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Research

The Study of Interconnections Between Human Immune System and the Characteristics of Urban Landscapes

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Abstract | The concept of urbanism in the era of medicine and the interconnection between these two apparently separate territories of study dates back to more than seven decades ago. The reason for this research and the study of relationship of urban life elements with physical & mental health of citizens is due to the presence of frequent statistical and scientific data showing the higher rates of health disorders among the inhabitants of industrial cities and urban area compared to the sub-urban and rural places such as stress, mental disorders and autoimmune diseases. At the beginning of the twenties century by entering the term of urban-life to human encyclopedia, the concept and the potential impacts of it on different aspects of human life from public health to psychological disorders becomes highlighted. It is argued that these two discipline although have been arisen from a common root of industrial revolution at the early of 19th century, but they have been departed and there has been some divergence in master planning of these two disciplines in 20th century, since each were focusing on their own area, the urban planners on building environment and the public health specialists on the root cause of human diseases separately. Therefore the reuniting of these two disciplines is a new paradigm requires multidisciplinary approach such as “Health ecology” and “Health landscape” to redefine urban planning and public health by calling the professionals of these areas.

The research question raised here is that what type of relationship is there between human health, specifically his immune system, as a defense barrier against harmful factors on the one hand, and its environment, specifically in this study the "urban body", in which human as an urban user reside in it, on the other hand? And if there is a significant damage to the human body from its environment while transiting from this purely industrial and machine life to post-industrial life, what considerations do urban planners need to take into account in future urban structures to minimize the damage to physical and mental health of urban habitants or even to get close to zero damage?

Keywords | Exposome, Human Niche, Epigenetic, Human Immune System, Urban Health Landscape.

Introduction | With the emergence of a phenomenon called the Industrial Revolution, the components of human individual and social life underwent fundamental changes, so that his exposure to environmental factors changed from natural elements to artificial agents. As he transitioned from natural life to machine life, his sensory experiences of encountering natural elements such as "water" and "plant" that he used to meet in his non-industrial ecosystem daily, turned into the elements present in urban structures and their constituents such as metal and glass.

Apart from changing the visual experience of the modern man as a user of industrial life, his olfactory and tast-

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ing experiences have also been manipulated by absorption of chemicals from the activities of industrial plants, changing in his lifestyle and the low-value diet imposed by machine life.
Similarly, his hearing experience has turned into annoying sounds such as car horns and sound of industrial plants from what he used to hear as sounds of water and birds in his natural life. This changes in sensory experience of an urban habitant, by occupying all five human senses, collectively in the environmental sciences known as damaging environmental factors and studying their effects on human health, is known as 'health ecology', which in the 'urban landscape' science is regarded as undesirable urban elements or an unhealthy landscape, as in sustainable development approach efforts are being made to eliminate these factors and move towards maintaining a 'health landscape'. The effects of these environmental factors in biomedical interdisciplinary sciences are referred to as epigenetic factors[1]- or the set of environmental factors that lead to altered expression of the gene expression pattern.
According to numerous studies in the field of health, the statistics of autoimmune and inflammatory diseases in industrial cities and metropolitan areas are significantly higher than in suburban areas with more natural ecosystems(Cooper; Amorim; Figueiredo; Esquivel; Tupiza; Erazo; Oviedo; Vaca, & Barreto, 2015).
Given that the studies of past decades in the field of urban planning have generally been carried out without considering human factors and health priorities, and on the other hand the research studies on human diseases in the field of health, specifically in this study, the chronic complications as autoimmune diseases have similarly been implemented regardless of the environmental factor- as a whole, made up of multiple components, the specialists in areas of urban policymaking and planning, as well as in the area of public health, have been alert to the damages caused by urban life and its adverse impact on human physical and mental health. Increasing attention to this area in research atmospheres has called for experts in interdisciplinary fields such as 'healthy urban landscape' to recreate and design healthy spaces for urban people by incorporating the 'health ecology' considerations.
Due to the lack of interdisciplinary research in the field of 'environmental health' in metropolitan planning in the country, the main purpose of this paper is to specify the effective urban landscape elements that influence the human physical and mental health - specifically the immune system - and propose to incorporate them into the priorities of urban planners due to their impacts on the health of urban people. Therefore, calling for the integration of healthcare professionals with urban landscape planners in drawing metropolitan perspectives is of great importance in recent research studies around the world.
The significant statistics of health impacts on inhabitants in industrialized cities affected by the harmful components of urban environments and the presence of higher prevalence of diseases caused by industrial life style in these places, compared to more natural areas (Ibid), require integration of health policy making with urban planning.
In order to study how these factors may impact, it is necessary to address the key features of these two themes: the “urban health landscape” and the “human immune system” after redefining the keywords. The method of study is based on comparing the cell environment with that of the human body by generalizing the role governing the cell as a particle to human body as a whole. The pervasive environment of the human body is a defined space inscribed in a larger environment -called neighboring spaces-which is not infinite but rather its sensory radius varies along with changes of human body in time and place.

Defining the Environment and its driving role
In the acquisition of acquired traits

Theorizing about the effect of environment on living organism goes back two centuries in the history of biology. There have been many theoretical and practical debates about the effect of the environment on the alteration of the characteristics of living things from centuries ago in the field of biology. Jean Baptiste Lamarck[2] (1744-1829) 50 years before Darwin's theory believed that the environmental changes plays a vital role in altering the acquired attributes of organisms and proposed the theory of inheritance of acquired characteristics. However, the inheritance of acquired traits in the order that Lamarck believed was later questioned (Burkhardt, 2019). Half a century after Lamarck, British naturalist and author Charles Robert Darwin (1882-1809), in his theory of natural selection, later transformed into "modern theory of evolution", emphasized the role of the environment as a driving factor in the evolution of living organisms (Desmond, 2019). This article here will not deal with more detail on theories of environmental effect, and would end talking over the theories by pointing to the recent achievements of modern epigenetic science as a key witness of environment role in modifying gene expression patterns resulting in diverse acquired traits in organisms and especially humans.
Since the phenomena of "urban planning" and "public health" were considered as two major outcomes of industrial revolution, it is not far from topic to point to a key example of the role of environment in natural selection of organisms that in ancient biology texts it is referred to as

a classic example to illustrate the effect of natural selection and its driving force on animal population change.
On the eve of the Industrial Revolution, which began in the mid-eighteenth century and continued into the mid-nineteenth century, due to the presence of industrial plants in England, the trunk of the tree, which was a habitat of a peppered moth[3], changed from white to dark. This change made the white populations of moth to be decreased, which were higher prior to the Industrial Revolution, and the black moth population was started to increase due to camouflage in the black trunk of trees and less chance of predation (Cook & Saccheri, 2013), (Fig. 1).
Knowing that the environment has a direct effect on gene expression patterns of organisms and consequently on the expression of acquired traits, we consider the human environment as an influencing 'Niche' in altering his acquired traits and behavioral patterns, both in the physical and psychological dimensions; with this presumption the validity of proposed hypothesis will be examined.

• **Human Niche:** In biology, every living particle lives in its own environment: organelles in cells, cells in tissues, tissues in organs, organs in the body's internal environment and finally the human body, as a whole, in a space called the environment. It is widely accepted that the slightest change in the physical conditions of the environment in which the particle lives, such as pressure, temperature, humidity, and acidity, can affect the natural behavior of the particle. It is therefore plausible that any unintended change in the human environment as a whole would affect his natural behaviors and physiological correct functioning, especially as these adverse changes would affect human physics and mental health over a long period of time. Therefore, the added factor of time in long-term increases the unhealthy impact of environment on the health of citizens. The mentioned niche hypothetically is, a place with an irregular shape and a specific radius for each sensory perception, so that all the experiences of a citizen inscribed in it, from time to place, occur in the same niche; the specified niche in perfect urban condition, in the 'Utopia', turns into a Lotus shape, therefore all human sensory perceptions and social interactions, as a sixth dimension, are limited in specific shape and within their proper radius (Fig. 2). The counterpoint is an urban space in which one or more elements affecting the physical and mental health of citizens are out of standard, so the hypothetical shape of a healthy and standard niche in these places turns into an amorphous shape, according to Fig. 3; It shows one day of a hypothetical citizen from the point of origin (A), entering the workplace (C) and returning to the point of origin by passing through the public place of (B).

The human environment, as a whole com-

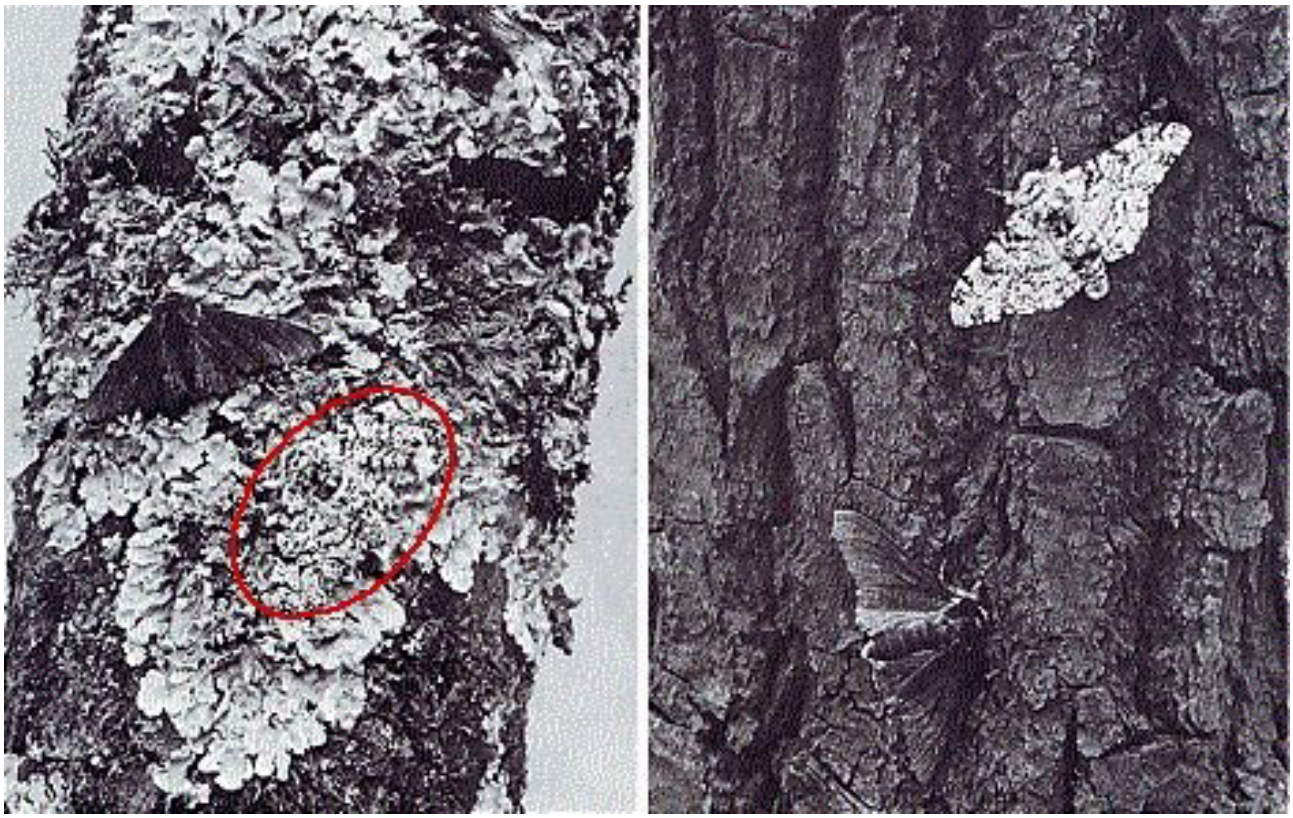

Fig. 1: Left, The camouflage of white peppered moth, Biston betularia on the light trunk of the trees, before the industrialization which led to an increase in the population of white moth. Right, the camouflage of black moth on the dark trunk of the trees which led to an increase in the population of black moth in consequence of selective predation of the white moth to a higher rate compared to black moth Arizona, blc, 2016.

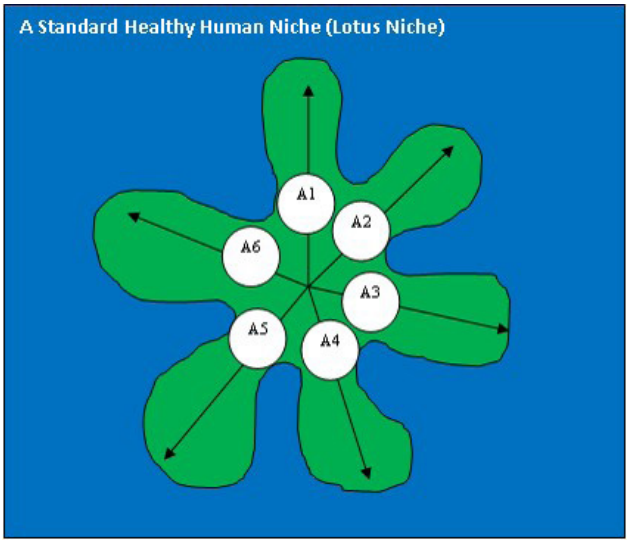

Fig. 2: A theoretical shape of standard healthy human niche (Lotus Niche) which proposes a healthy level of senses (five senses; A1: sight, A2: hearing, A3: smell, A4: touch, and A5: taste) plus a dimension which represent "social connection": A6, all together make a 6 petal lotus. Coincidentally, in the selected image of a Utopia, the water lilies covered the surface of the river passing through the Utopia. See the Figure (4). Source: Author. In Utopia, the lotus flowers in green color have covered the water element in blue color.
Note: The theoretical shape is drawn by author for the first time in this research journal ambiance/ The picture is drawn by illustration shapes in Microsoft Word accessible from Insert tab.

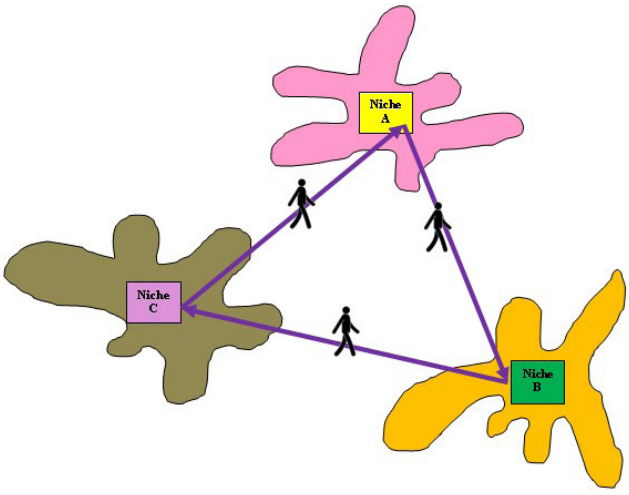

Fig. 3: An example of human urban journey from point of origin (A) to his/her activity area (C) via public location of (B). As the diagram shows a person who lives in an urban area can travels from his/her location or residency to a work place for example a factory/an industrial location- via traveling to a public place of B and get back to his point of origin. Comparing to the standard niche (lotus shape) we can see that some or all sensory elements are not at standard level. The summation of all sensory factors make one day of his experience in an urban area and effect on an urban habitant health condition. For example, his or her residence may be in the vicinity of an airport or highway, and the person may be exposed to noise pollution at rest, or his or her workplace may be in a noisy factory with industrial products with unhealthy inhalation condition. Therefore, the relative radius of the sensory niches is out of standard (a hypothetical idea has been drawn by the author in Microsoft Word accessible from Insert tab).

posed of the effective elements

The human environmental exposures, Exposome[5] , by considering the "element of time"

The space affecting the human body is an environment with dimensions of five human senses, an irregular shape ranges in the diameter extends to his hearing threshold (the presence of all audible sounds within the range of the human hearing threshold), as far as his field of vision – encompasses all visible elements around him. That is, to the extent that the human eye works - to the extent that its tactile sense touches the elements of the environment such as heat, cold, wind, water, humidity, pressure and acidity, giving access to particular foods to shape his taste experience as well . To this sensory experience, other elements such as exposure to other inhabitants should also be added as "social interaction".

The set of factors affecting the individual - from sensory experience to perceiving the location (including changing dimensions, sizes, shapes, and colors) and exposure to different people- is called "exposure", which is referred to in 'health ecology'. In other words, it is a set of environmental factors affecting the physics and mental of the human being that constitutes his one-day experience, which is called "the first-day experience of the environment" and represented by E_1.

The effect of the environment on creating a sensory experience for each person's day - here's a citizen - is the set of experiences of that day, plus the experiences of past days as long as the person remembers that experience, so if the set of factors affecting a person , on the first day of exposure to the environment (T_1), represent E1, the sum of the receipts on the second day, or E2, is the sum of the receipts on the second day, + the first day's set of experiences; $E_2=E\ (T_1+ (T_2-1))$, similarly, on the third day, the set of his perceives is equal to $E_3=E\ (T_1 + (T_2-1) + (T_3-2)$. Therefore, the human experience exposure to the environment on day 'N' is equal to:

Fig. 4: In one of the drawings by an artist for Utopia, drawn for the City of Sydney, the green-blue infrastructure is clearly visible and the lotus flowers are visible on the water surface. Source: Jenniferat, 2019.

$E_N = E\ (T_1 + (T_2\text{-}1) + (T_3\text{-}2) + \ldots + (T_N\text{-}(n\text{-}1))$

The number of 'N' varies for each person according to their age, and we all live on day 'N' with the exception of an infant has born today.

Which by definition, is equivalent to the experience of his present day composed of the received exposome from the environment plus the experiences of his past days to the farthest as he can remember. The ability to recall a person's past experiences is itself influenced by many factors such as age, gender, and genetics, which we call the short-term and long-term memory to avoid more complexity. Obviously, in people with dementia such as Alzheimer's, their perception of different environments and 'T_N' is equal to zero or zero, and is assumed to have a weaker immune system than the healthy one. The increasing impact of traumatic elements on human health in the city and the exponential role of time require comprehensive researches and further studies.

The necessity of an 'Urban Health Landscape'

There is a growing need around the world in designing a healthy environment for citizens of industrial cities, largely due to concerns about industrial life and its detrimental effects on the physical and mental health of citizens compared to more natural areas.

Interestingly, some molecules, for example collagen proteins that are one of the major constituents of connective tissue, in addition to known properties such as temperature, humidity, pressure, and acidity, are sensitive to direction changes, when compared to normal fibers and it loses its functionality if its fibers direction change its origin natural position. This physical property is called 'Anisotropy' and the molecules that have this property are called 'anisotropic' material in physics. In the physical environment, the elements such as glass and metal which are not susceptible to change in direction are called 'Isotropic' material that maintain their functionality in all directions, while wood and composites are anisotropic and lose their normal functionality along with change in direction. The reason for exemplifying this property is merely to illustrate the complexity of the behavior of elements that govern the environment and to reinforce its impact on the physical and mental health of citizens.

In the following lines with a quick definition of Immune system, the effect of urban landscape characteristics on this defensive system will be discussed.

Human Immune System and Its Function: It is one of the characteristics of the immune system to protect body in exposure to external damage factors. Acknowledging that changes in the immune system are not stochastic or under the influence of a set of random factors but rather is due to the influence of internal (genetic) and external (environmental) factors (Pollard; Hultman & Kono, 2010), the impact of environmental factors on the immune system will be discussed . According to scientific evidence, the influence of extrinsic (epigenetic) factors on the formation of the immune system is even more important than genetic factors (Anaya; Ramirez-Santana; Alzate; Molano-Gonzalez & Rojas-Villarraga, 2016).

Relationship between the immune system and epigenetics: the research studies have shown that autoimmune disease that targets the immune system, in addition to internal factors and genetic patterns, is strongly influenced by environmental and extrinsic factors (Pollard et al., 2010). It is argued that the effect of environmental factors on immune system formation is far more than genetic factors and is significantly dependent on the set of factors known as the "exposome" that encompasses all the internal and external factors affecting human health. The effect of environmental factors and their impact on human health and the immune system is in the field of knowledge called "Autoimmune ecology" that examines immune responses to environmental elements. Epigenetic factors within the cell are influenced by a number of intrinsic and extrinsic factors including hormones, changes in diet metabolism, medication, smoke, stress, and circadian rhythms that can influence "gene expression patterns" or "epigenomes" (Anaya et al., 2016).

Jasiulionis argues that people's lifestyle affects the epigenome, and epigenetic changes are one of the hallmarks of aging and diseases such as cancer. The immune regulators of the immune response are altered by the epigenetic changes of the cells and respond to these alterations that play a critical role in the differentiation and function of the immune cells (Jasiulionis, 2018).

The characteristics of a healthy urban landscape

From a health point of view, a healthy urban landscape is the urban environment where all elements of the human body, from physical conditions to social interactions, are at accepted and standardized level. The health environment at its ideal end of outcomes is nearing to Utopia. Some of the features of a healthy urban landscape and its effect on the immune system as a protective system against harmful factors include:

1. The presence of green-blue infrastructure

Incorporating water and plant elements or green space as the results of a recent case study in China in 2019 by examining the relationship between green space characteristics in the restoration of physical and mental health of park users showed that among high-stress people of park users, they preferred the multilayered green spaces and quiet environments adjacent to water compared to the cultural and social elements of parks (Gao; Song; Zhu

& Qiu, 2019). Another similar study on older adults in seven South Korean metropolises was carried out current year showed that green spaces can significantly improve physical and mental stress in people with depression and mental health disorders (Lee & Lee, 2019). Two of the more complex features of green spaces, including 'revitalizing, and being 'natural' apart from the other characteristics such as the size, consistency and density of green spaces, have been recognized as two characters with positive effect on mental health (Tsai; McHale; Jennings; Marquet; Hipp; Leung; Floyd, 2018). The presence of two elements of 'water' and 'plants' have been recognized as two influential elements for physical and mental health of individuals, elements that were abundant in urban spaces of the land of Iran before the emergence of modern architecture and industrial life (Mansouri & Mohseni Moghaddam, 2018) . The incorporation of these elements into the urban ecosystem is of great importance for moving towards sustainable development considering all the elements of a healthy landscape in future of an urban design. Green spaces, even in small size and dimensions, have many benefits to citizens' health, including the possibility of physical activity, increased social communication, and improved mental health.

2 - The absence of adverse environmental conditions altering the acidity of 'water, soil and air', as the main elements of the environment

The environment around humans is affected by temperature, atmospheric pressure and acidity, so that any change in these elements can reduce the level of environmental health and have an adverse effect on the citizens living there. With the onset of industrial life since the last 200 years, the "net acid load of the body" has gradually changed and has progressed to a more acidic state. The water pH content of the oceans also decreased from 8.2 to 8.1 and its acidity has been increased. Changes in the acidity of groundwater, along with changes in soil acidity caused by the presence of industrial materials and industrial wastewater, have had a detrimental effect on human health.

At acidic pH conditions, the amount of calcium (Ca) and magnesium (Mg) of soil plus the potassium to sodium ratio will decrease. This ratio, which has a significant effect on the body's acid load, was 10 to 1 before industrial life, now reduced to 1:3. This change in acid load has changed the human "blood chemistry" over the long term and has affected the function of bones and muscles. The importance of soil and water health in urban environments, where changes in the elements can have a direct impact on human health, highlights the role of urban planners and ecologists in designing healthy spaces and preventing unhealthy elements from entering to water, soil and air of citizens (Lardner, 2001).

3- Allow physical activity at standard level

The possibility of physical activity provided by an urban health landscape is a vital factor in ensuring the health of citizens, even when investing capital to develop green spaces, it is required to see whether the benefits to citizens' health both physically and mentally is fulfilled. It applies to all levels of society, especially children who have less freedom to choose their own environment (Quinton, 1988).

In a 2010 study by J. Romeo et al., Entitled "Physical Activity, Immune System, and Infection", it has been found that heavy physical activity suppressed the immune system, while moderate physical activity improved immune function through immune cell proliferation and differentiation. Determining the relationship between different levels of physical activity and immune function will be a potential tool for maintaining general health, especially for older people in addition to athletes. The extent to which physical activity can have a positive effect on immune function needs further investigation in the future (Romeo; Wärnberg; Pozo & Marcos, 2010).

Therefore, designing public spaces in the city that can provide physical activities for citizens - especially children and the elderly - is of great importance in promoting community health (Audrey & Batista-Ferrer, 2015).

4- Biodiversity and its interaction with the microbiota of the human body

The other key feature of urban landscape affecting human health is 'species diversity of the environment'. The prevalence of allergic and chronic inflammatory diseases in urban populations has been significantly higher than similar non-urban populations. According to the 'Biodiversity Hypothesis', reducing people's exposure to components of the natural environment reduces the microbial population of the human body, thereby reducing the immune system's tolerance and dysfunction, subsequently lead to spreading the autoimmune diseases. The decline in biodiversity of urban environments, specifically on the microbial population of the skin that lives commensally in the human body, called "microbiota", has shown a significant relationship with the health of the human immune system. Land use change and the presence of flowering plants have shown a direct and reciprocal effect on the incidence of asthma, allergies and inflammatory complications. Biodiversity in urban environments improves immune system function and reduces chronic diseases such as asthma and allergies (Hanski; von Hertzen; Fyhrquist; Koskinen; Torppa; Laatikainen; Karisola; Auvinen; Paulin; Mäkelä; Vartiainen; Kosunen; Alenius & Haahtela, 2012).

Discussion and conclusion

In spite of the historical background of health considerations in urban planning over 70 years (including: Morensal, 1948 and Saint Plancat (1965)) and the some common objectives of them, the master planning of these two areas of "public health" and the "urban landscape", despite their common origins since the Industrial Revolution, have shown two divergent paths, imposing problems for citizens' health that calls for interdisciplinary studies such as healthy urban landscape and public health planners to be reunited in industrial metropolises for addressing their current problems (including: Northridge & Freeman, 2011).

It has been frequently cited in scientific publications that another significant factor affecting the human health is available apart from the conventional factors such as genetics and other frequently cited risk factors for human health. This is called environmental factor, which is fully mixed of multi factors such as: the shape, color and dimensions of space, the presence of the water, plant and size of these green-blue spaces, the degree of mobility of urban spaces for humans- as urban users- and the environmental diversity of places. A number of them and the prominent effect of these environmental elements on physical and mental health, especially on the immune system were addressed here.

Since we are no longer live in forests, deserts, and natural landscapes, but in suddenly manmade artificial environments where partly designed by unprofessional urban planners, who were unaware of characteristics of a healthy urban landscape and the citizen's health considerations, it is not farfetched to face with multiple complications like obesity, asthma, mental health problems and the autoimmune disorders.

By reviewing the articles in the field of medical immunization in the country, it is evident that the focus of studies is on individual factors affecting human immune system. Despite the remarkable abundance of this new paradigm and the interplay of human health with the elements of urban landscape and the attention of the international community to the emergence of urban living diseases in scientific databases around the world, especially in Asian countries like China and Korea – that two key examples of their recent studies were dealt here, the lack of them in the country's academic environment is strongly felt due to the frequent number of industrial cities and the emergence of human-built habitats, including the industrial towns and mega mall arenas.

The lack of natural and regenerative spaces in the aforementioned areas and the emergence of higher frequency of chronic inflammatory diseases in industrialized cities, propose a growing challenge for interdisciplinary experts such as the 'healthy landscape' and 'health ecology' which study the environmental factors affecting the immune system. In today's world researches studies ,the relation between green spaces and urban parks with the health of the citizens have been greatly discussed and the weakness of applying a single study area for decision making on the health of the citizens in the international community has been felt strongly.

Acknowledging the necessity of integrating the disciplines of 'public health', 'urban planning' (Corburn, 2004) and 'health ecology' and holding the joint meetings of health professionals with environmental experts and urban planner are of important factors to consider all influential elements affect the human physical and mental health in urban environments.

It is undoubtedly the duty of city policymakers and planners to design a healthier environment for their citizens. Further study in this area and the study of urban elements interventions in human health require more detailed statistical studies, such as cohort studies, and call for experts in many fields such as social medicine, urban ecologists, and urban landscape planners.

In response to the question raised here, it should be noted that the role of environmental elements is recognized as one of the most important factors in the development of human social behaviors and the ability of him to cope with pathogens. Moreover, it is one of the challenging topics in the field of social and biomedical research in the present societies. The multiplicity of environmental factors illustrates the complexity of their cumulative effect on human physical and mental health, and expresses the need to collaborate in interdisciplinary study areas.

Finally, it is suggested to consider another key factor called environmental factor in future health studies by considering all its constituents, called 'Human Niche', which encompasses the physical and mental environment of the urban user.

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Footnote

1. Epigenetics is derived from the words epi and genetics, where "epi" in Latin means "beyond" or "above" something, and epigenetics is the science that examines the alteration of gene expression patterns by environmental factors beyond gene sequencing. In other words, it discusses how different environmental elements lead to different gene expression states or different behavior patterns in individuals. Investigating this interrelationship between genes and the environment is very important in the social sciences and biomedical disciplines, as it shows that the interplay of genes and environmental factors plays a vital role in shaping individuals' social behaviors, personality development, and ability to cope with pathogens. In other words, epigenetics acts as an interface between the environment and the genes, receiving environmental effects and changing gene expression patterns (Jasiulionis, 2018).
2. Jean-Baptiste Pierre Antoine de Monet, chevalier de Lamarck: Well known French naturalist and biologist
3. Biston betularia
4. This particular environment, which encompasses the urban human body, is composed of many influential elements – known as exposome, for the first time in this study is called "Human Niche."
5. A set of environmental factors or exposures affecting the human body

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