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► **To cite this version:**

Yohan Fayet. Place of integrative approaches in the study of spatial dimension of health outcomes. Integrative approaches in environmental health: Epistemological and practical issues, Palgrave Macmillan, 2023, 978-3-031-28431-1. <10.1007/978-3-031-28432-8\_8>. <hal-04459258>

**HAL Id: hal-04459258**

**<https://hal.science/hal-04459258v1>**

Submitted on 15 Feb 2024

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# Place of integrative approaches in the study of spatial dimension of health outcomes

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## Abstract

As the concept of exposome is nowadays emphasized for its integrative virtues, this holistic vision of pathogenesis was already shared by some illustrious and ancient figures of medicine. The question is not so much whether this holistic and integrative vision of the exposome represents a real novelty in the field of environmental health studies, but rather to determine the extent to which this concept and the techniques associated with it are really contributing to the set up of a more integrative and holistic knowledge of the environmental determinants of health. In this chapter, we propose to go back over the epistemological and methodological paths in the study of spatial dimension of health. With regards to these historical and scientific contexts, the exposome seems to extend a holistic and integrative scientific dynamic that already exists, for various reasons, in the field of spatial analyses in health. The development of exposomic studies represents a significant opportunity for better integration of environmental measures into health studies with high level of precision, thanks to molecular data. But the exhaustive measure of environmental factors potentially contributing to health status and inequalities is still limited by technical and financial constraints which questions the representativeness of the studies and their ability to address all public health issues, usually reported by studies in epidemiology and health geography. This should lead us to qualify not the scientific interest of the exposome but its claim to provide objective knowledge to support policies addressing public health issues, such as socio-spatial inequalities in health.

## Keywords

Exposome, environment; environmental health, health geography, spatial epidemiology, spatial inequalities in health

*“Whoever wishes to investigate medicine properly, should proceed thus: in the first place to consider the seasons of the year, and what effects each of them produces for they are not at all alike, but differ much from themselves in regard to their changes. Then the winds, the hot and the cold, especially such as are common to all countries, and then such as are peculiar to each locality. We must also consider the qualities of the waters, for as they differ from one another in taste and weight, so also do they differ much in their qualities.*

*In the same manner, when one comes into a city to which he is a stranger, he ought to consider its situation, how it lies as to the winds and the rising of the sun; for its influence is not the same whether it lies to the north or the south, to the rising or to the setting sun. These things one ought to consider most attentively, and concerning the waters which the inhabitants use, whether they be marshy and soft, or hard, and running from elevated and rocky situations, and then if saltish and unfit for cooking; and the ground, whether it be naked and deficient in water, or wooded and well-watered, and whether it lies in a hollow, confined situation, or is elevated and cold; and the mode in which the inhabitants live, and what are their pursuits, whether they are fond of drinking and eating to excess, and given to indolence, or are fond of exercise and labor, and not given to excess in eating and drinking.”*

*On Airs, Waters, and Places, Hippocrates*

In this guideline to physicians settling and discovering a new area of practice, Hippocrates (460-370 B.C.) provides a striking insight into his vision of what we now call "the determinants of health" and the potential interactions between environment and health. Insisting on local particularities in terms of physical environment characteristics or social behaviors, he also implicitly recognizes the existence of a spatial variation of health status whose origin would be complex and multifactorial. This concept of the role of the environment on pathology was taken up by Galen, another Greek physician (131-201 B.C.), whose encyclopedia favored the diffusion of Hippocratic thought.

If the concept of exposome is nowadays emphasized for its integrative virtues (Lioy and Rappaport 2011), we can see that this holistic vision of pathogenesis was already shared by some illustrious and ancient figures of medicine. The question is not so much whether this holistic and integrative vision of the exposome represents a real novelty in the field of environmental health studies, but rather to determine the extent to which this concept and the techniques associated with it are really contributing to the set-up of a more integrative and holistic knowledge of the environmental determinants of health. The challenge of this chapter will therefore be to situate the historical and scientific contexts in which these "new integrative approaches" is inserted and what their potential contributions or consequences may be. It will be based on a multidisciplinary epistemological analysis (spatial epidemiology, health

geography, public health) of past and contemporary research studying the spatial dimension of health and the interactions between health and environment.

## **1. The progressive exploration of spatial determinants of health**

### **1.1. From early spatial analysis to the new geography of health**

As we can see with Hippocratic thinking as well as with the exposome in the scope of the development of precision medicine, some great periods of medical progress have been followed by significant reflection and contributions to the understanding of exogenous factors, and in particular spatial factors, of health. If the Renaissance will be especially marked by the progress in anatomy and in the mechanical understanding of the body, it is at the end of the eighteenth and at the beginning of the nineteenth centuries that the subject of the spatial distribution of the diseases is going to interest again, in particular thanks to the "diffusion of the information on the diseases, the nutrition, the food and the geographical variations in the medical systems" during the Lumières (Earickson 2009).

This recognition of the spatial dimension of health status is first achieved thanks to cartography and topography. In 1792, the Prussian Leonhard Ludwig Finke produced a world map of diseases, considered to be the first work of medical geography carried out on a global scale (Light 1944). The revival of Hippocratic thought, thanks to the rediscovery of ancient texts, also inspired certain physicians interested in the relationship between health and place. Through the exercise of medical topography, they carried out a cross description of the living environment and the epidemiological characteristics of the populations. In 1786, Jean-Jacques Menuret de Chambaud wrote an essay on the medical-topographical history of Paris. Initially descriptive, these topographies gradually moved towards a causal approach, thus giving rise to the first works of medical geography. They were particularly useful for understanding and analyzing new epidemics, caused by the first Industrial Revolution and the deterioration of the living conditions of workers in urban areas. In his topography published in 1822, Lachaise related the anemia of certain workers, stricken by tuberculosis, to the insalubrious conditions of their housing. John Snow's mapping of the cholera epidemic in the Soho district of London in 1855 allowed him to invoke the role of a polluted water fountain and thus to highlight the waterborne origin of cholera. Although strongly criticized at the time, Snow's conclusions were validated by the discovery of vibrio by Robert Koch in 1883. The multiplication of medical topographies and the development of public health during the nineteenth century will reinforce the awareness of the implication of living conditions and more globally of the place on health. This even infused the way the city was organized, since the urbanistic upheavals of the end of the nineteenth century in France, even if they were guided by safety imperatives, were also inspired by

hygienism and tackled the insalubrity of certain central districts. Nevertheless, these works remained highly monographic and often remained only at the stage of description, based on facts established in a few places. Thus, the mono-causal model used in these empirical studies quickly reaches its limits when it comes to considering the overall contribution of place on health status.

In France, Maximilien Sorre (1880-1962) was one of the first to go beyond this limit and to propose a theoretical model aimed at interpreting this global effect of place on health. Specialist in biological and human geography and strongly inspired by the conception of geography of Paul Vidal de la Blache (1845-1918), Sorre envisages geography as an "ecology of man, biological and social" (Picheral 2001), through the concepts of environment, milieu or region. In particular, he invented the concept of the "pathogen complex", as a set of factors conducive to the development of a disease. He thus provided the conceptual framework demonstrating that a pathogen is a necessary but not sufficient cause, and that the disease needs other specific conditions to develop, both in the host and in its environment. Moving away from Vidal de la Blache's deterministic approach focused on physical conditions, he also remains attentive to the role of human and social dynamics on geographical environments (Sorre 1947). Sorre's contribution, which established the scientific basis of medical geography, was taken up by Jacques Meyer May (1896-1975) in the United States, notably through the ecological approach to diseases (May 1958; Akhtar 2003; Browne et al. 2018).

The adoption of both an ecological and a systemic approach constitutes the great theoretical advance of medical geography founded by Sorre and May. The ecological approach, inspired by both Vidalian thought and American human ecology, focuses on the study of interactions between humans and their environment, in a relationship that is both dialectical and dynamic. Even if it remains well structured around the epidemiology of diseases on the one hand and the organization of care on the other, medical geography introduces tension with the biomedical model, by focusing more particularly on the spatial processes involved in the construction of health. Rejecting all geographical determinism, this approach integrates the actions of Man over his own environment and considers health as an outcome of the way in which Man integrates and adapts to his environment. These theoretical advances have shown the effect of place, in all its components, on the outcomes of its population. The spatial anchoring of health is not only the result of the configuration of the physical environment, but must also be considered as the result of the human and social dynamics in a place.

For a long time, the geographical analysis of health events was based on international comparisons or on monographs, targeting particular places. With the development of public health, epidemiology and medical geography, the spatial analysis of health states has been increasingly studied since the end of the 20th century, supported by the rapid improvement in the conditions of production, collection and processing of spatial and health data. And since the object of research is no longer the spatial

expression of a disease but the influence of place on health, many geographers will call from the 1980s onwards for a broadening of the field of study, through the foundation of a new geography of health. As geographers Moon and Kearns put it, health geography has shifted from a "preoccupation with the medical world to an increased interest in well-being and broader social patterns of health and health care" (Kearns and Moon 2002). It has moved away from the biomedical model, interested in all dimensions of well-being, adopting a critical stance towards the discipline but also towards society, towards social inequalities in health, their persistence and their reinforcement. According to Fleuret and Séchet, the objective is no longer "to study health as a function of places but to study places with regard to health, health care and health policies" (Fleuret and Séchet 2011).

This opening was part of the epistemological shift that geography was undergoing at the time, particularly in France, and which refocused the discipline in the field of social sciences. By focusing on lived space, Frémont had, as early as 1976, moved towards a much more phenomenological and behavioral science, thus taking the opposite direction from purely quantitative geography. It is notably from his work that the concept of territory as a portion of space appropriated by a social group, which projects its own system of representation onto it, will develop (Frémont 1976). This new humanistic approach, focused on Man and society, largely explains the progressive emancipation of health geography from traditional medical geography. Already drawn by Antoine Bailly in the early 1980s (Bailly 1981), this movement took shape in the 1990s with the launch of the journal *Health and Place* in 1995 and the explosion in the number of publications on these new themes, focused on well-being and social models. In his dictionary published in 2001, Picheral defines health geography as "the spatial analysis of disparities in the health of populations and the environmental factors (physical, biological, social, economic and cultural) that help explain these inequalities" (Picheral 2001). This definition gives health geography both descriptive and explanatory functions in relation to spatial inequalities in health, by mobilizing all the risk factors potentially involved in a resolutely integrative approach. This integrative approach is not specific to health geographers, but rather reflects a sensitivity specific to geography in general. According to Claval and Pitte, "geographers are interested in the physical, biological and human aspects of the earth. They therefore mobilize concepts that capture in one movement realities that most researchers carefully isolate" (Claval and Pitte 2001). For a long time, the spatial dimension of health remained at the stage of observation or hypothesis, and was therefore gradually investigated with the development of a dedicated discipline, a social science in its own right with its own theoretical baggage. While the emergence of this new discipline has given rise to several notable developments, such as the development of theoretical and critical reflections, the implementation of this integrative approach in the field of spatial analyses was not always as obvious in epidemiology.

## **1.2. Place as the proxy of missing social information at the individual level**

Analytical epidemiology is the study of the distribution and determinants of health and disease in human populations and the causes that determine this distribution. The goal is to prove the relationship between a disease and a risk factor by comparing the frequency of a disease in a group of people exposed to a suspect agent to that in a group of unexposed people. Epidemiology has primarily thought of this relationship at the individual level in order to be able to better control the risk for each individual and to be able to answer the question, "Why did this individual get this disease at this time?"

Thus, ecological studies generally have little consideration in epidemiology because they do not allow the results to be transposed with certainty to the individual level. Indeed, the objective of these studies is to observe variations in the occurrence of a disease in space (geographical study) or in time (temporal study) and to correlate these variations with environmental factors, in order to develop hypotheses on potential risk factors for the occurrence of pathologies. However, it is difficult to extrapolate inferences made at the (aggregate) population level to the individual level because of what is called the "ecological fallacy". Given this devaluation of the ecological approach in epidemiology, spatial analysis is generally used as a last resort, in particular to compensate for the lack of information at the individual level. The place was then used as a proxy, a way to measure the characteristics of the individual studied. This approach has been used in particular for social epidemiology studies, in order to observe the influence of social level on health. As medical data still do not often provide information on the social level of patients, the data and spatial analysis will be mobilized in order to overcome the great difficulty of collecting social data at the individual level.

This work led to the creation of composite indicators to measure social disadvantage. The choice of variables for the indicator obviously depends on the definition of social disadvantage. According to Townsend, social disadvantage is "an observable and demonstrable state of relative disadvantage with respect to the local community or society as a whole to which the individual, family and group belong" (Townsend 1987). The use of these ecological indicators emerged in the United Kingdom in the 1980s, and then spread to most industrialized countries, particularly in the Anglo-Saxon countries (Krieger et al. 2002). The Townsend index was developed in Great Britain in 1987 in the context of the publication of the Black report and it made it possible to show the correlation between deprivation and various health variables (premature mortality, prevalence of chronic diseases, birth weight of newborns) (Black et al. 1980). This famous report on health inequalities in Great Britain insists in particular on the social origin of health inequalities. Socio-economic index have also been produced in other geographical contexts (Salmond et al. 1998) or with some differences in terms of choice of variables (Jarman 1983; Carstairs and Morris 1989).

Initially focused on material deprivation, the method of constructing these indicators will gradually open up to new dimensions of deprivation. In the United Kingdom, the Index of Multiple Deprivation was developed in the 2000s to take into account a larger number of dimensions of deprivation than the strictly socio-economic indices of Townsend and Carstairs. First created in 2004, and then regularly updated, the indicator is based on different areas of disadvantage: income, employment, health, education, access to services, residential environment, and crime (Noble et al. 2006). In Canada, the Pampalon Deprivation Index is based on the Townsend model and complements it by integrating the social dimension of disadvantage (Pampalon et al. 2009). The idea is not to combine the two dimensions (material and social) into a single synthetic variable, but to take into account the singularity of each disadvantage. Unlike previous indicators that aim to measure the social vulnerabilities of a territory through a single variable, the final objective of the Pampalon indicator is to allow a more complete mapping of social vulnerabilities, which makes it a highly appreciated tool for health policy makers. Similarly, the DANDEX deprivation indicator developed in Denmark has two components, one measuring social disadvantage (average income, level of education or unemployment rate in the municipalities), the other dealing with material disadvantage with variables on the level of equipment in the territories, housing or car ownership. When compared with mortality data, the Danish indicator makes it possible to observe a "visible gradient" in mortality according to deprivation quintiles (Meijer et al. 2013).

The recognition of the role of the life context, alongside individual health determinants, brings us back to the debate in the human and social sciences on the role of collective dynamics on the individual, with the opposition between holistic and individualistic approaches. On the one hand, some argue that the experience of living in a milieu and sharing the same environment shape individuals and their behaviour. This idea of a downward causality from the environment to the individual is based on the work of great authors in the social sciences. On the other hand, the supporters of an individualist approach associate lifestyle and behaviours with a purely personal choice, and therefore independent of the context in which individuals live. As a result, risk is much more individually determined than socially determined from their point of view, so that all variables should be measured at the individual level, because the role of the individual would be much more important in explaining disease (Diez-Roux 1998). This conception of the primacy of individual analysis has long been marked by Robnson's famous work in sociology pointing out the limits of the ecological approach (Robnson 1950). Macintyre also links this supremacy of methodological individualism to the rise of liberalism in the 1980s, quoting Margaret Thatcher: "There is no such thing as society, there are only individuals". Macintyre also emphasizes the "important distinction" between indicators that use aggregate data for individual proxy purposes and those that analyze the effects of the social and physical environment on health (Macintyre et al. 2002).

To what extent is the health of a territory due to the characteristics of the individuals who compose it and the context in which the individuals live? In 2002, Shaw recognized that only a joint reading of compositional and contextual effects could provide a complete explanation of health phenomena (Shaw et al. 2002). The development of multilevel models will progressively make it possible to address this complexity and to definitively legitimize the relevance of an integrative and contextual approach to health determinants, by complementing the factors observed at the individual level.

### **1.3. Multi-level studies and the broad exploration of contextual determinants of health**

The interest of multilevel models, including both individual data and spatial variables measuring the characteristics of the life context of individuals, is to be able to distinguish what, in the state of health of an individual, can be linked to his or her own characteristics from what relates to his or her environment (Ellen et al. 2001). This mix within the same statistical model is essential to know and have recognized the importance of contextual effects, which is still contested by the biomedical paradigm. Indeed, as Duncan pointed out, until the use of multilevel models, there remained a problem in the interpretation of contextual effects and their importance (Duncan et al. 1998). These studies therefore provided the methodological tools necessary to recognize the influence of the territory as such on health, independently of any other factor or interpretation bias. Of the forty-seven studies included in Riva's literature review, forty-three showed a significant correlation between the socio-economic level of the area and one of the different health outcomes, independently of individual characteristics (Riva et al. 2007).

Another review of the literature on multilevel analyses focused on mortality, published by Meijer, shows the significant influence of the socio-economic characteristics of place on health, after control on individual social characteristics (Meijer et al. 2012). Meijer also notes that these effects of place are all the more pronounced when the number of inhabitants of the areas studied is low, which shows for the author the importance of working on small spatial units, at the local level. This effect of place, beyond individual characteristics, can be explained on the one hand by "the mutual influence of the inhabitants on the health behaviors of each of them, through the exchange of norms, values and social sanctions" (Meijer et al. 2012). The 2000s were marked by a gradual increase in the number of contextual studies using multilevel models. Whereas ecological studies could give rise to controversy in terms of the interpretation of results, the growing use of multilevel models will greatly contribute to the recognition of the legitimacy and relevance of spatial analysis in health, as a complement to the study of risk factors at the individual level.

In parallel with the use of social deprivation indices in the framework of multilevel models, the renewed interest in spatial analysis and the study of environmental factors in health will be reflected in the production of geographical indicators measuring new characteristics of the physical environment, beyond the localized measurement of exposure to air, water or soil pollutants. This broadening of the field of investigation of the physical environment has notably favoured the recognition of environmental determinants of certain health behaviours (diet, alcoholism, smoking), whereas the responsibility for these behaviours is attributed, in a far too exclusive way, to individuals and their non-compliance with prevention messages. Thus, several studies at the turn of the 2010s report that the spatial accessibility of supermarkets, for example, is associated with a higher consumption of fruits and vegetables (Zenk et al. 2009), and globally with a more balanced diet (Larson et al. 2009), confirming the evidence that the proximity of food stores constitutes an important determinant of dietary behaviors and obesity (Holsten 2009; Chaix, Bean, et al. 2012). Conversely, the proximity of fast-food outlets or alcohol and tobacco sales outlets is associated with an overconsumption of products sold in these facilities and known for their harmful impact on health. In an urban context, studies have focused on the impact of road quality and urban planning on walking (Roux et al. 2007) and have led to the production of walkability indices, measured by softwares and geographic information systems, particularly in large Anglo-Saxon cities.

It should be noted that this broadening of the field of study of the physical environment also allows for a better evaluation of the combined influence of these different determinants. For example, in a 2011 review of the literature, Leal and Chaix already show that certain characteristics of the physical environment, such as less pollution, better facilities in terms of shops and services, or the presence of facilities that encourage walking, are all associated with a reduction in risk factors for obesity, hypertension and diabetes (Leal and Chaix 2011). These new studies, which are more integrative in terms of measures of the physical environment, also allow us to reconsider the links between physical and social environments. For example, Cummins' research on the neighbourhood food environment has shown a significant correlation between the presence of McDonald's restaurants and the level of deprivation in communities in England and Scotland (Cummins et al. 2005). Other studies also show the greater presence of alcohol and tobacco outlets in the most socially deprived areas (Marashi-Pour et al. 2015; Shortt et al. 2015; Shortt et al. 2018).

The development of contextual and multilevel studies, on a growing number of health outcomes or risk factors, has thus considerably broadened the scope of geographic characteristics studied, to the point that they would be difficult today to list exhaustively. As a consequence of this integrative scientific dynamic, the multiplicity of the studied place effects and the richness of the results will also progressively fuel a reflection on how these health effects of place should be interpreted. Indeed, the highlighting of the multiplicity and complexity of the effects of place on health has shed a new light to

social indicators, until now often used in a restrictive way as a proxy. Finally, this progress supports a probably more exhaustive vision of the environmental factors influencing health outcomes, even if this amount of epidemiological knowledge cannot be sufficient to analyze and explain precisely the mechanism leading to spatial inequalities in health.

## **2. Integrative approaches and methods for the analysis of spatial inequalities in health**

The improvement of data collection, management and analysis tools for both health and geographic data, as well as the possibilities offered by Geographic Information Systems (GIS) in the processing and mapping of a large number of data, have greatly facilitated the description and analysis of spatial inequalities in health, through the production of maps at different scales. As a process of significant differentiation of health outcomes according to places, spatial inequalities in health constitute a specific research item that, unlike the work presented above, requires much more (if not almost exclusively) the use of holistic theoretical models and integrative measurement tools.

### **2.1. Measurement and interpretation of spatial inequalities in health**

In France, a comparative study of spatial inequalities in life expectancy since the 19th century has shown that these inequalities are not recent and that they also evolve according to geographical dynamics (Salem et al. 2000). Thus, the departments in the north of France had lower mortality rates than the rest of France at the beginning of the 19th century, whereas they have today the lowest life expectancies in metropolitan France. The economic and social crisis initiated by the deindustrialization of these areas, the weight of environmental and occupational exposures, as well as the persistence of some health risk behaviors may explain this relative deterioration (in comparison of the rest of the country) over two centuries. Conversely, we observe a continuous improvement over the last century in the departments of southeastern France. The latest maps of these mortality data confirm the persistence of excess mortality in the North-East of France and in Brittany, but also underline certain new dynamics such as the deterioration of the health situation in Languedoc-Roussillon (South of France) (Vigneron and Cartier 2011). Schematically, spatial inequalities in health in metropolitan France reflect different geographic cleavages and dynamics on three different scales: first, on a regional scale (Hauts-de-France, Brittany, Grand Est with unfavorable indicators compared to the Occitanie or Provence-Alpes-Côte d'Azur regions, for example), between metropolitan areas and rural margins following a center-periphery model, and finally on an urban scale according to the level of social deprivation of neighbourhoods.

In addition to describing the spatial distribution of these inequalities, maps using age- and sex-standardized rates can also be used to understand the extent of spatial inequalities in health, by analyzing the difference between the values of the extreme classes on each map. In the case of an atlas of spatial inequalities in health according to the cantons (supra-municipal level) of Metropolitan France, mapping general mortality (all causes of death) according to five color classes, the standardized rates of the class most affected by general mortality are at least twice as large as those of the least affected class (Trugeon et al. 2006). This means that if all French cantons had identical populations, in terms of size and structure by age and sex, we would still observe twice as many deaths per year in some cantons as in others. It is difficult, in the face of such a discrepancy, to implore a random distribution of mortality and to deny the impact of environmental characteristics in the construction of these health disparities. Above all, the comparative analysis of maps carried out on different pathologies but using the same methodology in the same geographical area also allows us to observe that these differences vary according to the health results used. In the same French atlas (Trugeon et al. 2006), it can be noted that, for cancers of the upper aerodigestive tract or alcohol-related diseases, the rates between the two extreme classes are not multiplied by two as in the case of general mortality, but by three or even four. Conversely, the differences are smaller for certain diseases such as breast cancer. These variations in the intensity of spatial inequalities mean that the impact of spatial determinants, and therefore the relevance of their analysis, varies according to the disease.

Although they may sometimes seem too descriptive, these maps are further proof of the spatial dimension of health inequalities because they can provide a concrete view of environmental influences on health and help to raise awareness, particularly among public actors, of the importance of these spatial health inequalities and their interconnections with other local issues. The diversity and multiplicity of spatial health inequalities according to the health variables used show the extent to which these inequalities are rooted in specific local differences in living standards, medical infrastructures, environmental exposures and health behaviors. While the spatial analysis of health outcomes has often led to the study of the specific influence of certain environmental risk factors on particular health variables, spatial inequalities in health should be considered as the materialization of the unequal geographical distribution of a set of environmental factors that can act positively or negatively on health.

## **2.2. Spatial inequalities in health as the result of a holistic process**

Spatial inequalities in health cannot be summarized by a single statistical correlation between one or more environmental characteristics and a health variable, as in the case of the spatial analyses traditionally deployed in health, but are characterized by the multiplicity and complexity of the factors

involved in a holistic process of spatial differentiation of health outcomes. This specificity of spatial inequalities in health is not necessarily easy to identify because it does not necessarily correspond to a well-established disciplinary division. Indeed, health geographers can also adopt this analytical approach, measuring the statistical correlation between health criteria and territorial characteristics. Nor does the distinction concern the use of different tools, as we have seen with the example of geographical indicators, whether social or environmental, which can be used both to measure an individual's exposure and to characterize territories. The work of Geoffrey Rose can probably help us to establish this subtle specificity of the analysis of spatial inequalities in health.

Indeed, in parallel with the development of spatial analyses in epidemiology, some began to express certain criticisms of the focus on individual risk factor of health. As early as the mid-1980s, Rose advocated awareness of the specificity of a population-based approach to health, which would not answer the same questions as the individual approach traditionally used. According to Rose, it is not the same thing to look for the causes of cases or the causes of incidence for the same pathology: "Why do some individuals have hypertension?" is quite a different question from 'why do some populations have hypertension, while it is rare in others?' These questions require different types of studies, and they have different answers" (Rose 1985). Rose clearly calls for a distinction to be made between etiological research, which focuses on the individual, and research into the causes of incidence, which is measured at the population level. Through various examples from Anglo-Saxon public health, he shows how research focused on the explanation of cases has made it possible to identify "individual susceptibilities" but that this research has failed to identify the underlying causes of disparities in incidence. Rose thus argues for a "Population Strategy" to give priority to finding and controlling the causes of incidence. The interest of Rose's work is to show the intrinsic importance of population studies in health, to the point of making them an object of research in their own right. This claim for a Population Strategy, complementing the individual approach, generally reflects a renewed interest in environmental factors that may explain health disparities beyond individual characteristics (Macintyre et al. 1993).

The diversity of methods and indicators used to study the relationship between health and place should not hide their almost unanimous contribution to the identification of environmental "susceptibilities" at the individual level. The major point of differentiation between the study of spatial inequalities in health and the spatial analyses traditionally deployed in health is therefore mainly the nature of the mechanism studied. Spatial analyses involved in identifying environmental susceptibilities at the individual level make it possible to grasp the biological mechanism by which a social/environmental exposure leads to the appearance of a pathology. In the case of spatial inequalities in health, the aim is to measure, through health data, a social mechanism of differentiation between different populations in terms of social class or geographical context for example. This holistic principle is thus applied to the

study of social inequalities in health, comparing different health indicators according to socio-professional categories, and which share the same concern to decipher the social process responsible for health inequalities, by seeking the causes of this differentiated social construction. The analysis of spatial inequalities in health is therefore fundamentally part of a deeply holistic and integrative approach, aiming to consider all the environmental characteristics involved in this process of spatial differentiation of health outcomes.

### **2.3. Integrative tools supported by the analysis of spatial inequalities in health**

The extensive revelation of spatial determinants of health suggests the geographic contexts' potential to produce health inequalities. However, estimating this impact of the geographic context on health inequalities remains difficult, partly because epidemiological studies aiming to identify associations between spatial characteristics and health outcomes most often investigate one spatial factor at a time, according to the objectives of the study. As a result, geographic contexts may be variously measured, in terms of characteristics and spatial scale. In addition, spatial indices may be combined differently across studies, due to methodological choices and study objectives. Some international collaborations have aimed to develop methodologies for standard indices using spatial data, as in the case of the European Deprivation Index (Pornet et al. 2012; Launoy et al. 2018). However, for many geographic characteristics, data availability and scale are too variable between and within countries to develop the set of standard indicators needed to measure and compare spatial health inequalities in a consistent way. Consequently, studies analyzing spatial inequalities in health often used specific indices, limiting the comparability of the results (Abel et al. 2016).

Furthermore, the separated analysis of risk factors in epidemiological studies mostly impedes a comprehensive review of all the vulnerabilities related to the place of residence. Some epidemiological studies using a social deprivation index took this limit into account, investigating a potential difference in their analysis between rural and urban deprived areas (Bertin et al. 2014). Considering this challenge, developing geographical classification (or typology) can help to summarize all the geographical determinants on health in a meaningful way and to develop a common geographical frame of reference for the study of spatial inequalities in health. The use of geographic classifications to compare health outcomes is relatively recent (Gershoff et al. 2009), but some significant examples can be mentioned worldwide. Using data on the characteristics of the physical environment (built environment and housing) and the population (social level, ethnic origin and communities, demography), Weden creates a territorial typology for the study of geographic health inequalities throughout the United States (Weden et al. 2011). In the end, the typology distinguishes six "archetypes" of territories and observes their evolution between 1990 and 2000. The authors insist on

the stability of the numbers between 1990 and 2000, which proves the viability of this typology over time and the capacity of the model to measure the temporal evolution of geographic health inequalities. Still in the United States, Arcaya uses 55 variables for its typology of the state of Massachusetts, divided into six different domains: health behaviors, housing and land use, transportation, services, social composition and demographic composition. The authors see this typology as an aid to programming, communication and evaluation of local health policies (Arcaya et al. 2014). In Brasil, Santos presents a five-class typology, based on demographic, social and housing conditions data in 794 micro-neighborhoods (>5000 inhabitants) in Rio de Janeiro (Santos et al. 2010). The classes are distinguished according to socioeconomic level and urban/rural character, and will be used for future work in health (accidents, violence, communicable diseases and mortality).

In France, this comprehensive classification approach to address the geographical context's contribution into health inequalities has been also implemented with the production of the "Geographical Classification for Health studies" (Fayet et al. 2020). This classification was computed, through k-means clustering, from ten spatial variables measuring physical environment, social deprivation and health care accessibility at the municipality level. The classification distinguishes 5 types of municipalities (Wealthy Metropolitan Areas, Precarious Population Districts, Residential Outskirts, Agricultural and Industrial Plains, Rural Margins) which enables to highlight significant spatial inequalities in standardized mortality between the 5 classes. Indeed, significant lower mortality rates compared to the mainland France population were found in the Wealthy Metropolitan Areas (SMR=0.868, 95%CI: 0.863-0.873) and in the Residential Outskirts (SMR=0.971, 95%CI: 0.964-0.978), while significant excess mortality were found for Precarious Population Districts (SMR=1.037, 95%CI: 1.035-1.039), Agricultural and Industrial Plains (SMR=1.066, 95%CI: 1.063-1.070) and Rural Margins (SMR=1.042, 95%CI: 1.037-1.047).

At the level of the Paris metropolitan area, Van Hulst also produces a spatial classification for the analysis of spatial inequalities in cardiovascular disease (Van Hulst et al. 2012). This typology distinguishes six profiles of territories, mainly according to their degree of urbanization and their social composition (Van Hulst, 2012). The description of the typology shows, for many characteristics, strong contrasts between the different space profiles. These geographic contrasts can therefore be thought to result in important differences in cardiovascular risk exposures, between populations in these different territories. Data from the RECORD (Residential Environment and Coronary Heart Disease) cohort, which measures systolic (maximum pressure at the time of heart contraction) and diastolic (minimum pressure at the time of "relaxation" of the heart) blood pressure in more than 7000 French people living in the Paris metropolitan area, have verified this hypothesis of a differentiated exposure to cardiovascular risk, depending on the type of territory and its characteristics.

The results show a significantly higher systolic blood pressure in people living in deprived urban areas, after adjustment for individual risk factors. There was also a consistent decrease in diastolic blood pressure as one moved away from urban centers. Finally, at equivalent urban density, the social disadvantage of the neighborhood also influences the increase in diastolic blood pressure and thus the cardiovascular risk. This study highlights the relevance of an integrative spatial approach to observe inequalities in cardiovascular risk. At the end of the paper, Van Hulst highlights that “the typology makes it possible to examine the combined exposure to multiple environmental characteristics that are highly correlated and whose effects could not be separated through multivariable regression analysis. By regrouping similar neighborhoods based on a multidimensional profile it is possible to examine the impact of a constellation of neighborhood environment features that may jointly rather than individually influence health and health behaviors” (Van Hulst et al. 2012).

Published in 2012, Van Hulst's article presents a precursory example of a study combining an integrative spatial approach and the use of biological data to measure the incorporation of socio-spatial inequalities in health. At a time when these same virtues are being emphasized for exposome supporters, it is appropriate to evaluate the impact of these new exposomic studies in the field of research studying the spatial dimension of health events.

### **3. Exploring health and place through the exposome: opportunities, knowledge and challenges**

Exposomic studies aims to use biomarkers to trace the lifecourse effects of environment on health, following an integrative approach of exposures. It represents therefore a significant opportunity for better integration of environmental measures into health studies with high level of precision, thanks to molecular data. The exposome is claimed to improve knowledge about environmental factors impacting health outcomes at the individual level, taking cumulative effects of different exposures over the lifecourse into account. Raising the benefit of the concept of exposome for health geography, Prior also points that “the holistic nature of the exposome is particularly beneficial to the integration of biosocial ideas into geographic health enquiry” (Prior et al. 2019). Indeed, “biosocial theorisations enable both body and environment to be repositioned as active components in fluid health and place relationships, acting in interchange and accumulation over time” (Prior et al. 2019). However, the high precision of the biological data collected in these cohorts very often comes up against the scarcity of spatial data measuring exhaustively and/or precisely the exposure to different environmental factors, whether physical or social. Even if conditions for collecting and sharing spatial data measuring these environmental characteristics is gradually improving, these imbalances in terms of precision between

biological data and environmental data, and even between the environmental data themselves, call into question the ability of the exposomic approach to actually implement its integrative ambition.

### **3.1. What about the integration of spatial data in exposomic studies?**

The first large studies concretely implementing the exposomic approach were born in the early 2010s, within the framework of major international collaborations bringing together different cohorts on the same subject. This first generation of large exposomic studies is characterized in particular by its marked focus on the analysis of biomarkers associated with certain physical environmental exposures, in particular to air pollutants. For example, the HELIX (Human Early Life Exposome) study was initiated in 2013 to describe the multiple environmental exposures during pregnancy and childhood and childhood, in order to identify associations between these early exposures, "molecular signatures" and mala diseases in children (Maitre et al. 2018). Bringing together different European cohorts on neonatal health (9 regions and 6 countries for a total of 31 472 women), HELIX integrates the measurement of 17 different exposures (climate, air pollution air pollution, built environment, chemical agents, etc). Nevertheless, the study integrates only the geographical areas (region, metropolitan area, etc.) for which on air pollution and the built environment are available (Maitre et al. 2018), which shows the importance of data availability in the design of the studies and the factors considered. Another example is the EXPOSOMICS study, funded by the European Union and involving 13 European and American research centers "to develop a novel approach to the assessment of exposure to high priority environmental pollutants" and which is clearly focused "on air and water contaminants during critical periods of life" (Vineis et al. 2017). Note that within this first generation of exposomic studies, only the LIFEPAATH study does not incorporate measures of physical environment exposures and instead focuses on the biological effects of the social environment on health aging, from 8 cohorts in France, Italy, Portugal, Ireland, the United Kingdom, Finland, Switzerland, and Australia (Vineis et al. 2017). According to Prior, "the lack of the social is damaging to exposomic studies" because "environmental exposures and their biological correlates cannot be separated from the broader social, economic, political and cultural relations in which they are embedded" (Prior et al. 2019).

This unbalanced integration of spatial variables and factors in the first exposomic studies could be explained by the greater availability and better precision of some data on physical environments (mainly air pollution), that are routinely produced by national and/or local institutions in European countries. One can also think that air pollution, which can be measured by a "simple" concentration rate of particles, was a good model for the implementation of an exposomic approach correlating measurements of internal and external exposomes. While the measure of some other risk factors of physical environment (e.g. accessibility of green/blue spaces or facilities, walkability) was not often

routinely produced and required the construction of more complex indicators, air pollution data were ready to use and to be integrated into early exposomic studies.

Launched in 2020, the European Human Exposome Network (EHEN) brings together 9 research projects on exposome, receiving over €100 million from Horizon 2020, the EU's framework program for research and innovation. Presenting itself as the world's largest network of projects studying the impact of environmental exposure on human health, this EHEN seems to support a second generation of exposomic studies, more integrative in terms of spatial data. Indeed, even if air pollution data are still used, most of the nine projects more or less aim to include some other spatial data measuring physical (e.g. food/alcohol outlets; urban land uses, population density, walkability, green/blue spaces, climate, odour, noise) or social environments (e.g. lifestyle and behaviours, income, social capital or networks). While most of them clearly display their commitment to a holistic and integrative approach to exhibitions, this ambition is more visible and advanced for some projects in particular, such as Expanse (Vlaanderen et al. 2021), Athlete (Vrijheid et al. 2021) and Equal-life (Kamp et al. 2022). However, the EHEN projects do not seem to be able to grasp the geographical diversity of the health and place interactions. Indeed, several projects now mention or even clearly assume a specialization of their studies on urban exposome. Moreover, most of the spatial variables integrated measuring physical environments (walkability, accessibility of food/alcohol outlets, accessibility of green/blue spaces) are mostly designed for urban context. Knowing that studies may choose not to include in their analyses patients for whom spatial data would not be available (Maitre et al. 2018), one can therefore ask the question of the representation of non-urban health issues.

### **3.2. Novelties and challenges of the exposomic approach for the study of spatial dimension of health outcomes**

The concept of exposome is not only presented as an interesting opportunity but often as a real innovation, a turning point bringing a major change in the study of interactions between health and environment (Rappaport 2018; Vineis 2018; Vineis et al. 2020). However, this chapter reported previous experiences and progress in the study of spatial dimension of health outcomes that are not without interactions with the holistic and integrative approach claimed by the exposome concept. This narrative on the alleged novelty of the exposome has already been criticized (Canali 2020). We have already shown that the integrative approach to health determinants was already widely advocated in other disciplines, such as health geography (see 1.1.), and that it was also necessary for the understanding and analysis of some issues such as socio-spatial inequalities in health (see 2.2.). We have also seen that multilevel analyses also aim to bring together all environmental exposures and individual susceptibilities within a single causal model in order to estimate the influence of each of

these factors. Some of these studies even used biomarkers to quantify the effects of different exposures on health through a process of biological incorporation. This is the case, for example, of the RECORD study which, since the end of the 2000s, has combined biological measurements, socio-demographic information at the individual level and data measuring the physical and social environment in order to study the impact of the residential environment on coronary heart disease (Chaix et al. 2012; Van Hulst et al. 2012). Presenting final results of the EXPOsOMICS study, Turner and his/her co-authors recognize that “on a basic level, exposome research can be seen as replicating the approaches of classic risk assessment with higher resolution and greater accuracy” (Turner et al. 2018). The allegedly "holistic" or integrative dimension of exposome would be related for some to the several exposures taking into account at the same time, making it possible to examine “the effects of multiple classes of agents as part of a more holistic approach to risk assessment” (Turner et al. 2018).

Actually, the exposome seems rather to extend and intensify a holistic and integrative scientific dynamic that already existed, for various reasons, in the field of spatial analyses in health. Even if former studies combined biological, individual and environmental data in a life-course perspective, what is striking about these exposomic studies is the scale at which they are implemented. These studies often take shape around large international consortia bringing together numerous scientific disciplines, pooling their data, their tools and their study populations. The exposome thus seems to be the concept capable of federating a scientific community, originally plural, around a single approach and of supporting a massification of studies on environmental health. These advances in data integration, however, require exposomic studies to deal more with variability in data accuracy and measurement tools. While they benefit from the greater precision of biological measurements, studies have more difficulties in routinely collecting precise data on the socio-demographic and residential trajectories of individuals, but also on their current and past exposures. While exposomic studies incorporate more exposures of different types, there is a risk of combining data from various measures whose robustness, quality and completeness may be very uneven (see Giroux in this volume).

The limited availability and accuracy of precise spatial data, compared to individual and biological data, therefore represent a major obstacle and challenge for the continuation and balance of exposomic studies. Indeed, these problems lead teams to make choices that are sometimes contradictory with the integrative ambition of the exposome, such as excluding patients for whom spatial data are not available (Maitre et al. 2018) or the non-inclusion of cohorts not collecting certain spatial data. Thus, the included cohorts in the Lifepath project "represent only a small proportion of the total cohorts available in Europe cohorts available in Europe" because they had to combine "good measures of socioeconomic status, risk factors for risk factors for non-communicable diseases and biomarkers already measured" (Vineis et al. 2017). While the EHEN projects benefit from significant political and financial support from the EU Commission, massive investment in tools for routine measurement and

collection of environmental exposures and characteristics could also have been very useful considering the limited availability and accuracy of spatial data. The improvement of environmental measurement tools is all the more important as the temptation to identify and use biomarkers to measure exposures directly in the body becomes stronger and stronger, in a movement of biologization of socio-spatial inequalities whose risks are still far from being controlled (Lynch 2017; Serviant-Fine et al. 2023).

The integrative virtues of the exposome thus fortuitously highlight the significant imbalances between the tools and data grouped within exposomic studies. This reality is well taken into account by scientists, as evidenced by certain methodological choices, and these current constraints could foster an awareness of the need for investment in environmental data measurement and production tools. While waiting for a potential improvement in data homogeneity that would allow for an even more integrative implementation of the exposome concept, we can observe that exposome studies are being carried out primarily in urban or even metropolitan environments and based on direct data on exposure to pollution. Certain environmental factors or areas, initially considered in the cohorts, may also be excluded from the analyses in the end, due to the variable availability of precise spatial data. It can be seen here that the integrative ambition of exposomic studies leads them in practice to a spatial and factorial reductionism which may question their claimed capacity to respond to major public health issues. In France, for example, a recent study shows that some metropolitan areas stand out for their high under-mortality, even though these areas are the most exposed nationwide to air pollution (Fayet et al. 2020). Exposomic studies may therefore increase socio-spatial inequalities in health since it will produce useful knowledge to assess the impact of urban exposome and support policies to reduce exposures in the densest urban areas at the expense of others areas. Moreover, socio-spatial inequalities in health are primarily linked to social environment and health-related behaviors (tobacco, alcohol, diet), which are currently significantly underrepresented in these studies.

## **Conclusion**

Considered at different times in the spatial analysis of health outcomes and now necessary for the analysis and understanding of socio-spatial inequalities in health, the holistic and integrative approach to interactions between health and place is undoubtedly experiencing a new dynamic under the effect of exposomic research. The intensification of this integrative dynamic allowed by the exposome concept is also characterized by the massification of studies, reaching unprecedented scales in terms of infrastructures, study populations, data and disciplines mobilized thanks to the rise of big data. However, the exhaustive and precise measure of environmental factors potentially contributing to health outcomes and inequalities is still limited by technical and financial constraints which questions the representativeness of the studies and their ability to address all public health issues, usually

reported by studies in epidemiology and health geography. This should lead us to qualify not the scientific interest of the exposome but its claim to provide objective knowledge to support policies addressing public health issues, such as socio-spatial inequalities in health.

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