakeholders' opinions need to be integrated and expanded along with exposomic profiles, such as metabolomics or other -omics platforms and human biomonitoring protocols.

Thus, we need to develop specific urban exposome studies where city-specific characteristics and within-city interactions and networks, can be used to redefine city health profiles. Evidence-based and city-specific studies will help authorities reach informed decisions about everyday life, about city infrastructure changes and their effects on urban health and personal exposures. This will help the interpretation of inter-city difference and will allow the timely evaluation of within-city challenges.

ACKNOWLEDGEMENTS

We would like to thank the Municipality of Limassol and all the study participants. Special thanks to Ms. Andriana Till for her contribution to participant recruitment and to Dr. Stephanie Gaengler for the fruitful discussions during data analysis. We would also like to express our gratitude to Drs. Athos Agapiou and Diofantos Hadjimitsis for sharing the map templates for the quarters of Limassol.

ADDITIONAL INFORMATION AND DECLARATIONS

Funding

The study was conducted with internal funding provided by Konstantinos C. Makris. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Grant Disclosure

The following grant information was disclosed by the authors:
Internal funding provided by Konstantinos C. Makris.

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

- Xanthi D. Andrianou conceived and designed the experiments, performed the experiments, analyzed the data, contributed reagents/materials/analysis tools, prepared figures and/or tables, authored or reviewed drafts of the paper, approved the final draft.
- Chava van der Lek performed the experiments, analyzed the data, prepared figures and/or tables, approved the final draft.
- Pantelis Charisiadis performed the experiments, approved the final draft.
- Solomon Ioannou performed the experiments, approved the final draft.
- Kalliopi N. Fotopoulou performed the experiments, approved the final draft.
- Zoe Papapanagiotou performed the experiments, approved the final draft.
- George Botsaris performed the experiments, approved the final draft.
- Carijn Beumer contributed reagents/materials/analysis tools, approved the final draft.
- Konstantinos C. Makris conceived and designed the experiments, analyzed the data, contributed reagents/materials/analysis tools, authored or reviewed drafts of the paper, approved the final draft.

Human Ethics

The following information was supplied relating to ethical approvals (i.e., approving body and any reference numbers):

The study was approved by the National Bioethics Committee of Cyprus (decision number: 2017/23).

Data Availability

The following information was supplied regarding data availability:

Raw data are available in the Supplemental Files.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.6851#supplemental-information.

REFERENCES

Achilleos S, Evans JS, Yiallouros PK, Kleanthous S, Schwartz J, Koutrakis P. 2014. PM10 concentration levels at an urban and background site in Cyprus: the impact of urban sources and dust storms. *Journal of the Air & Waste Management Association* **64(12)**:1352–1360 DOI 10.1080/10962247.2014.923061.

Albouy-Llaty M, Limousi F, Carles C, Dupuis A, Rabouan S, Migeot V. 2016. Association between exposure to endocrine disruptors in drinking water and preterm birth, taking neighborhood deprivation into account: a historic cohort study. *International Journal of Environmental Research and Public Health* **13(8)**:796 DOI 10.3390/ijerph13080796.

Andra SS, Austin C, Wright RO, Arora M. 2015. Reconstructing pre-natal and early childhood exposure to multi-class organic chemicals using teeth: towards a retrospective temporal exposome. *Environment International* **83**:137–145 DOI 10.1016/j.envint.2015.05.010.

Andrianou XD, Makris KC. 2018. The framework of urban exposome: application of the exposome concept in urban health studies. *Science of the Total Environment* **636**:963–967 DOI 10.1016/j.scitotenv.2018.04.329.

Becker K, Seiwert M, Casteleyn L, Joas R, Joas A, Biot P, Aerts D, Castaño A, Esteban M, Angerer J, Koch HM, Schoeters G, Hond ED, Sepai O, Exley K, Knudsen LE, Horvat M, Bloemen L, Kolossa-Gehring M. 2013. A systematic approach for designing a HBM Pilot Study for Europe. *International Journal of Hygiene and Environmental Health* **217(2–3)**:312–322 DOI 10.1016/j.ijheh.2013.07.004.

Buck Louis GM, Smarr MM, Patel CJ. 2017. The exposome research paradigm: an opportunity to understand the environmental basis for human health and disease. *Current Environmental Health Reports* **4(1)**:89–98 DOI 10.1007/s40572-017-0126-3.

Charisiadis P, Andra SS, Makris KC, Christodoulou M, Christophi C, Kargaki S, Stephanou E. 2014. Household cleaning activities as noningestion exposure determinants of urinary trihalomethanes. *Environmental Science & Technology* **48(1)**:770–780 DOI 10.1021/es404220z.

Charisiadis P, Andra SS, Makris KC, Christophi CA, Skarlatos D, Vamvakousis V, Kargaki S, Stephanou EG. 2015. Spatial and seasonal variability of tap water disinfection by-products within distribution pipe networks. *Science of the Total Environment* **506–507**:26–35 DOI 10.1016/j.scitotenv.2014.10.071.

Cui Y, Balshaw DM, Kwok RK, Thompson CL, Collman GW, Birnbaum LS. 2016. The exposome: embracing the complexity for discovery in environmental health. *Environmental Health Perspectives* **124(8)**:A137–A140 DOI 10.1289/EHP412.

Dai D, Prussin AJ, Marr LC, Vikesland PJ, Edwards MA, Pruden A. 2017. Factors shaping the human exposome in the built environment: opportunities for engineering control. *Environmental Science & Technology* **51(14)**:7759–7774 DOI 10.1021/acs.est.7b01097.

Escher BI, Hackermüller J, Polte T, Scholz S, Aigner A, Altenburger R, Böhme A, Bopp SK, Brack W, Busch W, Chadeau-Hyam M, Covaci A, Eisenträger A, Galligan JJ, Garcia-Reyero N, Hartung T, Hein M, Herberth G, Jahnke A, Kleinjans J, Klüver N, Krauss M, Lamoree M, Lehmann I, Luckenbach T, Miller GW, Müller A, Phillips DH, Reemtsma T, Rolle-Kampczyk U, Schüürmann G, Schwikowski B, Tan Y-M, Trump S, Walter-Rohde S, Wambaugh JF. 2016. From the exposome to mechanistic understanding of chemical induced adverse effects. *Environment International* **99**:97–106 DOI 10.1016/j.envint.2016.11.029.

EU Council. 1998. Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption. Brussels: EU Council.

European Urban Health Indications System Part 2. 2012. *EURO-URHIS. Available at https://web.archive.org/web/20190308170137/http://results.urhis.eu/Default.aspx?Code=YY&Group=B* (accessed March 2019).

Eurostat. 2017. *Statistics explained. Available at http://ec.europa.eu/eurostat/statistics-explained/index.php/Statistics_on_European_cities* (accessed 3 February 2017).

Gängler S, Makris KC, Bouhamra W, Dockery DW. 2018. Coupling external with internal exposure metrics of trihalomethanes in young females from Kuwait and Cyprus. *Journal of Exposure Science and Environmental Epidemiology* **28(2)**:140–146 DOI 10.1038/jes.2017.27.

Kramer D, Lakerveld J, Stronks K, Kunst AE. 2017. Uncovering how urban regeneration programs may stimulate leisure-time walking among adults in deprived areas: a realist review. *International Journal of Health Services* **47(4)**:703–724 DOI 10.1177/0020731417722087.

Massoud MA, Maroun R, Abdelnabi H, Jamali II, El-Fadel M. 2013. Public perception and economic implications of bottled water consumption in underprivileged urban areas. *Environmental Monitoring and Assessment* **185(4)**:3093–3102 DOI 10.1007/s10661-012-2775-x.

Ministry of Finance of the Republic of Cyprus. 2014. *Population census 2011. Available at http://www.mof.gov.cy/mof/cystat/statistics.nsf/census-2011_cystat_en/census-2011_cystat_en?OpenDocument* (accessed 9 September 2014).

National Research Council. 2012. *Exposure science in the 21st century: a vision and a strategy.* Washington, D.C.: The National Academies Press.

Patel CJ, Bhattacharya J, Butte AJ. 2010. An environment-wide association study (EWAS) on type 2 diabetes mellitus. *PLOS ONE* **5(5)**:e10746 DOI 10.1371/journal.pone.0010746.

Patel CJ, Manrai AK. 2014. Development of exposome correlation globes to map out environment-wide associations. In: Altman RB, Dunker AK, Hunter L, Ritchie MD, Murray TA, Klein TE, eds. *Biocomputing 2015.* Kohala Coast: World Scientific, 231–242.

Pope D, Puzzolo E, Birt C, Guha J, Higgerson J, Patterson L, Van Ameijden E, Steels S, Owusu MW, Bruce N, Verma A. 2016. Collecting standardised urban health indicator data at an individual level for adults living in urban areas: methodology from EURO-URHIS 2. *European Journal of Public Health* **27(Suppl_2)**:42–49 DOI 10.1093/eurpub/ckv220.

Probst-Hensch N. 2017. Happiness and its molecular fingerprints. *International Review of Economics* **64(2)**:197–211 DOI 10.1007/s12232-017-0269-4.

R Core Team. 2017. *R: a language and environment for statistical computing.* Vienna: The R Foundation for Statistical Computing. *Available at http://www.R-project.org/.*

Republic of Cyprus, Ministry of Finance. 2014. *European Health Interview Survey. Available at http://www.mof.gov.cy/mof/cystat/statistics.nsf/All/4DE6CF465BC4DDCAC2258068003729?OpenDocument&sub=3&sel=1&e=&print* (accessed 14 July 2018).

Robinson O, Basagaña X, Agier L, De Castro M, Hernandez-Ferrer C, Gonzalez JR, Grimalt JO, Nieuwenhuijsen M, Sunyer J, Slama R, Vrijheid M. 2015. The pregnancy exposome: multiple environmental exposures in the INMA-Sabadell birth cohort. *Environmental Science & Technology* **49(17)**:10632–10641 DOI 10.1021/acs.est.5b01782.

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, Dėdelė A, Donaire-Gonzalez D, Gražuleviciene 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, Basagaña X. 2018. The urban exposome during pregnancy and its socioeconomic determinants. *Environmental Health Perspectives* **126(7)**:77005 DOI 10.1289/EHP2862.

Rohart F, Gautier B, Singh A, Lê Cao K-A. 2017. mixOmics: An R package for 'omics feature selection and multiple data integration. *PLOS Computational Biology* **13(11)**:e1005752 DOI 10.1371/journal.pcbi.1005752.

Rojas P, Neutra R. 2008. Stakeholder and participant involvement. In: Baker D, Nieuwenhuijsen MJ, eds. *Environmental Epidemiology.* New York: Oxford University Press, 296–299.

RStudio Team. 2015. *RStudio: Integrated Development for R.* Boston: RStudio, Inc.. *Available at http://www.rstudio.com/.*

Samaniego L, Thober S, Kumar R, Wanders N, Rakovec O, Pan M, Zink M, Sheffield J, Wood EF, Marx A. 2018. Anthropogenic warming exacerbates European soil moisture droughts. *Nature Climate Change* **8(5)**:421–426 DOI 10.1038/s41558-018-0138-5.

Serag El Din H, Shalaby A, Farouh HE, Elariane SA. 2013. Principles of urban quality of life for a neighborhood. *HBRC Journal* **9(1)**:86–92 DOI 10.1016/j.hbrcj.2013.02.007.

Urban Development Overview. 2018. Washington, D.C.: World Bank. *Available at* http://www.worldbank.org/en/topic/urbandevelopment/overview#3 (accessed 9 July 2018).

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. 2007. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* **370(9596)**:1453–1457 DOI 10.1016/S0140-6736(07)61602-X.

World Health Organization. 2018. Health impacts. *Available at* http://www.who.int/airpollution/ambient/health-impacts/en/ (accessed 5 August 2018).

Wild CP. 2005. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiology Biomarkers & Prevention* **14(8)**:1847–1850 DOI 10.1158/1055-9965.EPI-05-0456.

Zhang XQ. 2011. *The economic role of cities*. Nairobi: United Nations Human Settlements Programme.