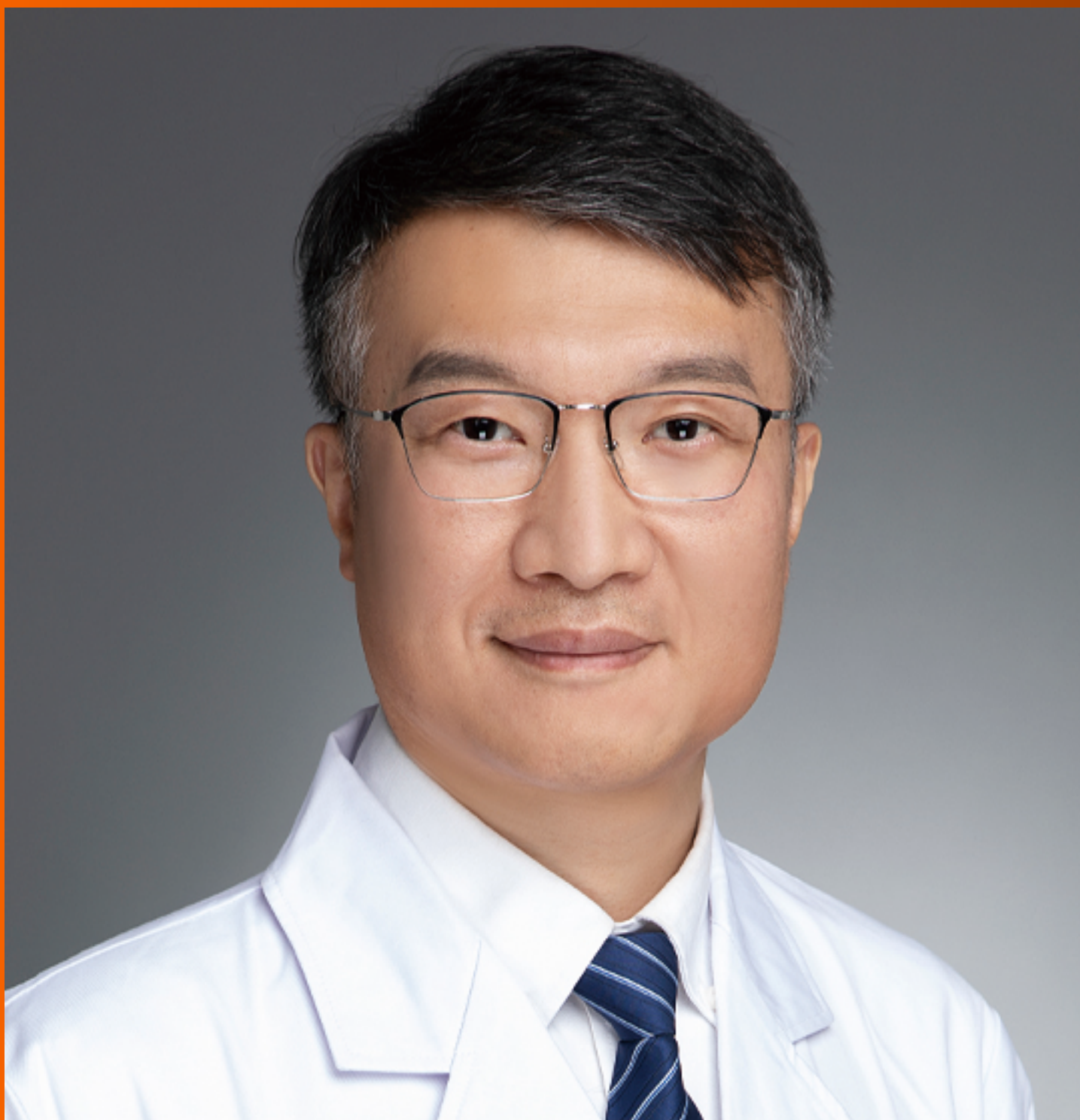


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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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Spatial epidemiology of diabetes: Methods and insights

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Abstract

Diabetes mellitus (DM) is a growing epidemic with global proportions. It is estimated that in 2019, 463 million adults aged 20-79 years were living with DM. The latest evidence shows that DM continues to be a significant global health challenge and is likely to continue to grow substantially in the next decades, which would have major implications for healthcare expenditures, particularly in developing countries. Hence, new conceptual and methodological approaches to tackle the epidemic are long overdue. Spatial epidemiology has been a successful approach to control infectious disease epidemics like malaria and human immunodeficiency virus. The implementation of this approach has been expanded to include the study of non-communicable diseases like cancer and cardiovascular diseases. In this review, we discussed the implementation and use of spatial epidemiology and Geographic Information Systems to the study of DM. We reviewed several spatial methods used to understand the spatial structure of the disease and identify the potential geographical drivers of the spatial distribution of DM. Finally, we discussed the use of spatial epidemiology on the design and implementation of geographically targeted prevention and treatment interventions against DM.

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Core Tip: With more than 400 million people having diabetes mellitus (DM), this disease emerges as one of the biggest public health challenges of our current times. However, one of the most significant public health advances in the study of DM is the demonstration that it can be prevented by the implementation of effective interventions targeting the factors that exacerbate the risk of the disease. Spatially informed tailored strategies that allocate resources in the high-risk areas where the most vulnerable populations reside would be an effective approach aimed to control and reduce the burden of the disease. Spatially explicit community-level policy interventions would offer great promise in effectively addressing the obesogenic and diabetogenic environment aimed to control the global DM epidemic.

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INTRODUCTION

Diabetes mellitus (DM) is an illness triggered by an incapacity of the insulin generated by the pancreas to effectively transfer glucose into cells *via* transporter recruitment, leading to uncontrolled hyperglycemia[1]. The common classifications of DM are the polygenic forms type I (T1DM) and type II (T2DM)[2]. T1DM is described by the absence of insulin production generated by the autoimmune destruction of pancreatic beta cells, whereas T2DM is an acquired disorder in which the pancreas either becomes insulin deficient or sufficient insulin is produced but the body cells cannot respond to the insulin, labeled insulin resistance[3,4]. In general, more than 90% of all DM diagnoses are T2DM. Other types of DM include gestational DM (any degree of glucose intolerance during pregnancy), monogenic DM syndromes, and drug (*e.g.*, steroid) or chemical induced DM, among others[4,5]. DM increases the risk of developing different comorbidities and other health complications including cerebrovascular accidents, hypertension, retinopathy and other ocular diseases, nephropathy, cardiovascular diseases, mental health conditions (*e.g.*, anxiety and depression), skin infections, and lower-limb compromise, among others[6].

Several genetic factors trigger the development of DM[7,8]. To date, more than 60 gene variants have been linked with the development of DM, but the actual effect size of each of these individual gene variants is largely unknown[9]. Behavioral, health-related, and environmental risk factors are also linked to increased risk of DM including obesity, physical inactivity, obesogenic environments, pollution, history of gestational DM, hypertension, and dyslipidemia, among others[10-13].

In 2019, 463 million adults aged 20-79 years (8.8% of the adult population) was estimated globally to be living with DM[14]. Among these people presenting the condition, 327 million were within the working age group (20-64 years), and 136 million people were aged 65-79 years. More than four million deaths were attributed to DM in 2019, ranking it as the ninth leading cause of death globally in that year. The latest evidence shows that DM continues to be a significant global health challenge and is likely to continue to grow substantially in the next coming decades. As a result, the global epidemic of DM has key implications for healthcare costs, with most countries allocating between 5% to 20% of their total healthcare resources to treat DM and its complications[15]. Likewise, an optimal DM treatment access at lower cost would increase the success of any intervention plan, particularly in developing countries.

The emergence of the global DM epidemic can be attributed to well-documented drivers like the increasing number of older people and increasing levels of physical inactivity and obesity. However, concerns have been increased in people under the age

of 60 since more than one-third of the DM-related deaths are occurring in this age group[16]. Increased consumption of unhealthy food and sedentary lifestyle boosting an obesogenic environment have been identified as potential drivers of these growing trends[17]. Likewise, an increased risk of DM has been linked to several other sociodemographic and economic factors including age, sex, ethnicity, education, health services, employment security, housing, and access to nutritious food. For example, it has been found that in regions with increased wealth, the rates of DM increase between two and four times in individuals with low socio-economic status, potentially linked with poor access to healthy food and adequate healthcare[18,19]. Poorer individuals are less likely to be diagnosed and to get treatment early enough, resulting in earlier adverse outcomes. These socio-economic determinants can also boost the development and progression of DM through the pathways of psychological, physiological, and behavioral responses like the development of mental health conditions and chronic stress[15].

Despite significant investments in research, public health interventions, and clinical care, the slackening of the growth rate of DM has been rather modest. This epidemic will involve an urgent and steady commitment aiming to implement assertive solutions at local and national levels with public health funding oriented towards public policies and economic boosting for local communities to start DM prevention programs. However, we first must understand the global burden of DM to plan for current needs, and to inform the design and implementation of cost-effective interventions. Geographic Information Systems (GIS) methods and spatial epidemiology concepts are important tools for recognizing the spatial and temporal dynamics of the epidemic. Understanding the critical geographical characteristics of the DM epidemic will provide valuable information to identify the potential environmental, demographic, and socio-economic drivers of the epidemic as well as the geographic areas where vulnerable populations are located, and where interventions should be implemented.

The main aim of this review is to summarize the main concepts and methods used in the spatial epidemiology of DM, and to discuss the advances in the study of the spatial structure of DM epidemics. The article starts with a brief summary of the general concepts and advances in the study of the spatial dynamics of diseases followed by a summary of the current knowledge of the spatial structure of DM. The article continues with a section discussing the interaction between DM and other communicable and non-communicable diseases. It finishes with the conclusions and the advances in the study of the spatial epidemiology of DM.

SPATIAL EPIDEMIOLOGY AND GIS

Epidemiology involves the study of the distribution and determinants of diseases in populations, particularly in human populations. Epidemiologic studies have focused on identifying the type and extent of illnesses affecting human populations, and recognizing the factors linked to disease outcomes[20]. Epidemiologists examine the interactions that emerge among the host, agent, and environment (the epidemiologic triangle) to identify the underlying causes of a disease and generate interventions for prevention and control[21]. Epidemiological studies aim to explain the amount and distribution of disease within a particular population by identifying the persons at risk, the time of disease onset, and the places where they are located[22].

Traditional epidemiology has historically focused on persons and time but less on place[23]. Only recently, the geographical place at which epidemics emerge and disperse started gaining relevance as an essential element for the understanding of epidemic dynamics, and for identifying the underlying factors boosting the epidemic. As a result, spatial epidemiology has emerged as a novel approach for the understanding and control of current epidemics. In spatial epidemiology, place is a very broad concept that refers to the 'lived space' in which individuals of a given community interact. The lived space includes the natural and built environment, and human social networks and interactions. It exists in different scales, from the global and regional spaces to the individual scale[24]. Place in spatial epidemiology involves exploring beyond individual characteristics to consider the social and environmental contexts experienced by individuals and how these interactions affect their health.

The capacity to study and understand the role of places in disease dynamics has substantially increased in the past several decades. This advance is mostly linked to advances in quantitative methods and geospatial technologies such as spatial analysis and GIS. Equally important, this development is linked to new concepts and

understandings about the social conformation of places, how people interact with these social and environmental elements, and ultimately, how these interactions affect an individual's health[25]. Alongside the rapid development of geographic tools, GIS methods, and spatial analysis, massive amounts of geocoded environmental and social data are now available[26,27]. These data and the methodological tools available for analyzing spatial data, provide a strong foundation for innovative spatially explicit approaches in epidemiological research by shedding light on the etiology of health outcomes, and providing a geographical foundation for health policy-making[28]. Spatial analysis methods can be used to understand mapped information by identifying patterns and drivers of disease distribution. These methodological tools also facilitate data exploration and pattern identification by detecting unusual geographical distributions of health events and following their evolution in space over time.

Spatial epidemiology has been mostly used for studying communicable diseases, but its application has currently expanded to the study of non-communicable diseases like DM[29-32]. The quantitative methods in spatial epidemiology for estimating the net contribution of geographical hotspots (areas experiencing a disproportionately large burden of the disease) and the disease burden determinants at the ecological and individual-level may facilitate the design and implementation of control measures. The identification of these areas can uncover the locations of high-risk populations as well as revealing the factors that facilitate the persistence and spread of epidemics. In this context, spatial epidemiology has become essential tool in the fight against devastating epidemics such as malaria and HIV[33-36], but it is also becoming a widely implemented approach for the study of non-communicable diseases like cancer [37] and cardiovascular diseases[38]. Geospatial analysis has significant potential for enhancing the effectiveness of both a single program at a given level of spending and the allocation of limited resources across several programs. In sum, one of the specific implementations of spatial analysis can be to investigate how prevention and treatment interventions can be combined in different geographical places and populations for maximizing cost-effectiveness under local or national funding constraints.

SPATIAL MAPPING OF DIABETES AND DISEASE DISTRIBUTION

Disease mapping is one of the first steps for understanding the spatial structure and dynamics of a disease. Spatial maps of diseases illustrate the distribution and intensity of a disease, facilitate the identification of the heterogeneous distribution of the disease in a specific region, and elucidate high burden areas in which the disease is concentrated in space. In this context, it has been shown that the burden of DM has considerable regional variation, with developing countries being the areas disproportionately affected by the current global DM epidemic, with approximately 75% of people with DM residing in low and middle-income countries[39,40]. Meanwhile, general distribution patterns of the global DM prevalence are consistent with socio-economic development (Figure 1). Developed regions, such as Western Europe, show substantially higher DM prevalence rates that continue to increase despite the implementation of several public health measures. In 2019 the age-adjusted DM prevalence was 4.7% in Africa, 6.3% in Europe, 11.4% in the Western Pacific and Southeast Asia, 8.5% in South and Central America, 12.2% in the Middle East and North Africa, and 11.1% in North America and the Caribbean[39].

All regions in the world are expected to have an upsurge in the numbers of people living with DM. Overall, the estimated number of adults with DM will increase by 51% by 2045. While the African region currently holds the lowest prevalence of adults living with DM, it is expected to have the largest proportional increase in the numbers of adults with DM by 2045, with an increase of about 140%[41]. Moreover, the majority of people with DM in high-income countries are over the age of 50, whilst in the middle- and low-income countries are under the age of 50. The demographic patterns observed are likely to change considerably over the next generations, with improvements in life expectancy and higher rates of urbanization in these low- and middle-income countries[42]. Of notice, current general patterns indicate that there are more people living with DM in urban areas (65%) than in rural areas (35%)[15].

There is also substantial spatial variation of the distribution of DM at the subnational and local levels. To illustrate these variations, we mapped the subnational prevalence of DM in nine countries using data from the Demographic and Health Survey conducted in these countries (Figure 2). The description of the methods used

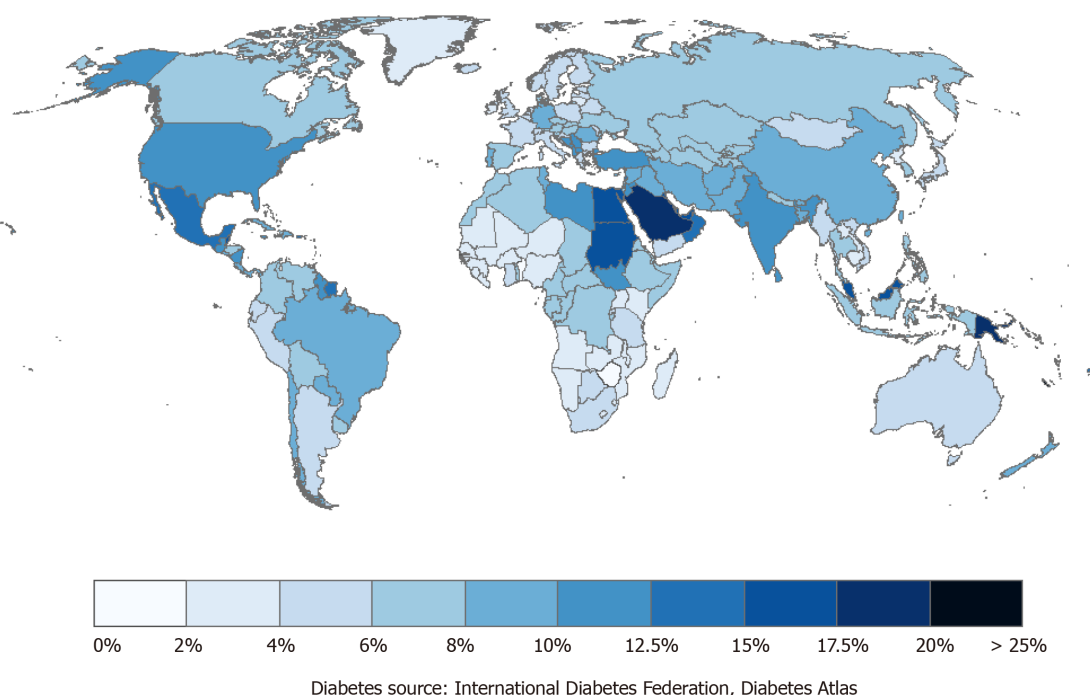


Figure 1 Global distribution of diabetes prevalence in 2017. Maps were created using ArcGIS® by ESRI version 10.5 (<http://www.esri.com>)[91].

for the generation of these maps can be found in Supplementary Material. The results of these maps illustrate the substantial local variation of DM prevalence within countries from different regions. The spatial structure of DM was characterized by local high DM prevalence areas where the burden of the disease was concentrated within a country (red areas in the map). These high burden areas identified locations in which the vulnerable population at high risk of the disease and the local drivers of the disease were concentrated. Such information would help to develop geographically targeted interventions tailored to the high-risk populations vulnerable to the disease at the subnational and local levels.

SPATIAL EPIDEMIOLOGY OF DIABETES

A spatial approach to disease analysis is relevant to any non-communicable disease linked to potential environmental and socio-economic drivers heterogeneously distributed in space. This approach is especially relevant to DM as recent research has identified potential associations between the spatial distribution of DM prevalence and geographical and environmental factors such as increased fast-food availability, green space, car-dominated transport, walkability and reduced spaces for exercise[43,44]. Many of these factors can be modified and included in health promotion programs, and spatial analysis can provide valuable evidence to inform resource allocation and public policy decisions targeting these potential geographical drivers of DM[45].

As mentioned previously, several demographic, clinical, and genetic factors are linked with an increased risk of developing DM[46]. In addition, there is now evidence of geographical and environmental factors associated with DM prevalence[47], and several of these factors are modifiable and candidates to be included in prevention programs, including lifestyle choices and associated cardiovascular risk, and other neighborhood factors amenable to health promotion programs. Therefore, the identification of areas where higher prevalence of environmental-related risk factors are concentrated would allow the design and implementation of geographically targeted health promotion programs oriented towards DM treatment and prevention. Moreover, spatial analysis designed to targeting health care needs at a local level can be essential in evaluating which areas are at higher risk of becoming unhealthy and thus need to be prioritized in the future by the identification of communities with a high-risk profile and the development of appropriate primary care interventions for DM prevention and treatment[48].

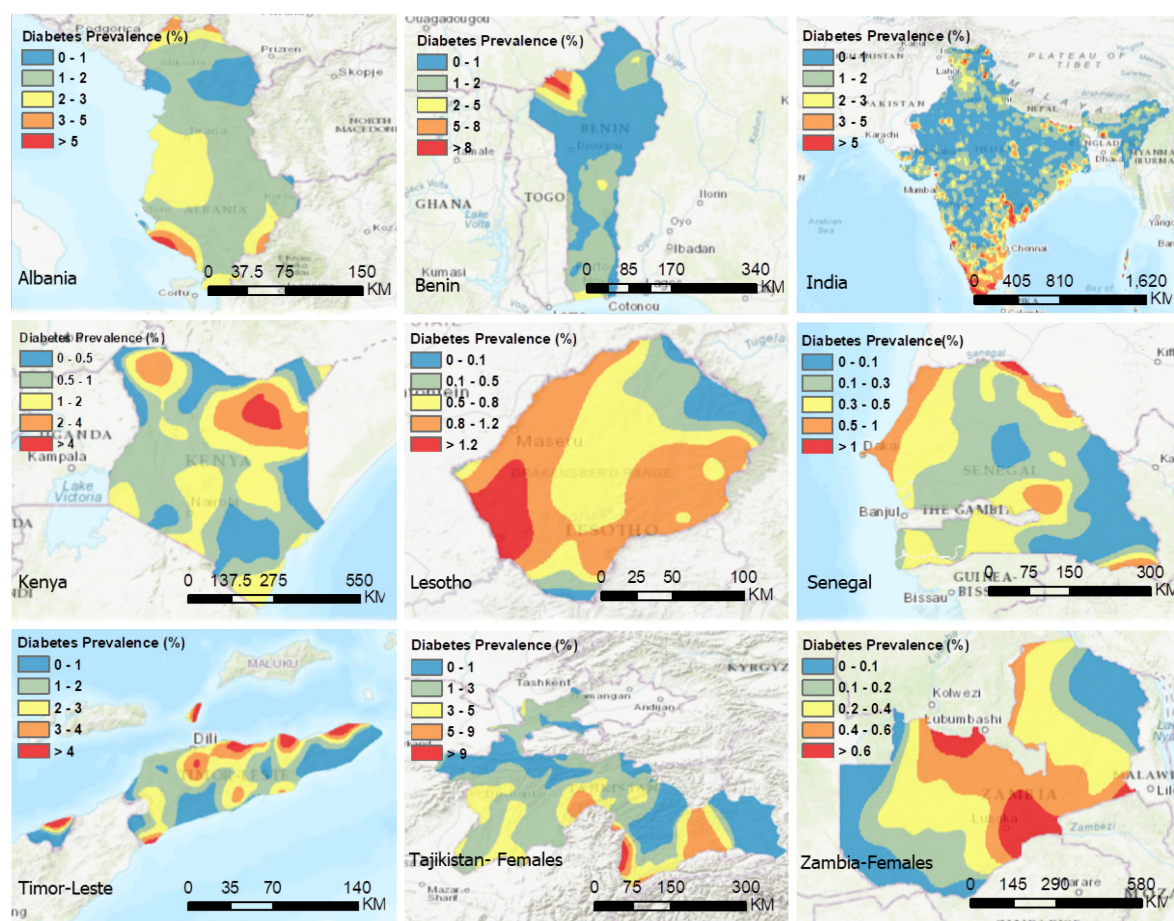


Figure 2 Spatial variations of diabetes prevalence in nine countries using a kernel smooth method. Maps were created using ArcGIS® by ESRI version 10.5 (<http://www.esri.com>)[91].

Several studies have identified geographical inequalities in the prevalence of risk factors and disease outcomes linked to complications of clinical DM. Disease clustering is observed not only among sociodemographic groups but also in urban geographies that boost obesity and physical inactivity[49-51]. Likewise, many built environment factors such as the rural-urban matrix[52,53], access to healthy foods[54], walkability [52], and crime levels[47] have been found to correlate with the heterogeneous distribution of DM prevalence. As the need for community-based interventions increases, it becomes essential to identify those communities at the highest risk of disease and DM complications in order to design suitable interventions based on their unique disease risk environment. Information on the relationship between DM prevalence and spatial factors such as the built environment could allow the design of better public health programs targeting populations at risk for DM. A short summary of several studies implementing different spatial methods to explore the spatial structure of DM is included in Table 1 and Supplementary Table 1.

Other recent important environmental factors have been linked with a higher risk of DM, particularly air pollution. Air pollution is an important global health problem, and $PM_{2.5}$, which is one of the most widely studied air pollutant, has been found to be associated with increased risk of several non-communicable diseases, including cardiovascular, pulmonary, kidney, and other diseases[55,56]. It has been estimated that this pollutant contributed to about 4.2 million premature deaths in 2015[57]. Growing evidence suggests a significant association between increased $PM_{2.5}$ exposure and the risk of DM, and it has been estimated that about 3.2 million cases of incident DM can be attributable to elevated concentrations of $PM_{2.5}$ in 2016[58]. Likewise, these studies have found substantial geographical variation in the burden of DM attributable to air pollution, and the link is stronger in less developed regions[58].

As countries develop economically and undertake an epidemiological transition, non-communicable diseases are likely to emerge even more prominent as major causes of disease and death, and the contribution of environmental factors including air pollution in the burden of non-communicable diseases in general, and specifically to DM, will probably become even more pronounced. The modifiable feature of these

Table 1 Methods for geospatial analysis with examples of applications and findings

Methods	Geospatial techniques	Ref.	Geographic unit and location	Key findings
Spatial clustering	Getis-Ord Gi	[92]	West Adelaide, Australia	Spatial distribution of dementia, depression, and type 2 diabetes varied across west Adelaide, respectively. Spatial convergence of the three diseases was identified in two large hot spot clusters
	Local Moran's I and the Getis-Ord Gi	[93]	Individual level in west Adelaide, Australia	Spatial heterogeneity in type 2 diabetes risk was present across communities, with significant clusters in the central part of the study area
	Moran's I	[31]	District level in India	The prevalence of diagnosed diabetes was substantially higher than that of self-reported diabetes in southern India (7.64% <i>vs</i> 2.38%) Diagnosed diabetes prevalence had positive moderate autocorrelation, and it varied from 10.52% in Goa to 4.89% in Telangana. The diagnosed diabetes prevalence was associated with higher proportion of people with secondary education and above, wealthy and Christian populations
	Moran's index and spatial regression	[94]	District level in Southern India	Spatial variations of high blood glucose (HBG) and very high blood glucose (VHBG) were observed across districts for women aged 15–49 years. District-level prevalence of HBG and VHBG were clustering across southern Indian districts. The HBG and VHBG prevalence were associated with district-level proportion of tobacco use, overweight, obese, and general caste
	Spatial statistic scan	[72]	Individual level in India	Substantial geographic variation in diabetes prevalence in India was found, with a concentrated burden at the southern coastline; Regional tuberculosis endemicity and diabetes spatial distributions showed that there is a lack of consistent geographical overlap between these 2 diseases
	Getis-Ord Gi	[95]	Individual and statistical area level 1 regions in western Adelaide, South Australia	The spatial heterogeneity of obesity, cardiovascular diseases (CVD), and type 2 diabetes was present across communities. Hot spots of these conditions clustered in three locations across western Adelaide. Area-level prevalence of CVD, obesity, and type 2 diabetes were negatively associated with socioeconomic status (SES)
	Global Moran's I, Local Moran's I and spatial regression	[32]	Individual and state level in Nigeria	Geographic clustering of diabetes mellitus (DM) and a DM pocket existed in the southeastern part of Nigeria. Obesity and education attainment were associated with the geographic variations of DM in the country
Spatial estimation models	Moran's I	[96]	Individual level in the city of Oslo, Norway	Diabetes prevalence clustered on the east side of Oslo. The diabetes prevalence was positively associated with neighborhoods with more fast foods and less healthy food shops and physical exercise facilities
	Spatial scan statistic and non-spatial linear regression	[47]	Administrative health area in the City of Winnipeg, Canada	Substantial clustering and small-area variations in DM prevalence existed in the city of Winnipeg. High rates of DM prevalence were associated with low SES, poor environmental quality and poor lifestyle
	Geographically weighted regression	[97]	Country-level of the continent United States	Significant spatial clustering of county-level diabetes prevalence was observed in the United State; the associations between diabetes prevalence and the percentage of poverty and percentage nonwhite population varied across regions in the United States.
	Geographically weighted regression	[98]	Country-level of the continent United States	The relationships between diabetes prevalence and poverty varied as a function of location
	Geographically weighted regression	[99]	Four-digit postal code level in Netherlands	Type 2 DM drug use is positively associated with population ageing, proportion of social welfare/benefits, proportion of low income, and proportion of pensioners. Spatial variabilities existed in these associations. Spatial analysis provided added value in predicting health care use at local level
	Tests of spatial autocorrelation and geographically weighted regression	[51]	Hospital referral regions in the United States	Lower-extremity amputation had spatial variations, with high rates clustered in southern states of the United States
	Spatial regression models	[100]	census-tract level in Chicago	Hypertension prevalence rates for patients were positively associated with areas with high rates of poverty, minority, and disability status. Neighboring tracts with high disease rates were the strongest predictor of cardiovascular-related chronic disease by several orders of magnitude. Diabetes had similar results
Multilevel models	Spatial autoregressive model	[101]	District-level in India	Spatial clustering was present in the burden of diabetes among women. The burden was relatively higher among women from the Southern and Eastern parts of the country. Diabetes was associated with obesity, hypertension, and living in urban areas
	Multilevel models	[102]	Individual level in Northern Netherlands	Individual risk factors at the neighborhood and municipality level explained 67.0% and 71.6% of the regional variations, respectively. Analysis on the smallest spatial scale best captured the regional variance. Individual and

				neighborhood body mass index (BMI) had significant interaction adjusting for the individual risk profile
	Multilevel negative binomial regression	[103]	Province level in China	Compared with the South, diabetes mortality was higher in the Northwest and Northeast. Diabetes mortality was higher in urbanized areas, with higher mean body mass index, and with higher average temperatures. Diabetes mortality was lower where consumption of alcohol was excessive
	Multilevel logistic regression	[104]	Province level in China	Diabetes prevalence and detection had widespread geographic variations across provinces in China. Adjusted regional diabetes prevalence was higher in the north (12.7%) than in the northeast (8.3%). Adjusted regional diabetes prevalence was higher in urban high socioeconomic circumstances (SEC) (13.1%) than in rural low-SEC counties/districts (8.7%). Adjusted diabetes detection was higher in the north (40.4%) and in urban high-SEC counties (40.8%) than in the southwest (15.6%) and the rural low-SEC counties (20.5%)
	Multilevel poisson regression	[105]	Canton-level in Southeastern France	Prevalence of treated diabetes was significantly higher in the more deprived and population-dense cantons
	Multilevel logistic regression	[106]	Census blocks in Paris, France	Prevalence of type 2 diabetes was higher in neighborhoods with the lowest levels of education attainment. Meanwhile, accounting for geographic variations in participation led to an 18% decrease in the log prevalence for low versus high neighborhood educations
Spatial analysis and GIS mapping	Choropleth mapping and logistic regression	[29]	County-level United States	Identifying a diabetes belt consisting of 644 counties in 15 mostly southern states in the United States. People in the diabetes belt were more likely being Non-Hispanic African American, leading a sedentary lifestyle, and being obese
	GIS methodology of spatial join	[107]	Census-tract level in greater Sacramento area United States	Neighborhood SES was a barrier to optimal glucose control, but not associated with low-density lipoprotein control. GIS analysis is useful for disease management programs
	Data aggregation to state-level and region-level	[108]	State-level United States	The spatial variations in the ratios of children with diabetes to pediatric endocrinologists were present: the ratios in Midwest (370: 1), South (335: 1), and West (367: 1) are twice as high as in the Northeast (144: 1). Across states, there is up to a 19-fold difference in the observed ratios of obese children to pediatric endocrinologists
	Data aggregation to district level and GIS mapping	[109]	Tower Hamlets, an inner city district of London, United Kingdom	Hot spots where up to 17.3% of all adults were at high risk of developing type 2 diabetes were identified. Small-area geospatial mapping is feasible for epidemiological and environmental data
	Data aggregation to electoral wards and Regression analysis	[110]	Electoral wards in England	The diabetes prevalence varied across different locations, ranging from 2.4% in Thames Valley to 4% in North East London. The methodology of prevalence estimates is applicable to developing small area prevalence estimates for a range of chronic diseases
	Data aggregation to electoral wards and GIS mapping	[111]	Electoral wards in Greater London	Environmental factors affected diabetes outcomes. The age-adjusted mortality rates in diabetic patients were higher in deprived areas than in prosperous areas
	Data aggregation to climato-geographic and administrative regions of the Ukraine	[112]	Administrative regions in Ukraine	Geographic variations in the insulin-dependent diabetes mellitus (IDDM) were present across various administrative regions of the Ukraine. The prevalence of IDDM varied from 1740 to 3813 patients per 1 million populations across Ukraine, with the west zone having lower prevalence than the average
Bayesian estimation approaches	Bayesian spatial analysis	[113]	Local administrative district level in Bangladesh	People of older age, higher education, better socio-economic condition, higher BMI were more likely to have hypertension and diabetes. Significant regional variations were observed with prevalence for hypertension ranges between 10% and 35% and for diabetes between 6% and 19% while their national prevalence were reported as 24% and 11%, respectively
	Bayesian hierarchical joint spatial analysis	[114]	Electoral wards in the Yorkshire, United Kingdom	Childhood lymphoblastic leukemia and type 1 diabetes varied across geographic locations, clustering in more rural areas
	Bayesian Small Area Estimates	[30]	County-level United States	Diabetes incidence was high in the southeastern United States, the Appalachian region, and in scattered counties throughout the western United States
	Bayesian estimation approach	[115]	Zip code census tract of United States	Significant spatial effects existed in the diabetes prevalence even after adjusting for age, education, ethnicity and known state predictors
Regression accounting for spatial variations	Regression-based β -convergence approach, accounting for spatial autocorrelation	[116]	County-level United States	County-level disparities in diagnosed diabetes prevalence in the United States broadened, while the disparities in diagnosed diabetes incidence narrowed. Demographic, socio-economic characteristics and risk factors of type 2 diabetes were associated with changes in disparities
	Sparse Poisson convolution; sparse Poisson missing-completely-at-random	[117]	County-level; Tract-level United States	The type 1 and type 2 DM incidences in young in United States varied across regions; the type 1 and type 2 DM incidences also differed across small areas within study region. The joint spatial correlation between type 1 DM and type 2 DM was present at the county level, but not at tract level

HBG: High blood glucose; VHBG: Very high blood glucose; SES: Socioeconomic status; DM: Diabetes mellitus; GIS: Geographic Information Systems; BMI: Body mass index; IDDM: Insulin-dependent diabetes mellitus.

attributes implies that changes in these factors can yield to positive reduction in risk and might generate substantial reductions in the burden of DM in high-risk areas.

DISEASE INTERACTIONS

Interactions between diseases are recently being recognized as a key factor that influences the natural history of the diseases[59-61]. Synergistic relationships between diseases coexisting in a population could influence epidemic dynamics, resulting in marked differences in health outcomes compared to the disease occurring isolated in the population[62,63]. Therefore, focusing on the dynamics of an isolated epidemic could prevent the identification of important processes that emerge from the syndemic relationship between diseases present in the affected population[61,63]. Understanding the mechanisms that shape within-population disease clustering could be essential for the design of disease control programs[61,63]. The spatial clustering of diseases and the identification of vulnerable populations to the disease must be recognized to integrate the key social and environmental risk factors that facilitate disease interactions among vulnerable populations. In this context, spatial epidemiology and disease mapping can help to provide effective information underlining the importance of the geographical clustering of several diseases within populations, the social and environmental contexts in which diseases cluster, the ways comorbidity affects the natural history of each other, the pathways of disease interaction, and how important these interactions can be to the health burden within affected populations.

The concept of disease interaction in the epidemiology of DM has been well documented at both population and individual levels. There is substantial evidence regarding the association between DM and other macro-and microvascular diseases such as hypertension, coronary arterial disease, and congestive heart failure. Other studies have also shown a significant association between DM and several cancer conditions such as colorectal cancer, pancreatic cancer, endometrial cancer, and prostate cancer. DM has also been associated with other non-communicable diseases such as acute pancreatitis, biliary disease, psoriasis, urinary tract calculi, and chronic obstructive pulmonary disease.

While the association between DM and other non-communicable disease are well investigated and repeatedly reported in the literature, the association between DM and communicable disease have been less investigated (and only within the last few decades) mainly due to the complex pathogenesis of the association. The comorbidity of DM and tuberculosis (TB) appears to be one of the syndemics between a non-communicable and communicable disease that have reached the interest of the public health practitioners[64-67]. The association between TB and DM has been documented first for over 1000 years ago by Avicenna (980-1027 AD). With the emergence of proper diagnostics and treatments (for both TB and DM) in the second half of the 20th century, the TB-DM association, along with its possible implications, had become neglected in policy and practice[68]. In recent decades, with the increasing DM (specifically T2DM) prevalence globally, particularly in low-income countries, the relationship has re-emerged as a significant public health problem—more so in developing countries where the prevalence of DM is rising, and TB is endemic[65]. DM increases susceptibility to TB by threefold and has an adverse effect on TB treatment outcomes[64,69-71]. The combination of TB and DM represents a global health threat, specifically in any setting where the overlap of populations at risk for both diseases is increasing. Regions like Western Pacific and Africa could be most affected by such interaction (*i.e.*, number of people with TB is high and DM is increasing substantially), while regions like Europe will not be substantially affected by such interaction. The spatial interaction between DM and TB has been explored and some evidence suggests that there is a spatial association between DM and TB. However, the evidence is inconsistent and more regional research is needed in this field[72].

Moreover, hepatitis C virus (HCV) infection and DM have been shown to coexist in an individual — DM modifies the course of HCV[73-75]. Based on the currently limited evidence, studies suggest that DM is associated with increased susceptibility to HCV infection[73,76-78]. This interaction could have an impact in countries such as

Egypt in which HCV prevalence is high and number of people living with DM is and will remain high. Malaria has also been documented to be more common in DM patients, in studies from Africa, but more evidence (and stronger) are needed in this regard as well[79]. Lastly, individuals with dengue fever and DM comorbidity seem to be at higher risk of developing complications and severe dengue compared to the general population[80,81]. However, a better understanding of the relevance of comorbidities in severe dengue are needed for regions with high prevalence of dengue infection (such as tropical and subtropical areas).

Some of the more recent evidence show that DM worsen the outcomes of other viral infections such as the severe acute respiratory syndrome coronavirus or the influenza A infection[82,83]. With the emergence of the novel RNA beta coronavirus, coronavirus disease 2019 (COVID-19) globally, DM has shown to affect the development and progression of COVID-19. Published evidence, though with limitations, has already reported that DM increases the risk of COVID-19 progression and severity of disease outcome[84]. A national-representative study that analyzed 61 million medical in-hospital records in the United Kingdom, reported that one-third of COVID-19 deaths occurred in people with T2DM[85]. Adjusted for previous hospital admissions with coronary heart disease, cerebrovascular disease, or heart failure, the study showed that odds of in-hospital deaths was 2.9 for T1DM and 1.8 for T2DM[85]. Data from the United States also highlighted that DM was reported as an underlying condition for approximately 4 in 10 COVID-19 patient and that about half of people younger than 65 who died from COVID-19 had DM. Hypotheses are still being explored to understand the biological mechanism(s) behind the collision of an old metabolic disease with a new infectious disease.

CONCLUSION

With nearly 400 million people around the world having prediabetes, DM emerges as one of the biggest public health challenges of our current times. However, one of the most significant public health advances in the study of DM is the demonstration that DM can be prevented by the implementation of effective interventions targeting the factors that exacerbate the risk of DM[86-89]. Early identification of vulnerable populations at higher risk of developing DM and the location of the areas where the risk is concentrated will help policymakers to tailor and target preventative interventions to communities with the greatest need. Likewise, more studies elucidating the direct role of spatial cofactors and the prevalence of diabetes are needed. Policymakers are interested in developing community-based interventions to manage DM, hence, it is of the greatest importance that we are able to identify communities at the highest risk so that appropriate intervention programs may be designed and implemented based on the community risk profile[90]. The value of spatial analysis could be fundamental in this task by identifying high burden areas or 'hotspots' of DM risk across high-risk communities. These spatial studies can highlight regions that can benefit from strategic geographically designed interventions aimed to manage and monitor the early emergence of DM epidemics, but also can identify potential areas with high burden of other diseases, where the interaction of these diseases and DM is high.

All countries, but particularly middle-and low-income countries with constrained resources, need to thoroughly maximize the benefits and reduce costs by efficiently allocate the scarce healthcare resources for targeted interventions for DM prevention and treatment. Spatially informed tailored strategies that allocate resources to prevent and treat DM would be an effective approach aimed to control and reduce the burden of the disease. Spatially explicit community-level policy interventions addressing key factors such as healthy food supply, a friendly built environment, tax policy, financial incentives and disincentives, and disease interactions would offer great promise in effectively addressing the obesogenic and diabetogenic environment aimed to control the global DM epidemic.

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