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Working Paper

The development of nations conditions the disease space

JRC Working Papers in Economics and Finance, No. 2019/9

Provided in Cooperation with:

Joint Research Centre (JRC), European Commission

Suggested Citation: Garas, Antonios; Guthmuller, Sophie; Lapatinas, Athanasios (2019) : The development of nations conditions the disease space, JRC Working Papers in Economics and Finance, No. 2019/9, ISBN 978-92-76-02924-3, Publications Office of the European Union, Luxembourg,
<https://doi.org/10.2760/793876>

This Version is available at:

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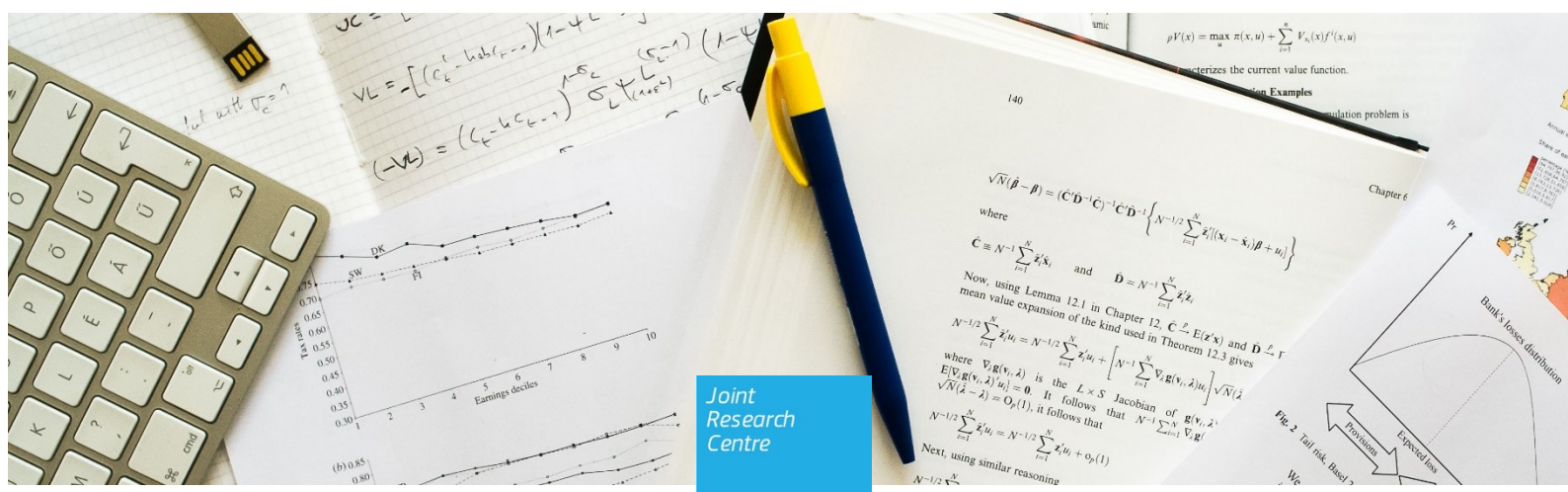
JRC TECHNICAL REPORTS

The development of nations conditions the disease space

Antonios GARAS,
Sophie GUTHMULLER,
Athanasios LAPATINAS

2019

JRC Working Papers in Economics and Finance, 2019/9



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JRC116399

PDF ISBN 978-92-76-02924-3 ISSN 2467-2203 doi:10.2760/793876

Luxembourg: Publications Office of the European Union, 2019

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How to cite this report: Garas A, Guthmuller S, Lapatinas A, *The development of nations conditions the disease space*, Publications Office of the European Union, Luxembourg, 2019, ISBN 978-92-76-02924-3, doi:10.2760/793876, JRC116399.

Contents

Acknowledgements	1
Abstract	2
1 Introduction	3
2 The country-disease network	5
2.1 Data on diseases and injuries	5
2.2 The country-disease bipartite network	5
3 The disease space and the health complexity index	8
3.1 The relative disease disadvantage	8
3.2 The disease space	8
3.3 Health complexity index	9
4 The geography of complex diseases	11
5 The effect of economic development on health complexity	11
5.1 Regression analysis	11
5.1.1 Control Variables	12
5.1.2 Instrumental variables	14
5.2 Regression results	14
6 Economic development and disease complexity	22
6.1 The disease complexity index	22
6.2 The disease-income complexity index	23
6.3 Linking disease complexity and economic development	24
7 Conclusions	25
References	26
List of figures	43
List of tables	44
Annexes	45
Annex 1. List of countries	45
Annex 2. List of diseases and injuries	46

Acknowledgements

The authors are grateful to Tor Iversen, Lisa Cameron, Enrica Croda for useful comments. They also thank all participants of the 10th Australasian Workshop on Econometrics and Health Economics (April 2019), and all participants of the 4th Edition of the European-American Health Economics Study Group (July 2019) for helpful comments and suggestions. All remaining errors are their own. This research was conducted while Sophie Guthmuller and Athanasios Lapatinas were in service at the European Commission's Joint Research Centre. The scientific output expressed does not imply a European Commission policy position. Neither the European Commission nor any person acting on behalf of the Commission is responsible for any use that might be made of this publication.

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Abstract

Using the economic complexity methodology on data for disease prevalence in 195 countries during the period of 1990-2016, we propose two new metrics for quantifying the relatedness between diseases, or the 'disease space' of countries. With these metrics, we analyze the geography of diseases and empirically investigate the effect of economic development on the health complexity of countries.

We show that a higher income per capita increases the complexity of countries' diseases. Furthermore, we build a disease-level index that links a disease to the average level of GDP per capita of the countries for which they have a relative disease disadvantage. With this index, we highlight the link between economic development and the complexity of diseases and illustrate, at the disease-level, how increases in income per capita are associated with more complex diseases.

Keywords: health complexity, disease complexity, economic development

1 Introduction

Popular belief holds that the European conquest of America was accomplished with guns and soldiers. However, (Bianchine and Russo, 1992) show that new illnesses brought from the Old World by European conquistadors, which resulted in devastating epidemics throughout the New World, were the major forces behind the aboriginal depopulation of the Americas. Our history, geography, culture, religion, and language have often been influenced by infections that have plagued humankind and shaped important events. Examples include the plague in fourteenth century Europe, how the yellow fever increased the importation of African slaves in the sixteenth century due to shortage of indigenous workers and the relative resistance of Africans to the disease, as well as the typhus deaths of the Napoleon's army during the 1812 Russian campaign, and Franklin D. Roosevelt's hypertension and heart failure, which worsened during his February 1945 dealings with Joseph Stalin in Malta (Post and Robins, 1995, Sherman, 2007, Taylor, 2016).

Furthermore, there is strong historical evidence that the wealth of nations is positively linked to the health of their populations. Since the eighteenth century, economic development associated with improvements in nutrition, access to sanitation, public health interventions, and medical innovations such as vaccination, have contributed to the reduction of major infectious diseases, the decline of premature death rates, and a longer life expectancy for children and adults in both developed and developing countries (Fogel, 1990, Fogel, 2004, Birchenall, 2007).

Nevertheless, many significant health problems have emerged in concert with economic development and technological modernization. Among them, stress, anxiety, sleep deprivation, and depression are mental disorders that are more prevalent in high-income countries. While they account for only 9% of the burden in low-income countries, this figure is 18% in middle-income and 27% in high-income countries (Prince, 2011). In OECD countries, a longer life expectancy is coupled with a higher rate of chronic and long-term illnesses in older populations (GBD2016 Dementia Collaborators, 2018). Industrialization has expanded the reach of existing food-related diseases and created new disorders and addictions (GBD 2015 Obesity Collaborators, 2017). Industrialization also stimulates urbanization, the process of population migration from rural areas to cities. This makes urban areas focal points for many emerging environmental and health hazards. According to the World Health Organization (WHO), *"as urban populations grow, the quality of global and local ecosystems, and the urban environment, will play an increasingly important role in public health with respect to issues ranging from solid waste disposal, provision of safe water and sanitation, and injury prevention, to the interface between urban poverty, environment and health."*¹ Industrialization is also linked to occupational accidents and work-related diseases (e.g., work-related cancers, musculoskeletal disorders, respiratory diseases, psycho-social problems, and circulatory diseases), which are worldwide problems resulting in important losses for individuals, organizations and societies (Driscoll et al., 2005, Nelson et al., 2005, Steenland et al., 2003, Park et al., 2002, Zahm and Blair, 2003, Hansen, 2001, Hoy et al., 2014, Punnett et al., 2005, Hoy et al., 2010).

From the above discussion, it becomes clear that economic development can affect population health in a number of ways, both positive and negative. To gain more insights on the link between economic development and countries' health status, we follow an innovative and holistic approach and study the country disease network and how countries are comparable or diverse in terms of diseases by building the disease space of countries, i.e., the network representation of the relatedness and proximity between diseases worldwide.

In fact, the country-disease network and the disease space reveal information about the health-related habits of populations, such as, lifestyle and dietary habits. There are also multiple reasons to expect the disease structures to be associated with their 'structural transformations' (i.e., the industrialization process by which economies diversify from agriculture to manufacturing and services (Hausmann and Klinger, 2006, Ngai and Pissarides, 2007, Gollin et al., 2002, Herrendorf et al., 2014, Laitner, 2000)), with their environmental performance (Künzli et al., 2000, Holgate et al., 1999, Chay and Greenstone, 2003, Kampa and Castanas, 2008), or with their adopted health-related policies (Glasgow et al., 1999, Whitlock et al., 2002, McKenzie et al., 2005, Drummond et al., 2015, Folland et al., 2007), as these contribute to their health status and living standards (Mankiw et al., 1992, Friedman, 2006). When a country is affected by a disease located in the core of the disease space,

¹WHO, 'Urbanization and health' <https://www.who.int/globalchange/ecosystems/urbanization/en/>

many other countries are also affected by this disease. These countries might share the same type of risks factors, population characteristics or life styles, and similar health care systems. However, this does not hold for diseases lying at the periphery of the disease space. Studying the structure of the disease space and knowing where a country is located in the country-disease network is therefore a useful tool to monitor the evolution of diseases and to plan global health policies.

We develop a new metric called the Health Complexity Index (HCI), that quantifies the disease space and encapsulates this information by assigning lower values to countries with diseases located at the periphery of the disease space and higher value to countries with diseases located at the centre of the disease space. This complexity index measures the composition of a country's pool of diseases by combining information on the diversity of diseases in the country and the ubiquity of its diseases (the number of other countries in which the disease exists). The intuition is that relatively high scores on the health complexity index indicate populations that are diverse and have diseases that, on average, have low ubiquity, i.e., these diseases are present in only a few other countries. In this view, the health complexity index does not refer to a complex treatment or to complex causes of a disease, but measures instead whether a disease is located in the densely connected core of the disease space i.e., whether many other related diseases are present in many other countries.

To compute the HCI, we follow the economic complexity methodology, which was initially applied to trade micro-data, measuring the amount of knowledge materialized in a country's productive structure (Hidalgo et al., 2007). Based on the ECI methodology, a number of recent contributions explain economic development and growth as a process of information development and of learning how to produce and export more diversified products (Abdon and Felipe, 2011, Bustos et al., 2012, Caldarelli et al., 2012, Cristelli et al., 2013, Felipe, 2012, Hausmann et al., 2007, Hausmann et al., 2014, Hidalgo and Hausmann, 2009, Hidalgo et al., 2007, Rodrik, 2006a, Tacchella et al., 2013, Albeaik et al., 2017b, Saviotti and Frenken, 2008, Cristelli et al., 2015, Hausmann and Hidalgo, 2011). Furthermore, (Hartmann et al., 2017) have recently shown that countries exporting complex products tend to be more inclusive and have lower levels of income inequality than countries exporting simpler products. In addition, (Lapatinas and Litina, 2018) find that countries with high intellectual quotient (IQ) populations produce and export more sophisticated/complex products, while (Lapatinas, 2019) shows that the Internet has a positive effect on economic complexity. Adopting the economic complexity methodology, (Balland and Rigby, 2017) compute a knowledge complexity index with more than two million patent records for US metropolitan areas between 1975-2010. They analyze the geography and evolution of knowledge complexity in US cities and show that the most complex cities in terms of patents are not always those with the highest rates of patenting. In addition, using citation data, they show that more complex patents are less likely to be cited than simpler patents when the citing and cited patents are located in different metropolitan areas.

The aim of this paper is fourfold: (i) to build two new metrics that quantify the disease space, following the economic complexity methodology; (ii) to estimate the effect of economic development on countries' health complexity using the new metrics and following dynamic panel data econometric techniques; (iii) to develop a disease-level index that links a disease to the average level of *GDP per capita* of the countries with a relative disease disadvantage; (iv) to illustrate how a country's economic development is associated with changes in its disease composition and verify the relationship between economic development and health complexity at the disease level.

The remainder of the paper is structured as follows. Section 2 describes the construction of the *country-disease network* and the the data on disease prevalence. Section 3 presents the methodology for developing the Health Complexity Index (HCI): the relative disease disadvantage and the disease space which form the analytic backbone of our study. Section 4 describes the geography of complex diseases, the link between ubiquity, diversity and the (HCI) with a particular focus on countries and regions. Section 5 empirically investigates the effect of economic development on health complexity using the HCI, data on *GDP per capita* and potential covariates. Section 6 introduces an index that decomposes economic performance at the disease level. Using this index, we highlight the link between disease complexity and economic development. We demonstrate, at the disease level, that better economic performance is associated with more complex diseases. Finally, in section 7, we offer some concluding remarks.

2 The country-disease network

2.1 Data on diseases and injuries

Information on diseases and injuries comes from the Global Burden of Diseases (GBD) study by the Institute for Health Metrics and Evaluation (IHME), an independent population health research centre at UW Medicine (University of Washington) (GBD Study 2016, 2016) that produces comparable estimates of prevalence of diseases and injuries across the world for 195 countries and over 300 diseases and injuries (<http://www.healthdata.org/>).

We use data from the 2016 version of the GBD study in which data are estimated based on various sources (input data come from administrative records, surveys, census, scientific literature, etc) with different methods to reflect the available data and the specific epidemiology of each disease from 1990 to 2016. Computational methods are detailed in the appendix of (GBD Study 2016, 2016).

Diseases and injuries are grouped by causes. The broader classification of causes (level 1) includes: (a) *communicable, maternal, neonatal, and nutritional diseases* such as HIV/AIDS and sexually transmitted infections, respiratory infections and tuberculosis, enteric infections (e.g., diarrheal diseases, typhoid fever), neglected tropical diseases (e.g. malaria, chagas disease) and other infectious diseases (e.g. meningitis and acute hepatitis), maternal and neonatal disorders (e.g., maternal abortion and miscarriage, ectopic pregnancy, maternal obstructed labor and uterine rupture), nutritional deficiencies (e.g., protein-energy malnutrition, vitamin A, iron, iodine deficiencies); (b) *non-communicable diseases* such as cancers, cardiovascular diseases, chronic respiratory diseases, digestive diseases (e.g., cirrhosis, gastritis, pancreatitis), neurological disorders (e.g., multiple sclerosis, epilepsy, Parkinson's and Alzheimer's diseases, migraine), mental disorders (e.g., schizophrenia, anorexia nervosa and bulimia nervosa, conduct and hyperactivity disorders), substance use disorders (e.g., alcohol and drug use disorders), diabetes, kidney diseases, skin diseases (e.g., dermatitis, bacterial skin diseases), sense organ diseases (e.g., glaucoma, cataract, vision loss), musculoskeletal disorders (e.g., osteoarthritis, rheumatoid arthritis); (c) *injuries* such as transport injuries (e.g., pedestrian road injuries, cyclist and motorcyclist road injuries), unintentional injuries (e.g., falls, poisonings, exposure to mechanical forces), self-harm and interpersonal violence (e.g., sexual violence, conflict and terrorism, executions).²

We use information for the most detailed level of causes in the GBD taxonomy (i.e., level 4, and when there is no level 4 classification, we use level 3). For example, among the non-communicable diseases (level 1), neoplasms (level 2) include the following level 3 categories: lip and oral cavity cancer, nasopharynx cancer, other pharynx cancer, esophageal cancer, stomach cancer, colon and rectal cancer, liver cancer, gallbladder and biliary tract cancer, pancreatic cancer, larynx cancer, etc. Then, liver cancer includes the following level 4 subcategories: liver cancer due to hepatitis B, liver cancer due to hepatitis C, liver cancer due to alcohol use, liver cancer due to non-alcoholic steatohepatitis (NASH), liver cancer due to other causes.

Two measures of disease prevalence are exploited: the rate of prevalence (number of cases per 100,000 population) for all ages, and the age-standardized rate of prevalence to account for the differences in age structures across countries. This is useful because relative over- or under-representation of different age groups can obscure comparisons of age-dependent diseases (e.g., ischemic heart disease or malaria) across populations.

The list of countries and diseases are detailed in Annexes.

2.2 The country-disease bipartite network

Instrumental to our analysis is the bipartite network mapping of countries and diseases. Bipartite, or bi-modal networks are abundant in the scientific literature, with examples including the city-tech knowledge network (Balland and Rigby, 2017), the city-firm network (Garas et al., 2019), firm-projects networks (Balland, 2012), predator-prey networks (Allesina and Tang, 2012), plants-pollinator networks (Bascompte et al., 2003) etc. Here, based on data from the GBD study 2016 that assessed the disease burden of countries in the period of 1990 to 2016, we generate an $l \times k$ country-diseases matrix \mathbb{E} , where

²In the remainder of the paper we use the word 'disease' to refer to all diseases and injuries classified in the GBD study.

the matrix element E_{cd} represents the number of cases of disease d per 100,000 population in country c .

The aforementioned matrix allows for the construction of an undirected, weighted country-disease network by linking each disease to the countries with disease cases. These networks are very dense, and in order to visually explore their structure, we apply the Dijkstra algorithm (Dijkstra, 1959) to extract a Maximum Spanning Tree (MST) that summarizes their structures. More precisely, the MST, which is usually considered as the backbone of the network, is a connected subgraph having $l + k - 1$ edges with the maximum total weight and without forming any loops.

In Figure 1 we illustrate the country-disease MST for 2016. From this MST, we can easily identify clusters of countries that are linked to specific types of diseases. The main node of the network is caries in permanent teeth (disease cause number 682, Appendix 2 reports the correspondence table between each disease number and its name.) This disease is the most common disease across the world, as it is present in the majority of countries. It is also the disease with the highest prevalence worldwide (2.44 billion cases in 2016 (GBD Study 2016, 2016))

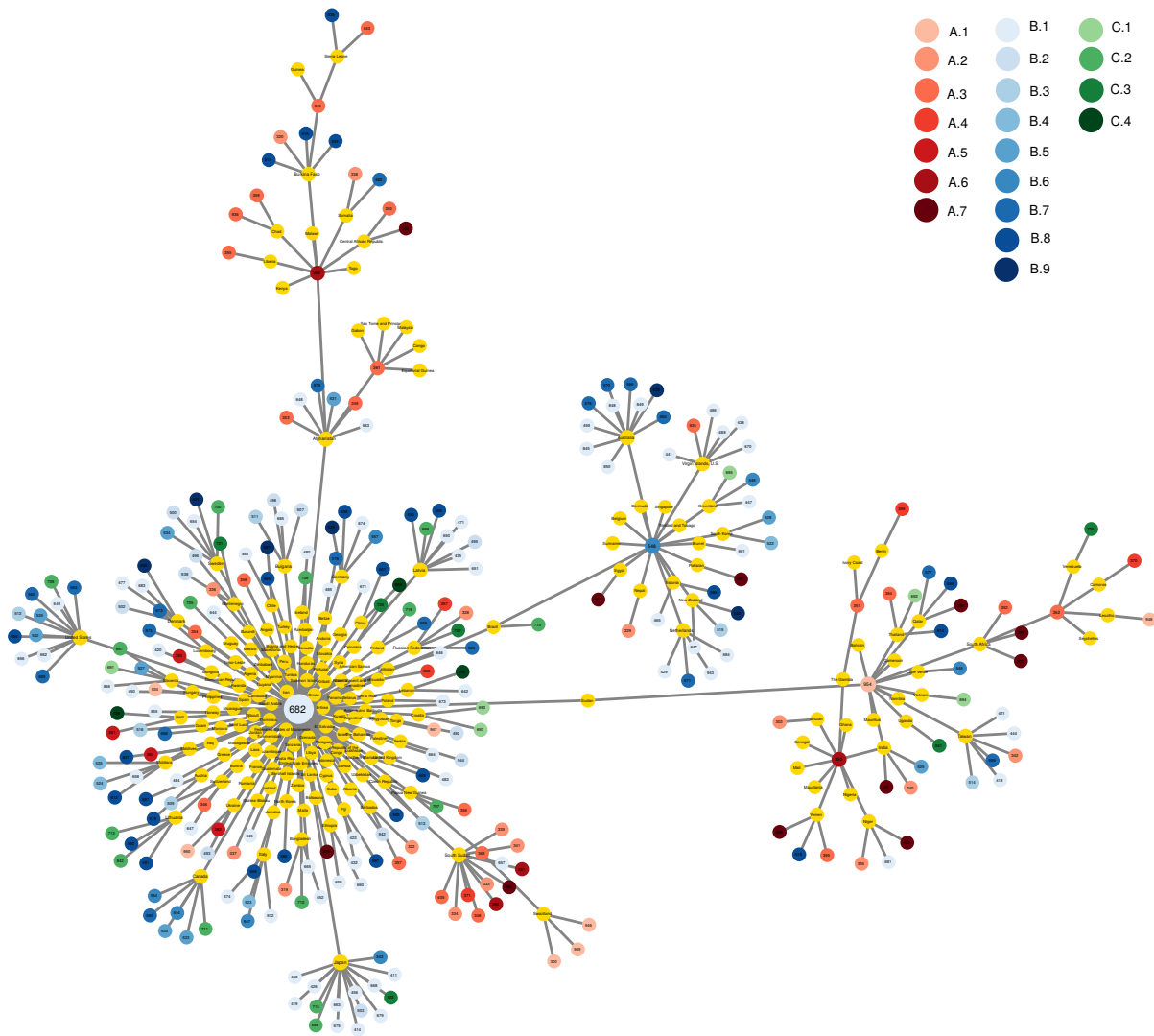


Figure 1: Maximum Spanning Tree of the country-disease bipartite network. Countries are represented by yellow nodes, and diseases cover the following categories: [A. 'Communicable, maternal, neonatal, and nutritional diseases'] A.1 'HIV/AIDS and tuberculosis', A.2 'Diarrhea, lower respiratory, and other common infectious diseases', A.3 'Neglected tropical diseases and malaria', A.4 'Maternal disorders', A.5 'Neonatal disorders', A.6 'Nutritional deficiencies', A.7 'Other communicable, maternal, neonatal, and nutritional diseases'; [B. 'Non-communicable diseases'] B.1 'Neoplasms', B.2 'Cardiovascular diseases', B.3 'Chronic respiratory diseases', B.4 'Cirrhosis and other chronic liver diseases', B.5 'Digestive diseases', B.6 'Neurological disorders', B.7 'Mental and substance use disorders', B.8 'Diabetes, urogenital, blood, and endocrine diseases', B.9 'Musculoskeletal disorders'; [C. 'Injuries'] C.1 'Transport injuries', C.2 'Unintentional injuries', C.3 'Self-harm and interpersonal violence', C.4 'Forces of nature, conflict and terrorism, and executions and police conflict'. Data for 2016. Annexe 2 reports the correspondence table between the disease number and the disease name.

3 The disease space and the health complexity index

To calculate *health complexity*, we combine information on diseases prevalence and how common these diseases are across countries, following the economic complexity methodology, i.e., the formulas in the pioneering work of (Hidalgo and Hausmann, 2009).

3.1 The relative disease disadvantage

In short, let us assume that we have disease information for l number of countries and k diseases. With this information, we can fill an $l \times k$ diseases matrix \mathbf{E} , so that matrix element E_{cd} is country c 's information for disease d . If there is no information for disease d in country c , then $E_{cd} = 0$.

From this matrix, it is easy to calculate the following ratio:

$$RDD_{cd} = \frac{X_{cd} / \sum_{d'} X_{cd'}}{\sum_{c'} X_{c'd} / \sum_{c', d'} X_{c'd'}}, \quad (1)$$

where X_{cd} is the number of disease cases d per 100,000 population in country c .

Similar to the economic complexity methodology and the discussion in (Hidalgo and Hausmann, 2009, Caldarelli et al., 2012, Hartmann et al., 2017), we claim that a country has a relative disease disadvantage in a disease when $RDD_{cd} \geq 1$. In other words, a country c has a RDD in disease d if the proportion of disease case d in the country's pool of all cases of diseases is higher than the proportion of disease case d in the world's pool of all diseases cases.

Using this threshold value, we obtain the $l \times k$ matrix \mathbf{M} , with matrix elements $M_{cd} = 1$ if country c has a RDD in disease d , and zero otherwise. A visualization of the matrix \mathbf{M} for this dataset is shown in Figure 2, where a dark point indicates that country c has a RDD in a given disease d .

The matrix is sorted using the NODF algorithm (Almeida-Neto et al., 2008), which highlights the existence of countries that are very well diversified and countries that have a relative disease disadvantage only in a small set of diseases.

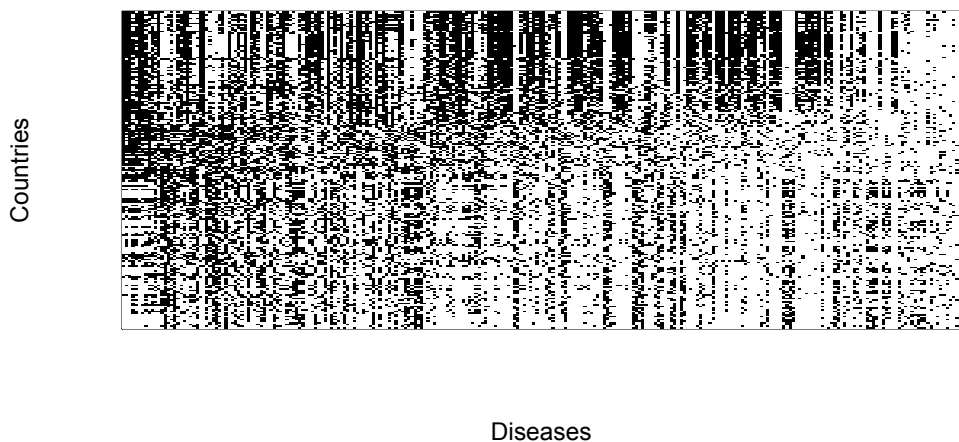


Figure 2: Matrix representation of the links between countries and diseases. A visualization of this matrix for the year 2016, where a dark point indicates that country c has a RDD in a given disease d . The matrix is sorted using the NODF algorithm (Almeida-Neto et al., 2008), which highlights the existence of countries that are very well diversified and countries that have a relative disease disadvantage only in a small set of diseases.

3.2 The disease space

To explore this further, we construct the disease space, similar to the product-space introduced by (Hidalgo et al., 2007).

Calculating the RDD for all country-disease pairs allows us to derive a matrix Φ , whose elements $\Phi_{i,j}$ define a proximity measure between all pairs of diseases. This proximity measure reveals diseases that are present in tandem, or in other words, with Φ , we measure the probability that a country c , which has a relative disease disadvantage in disease i , also has a relative disease disadvantage in disease j . The proximity measure is defined as:

$$\Phi_{i,j} = \min\{\Pr(\text{RDD}_i \geq 1 \mid \text{RDD}_j \geq 1), \Pr(\text{RDD}_j \geq 1 \mid \text{RDD}_i \geq 1)\}, \quad (2)$$

where $\Pr(\text{RDD}_i \geq 1 \mid \text{RDD}_j \geq 1)$ is the conditional probability of having a relative disease disadvantage in disease i if you have a relative disease disadvantage in disease j . Using the minimum of both conditional probabilities, we avoid issues of a rare disease being present in only one country. Additionally, we make the resulting matrix Φ symmetric (see Figure 3). The proximity matrix is highly modular and its block structure reveals the presence of 'communities', i.e., groups of diseases that are expected to occur together.

Next, we map this matrix onto a network, where each disease is represented by a node and every matrix element represents a weighted and undirected link. Similar to Figure 1, we start by applying Dijkstra's algorithm on matrix Φ which calculates the MST of the network. Following the rationale of (Hidalgo et al., 2007), we start from the strongest links that are not part of the MST and keep adding links to the network until the average degree is four. The resulting network is a visual representation of the disease space, which is shown in Figure 3.

From Figure 3, it is evident that in the disease space network, different disease categories are clustered together and the network is heterogeneous and follows a core-periphery structure. The external part of the network (the periphery) is mostly dominated by 'communicable, maternal, neonatal, and nutritional diseases'. On the other hand, the core of the network is dominated by 'non-communicable diseases'.

Figure 4 shows the patterns of disease localisation in the world's economies, classified by the World Bank into four income groups - 'high', 'upper-middle', 'lower-middle', and 'low'. Diseases in a region where more than half of its countries have a $\text{RDD} > 1$ are shown with black nodes. It seems that high-income countries occupy the core, composed of 'non-communicable diseases' such as 'pancreatic cancer', 'Parkinson disease', 'ischemic stroke' and injuries such as 'falls', 'poisonings' and 'other exposure to mechanical forces'. On the other side of the spectrum, low-income countries tend to have a RDD in 'communicable, neonatal, maternal and nutritional diseases' that lie in the periphery of the disease space such as 'diarrheal diseases', 'encephalitis' and 'malaria'. Most of the communicable diseases for which low-income countries have a $\text{RDD} > 1$ also appear in the periphery (for example, 'Turner syndrome', 'neural tube defects' and 'pyoderma'). Examples of injuries for which low-income countries have a RDD include 'venomous animal contact' and 'sexual violence', which again appear in the periphery of the disease space.

3.3 Health complexity index

From matrix \mathbf{M} , similar to (Hidalgo and Hausmann, 2009), we introduce the health complexity index (HCI) as a measure of countries' disease structures. To obtain the HCI, we first calculate the $l \times l$ square matrix $\tilde{\mathbf{M}}$. In short, matrix $\tilde{\mathbf{M}}$ provides information about links connecting two countries c and c' , based on the prevalent cases of diseases in both. The matrix elements $\tilde{M}_{cc'}$ are computed as

$$\tilde{M}_{cc'} = \frac{1}{k_{c,0}} \sum_d \frac{M_{cd} M_{c'd}}{k_{d,0}}, \quad (3)$$

where $k_{c,0} = \sum_d M_{cd}$ measures the diversification of country c in terms of its different diseases, and $k_{d,0} = \sum_c M_{cd}$ measures the number of countries with disease cases d . If \mathbf{K} is the eigenvector of $\tilde{\mathbf{M}}$ associated with the second largest eigenvalue, then according to (Hausmann et al., 2014), the HCI is calculated as

$$\text{HCI} = \frac{\mathbf{K} - \langle \mathbf{K} \rangle}{\text{std}(\mathbf{K})}. \quad (4)$$

The HCI reflects the disease-composition of a country's pool of diseases, taking into account the composition of the pools of all other countries. Populations with diseases that occur

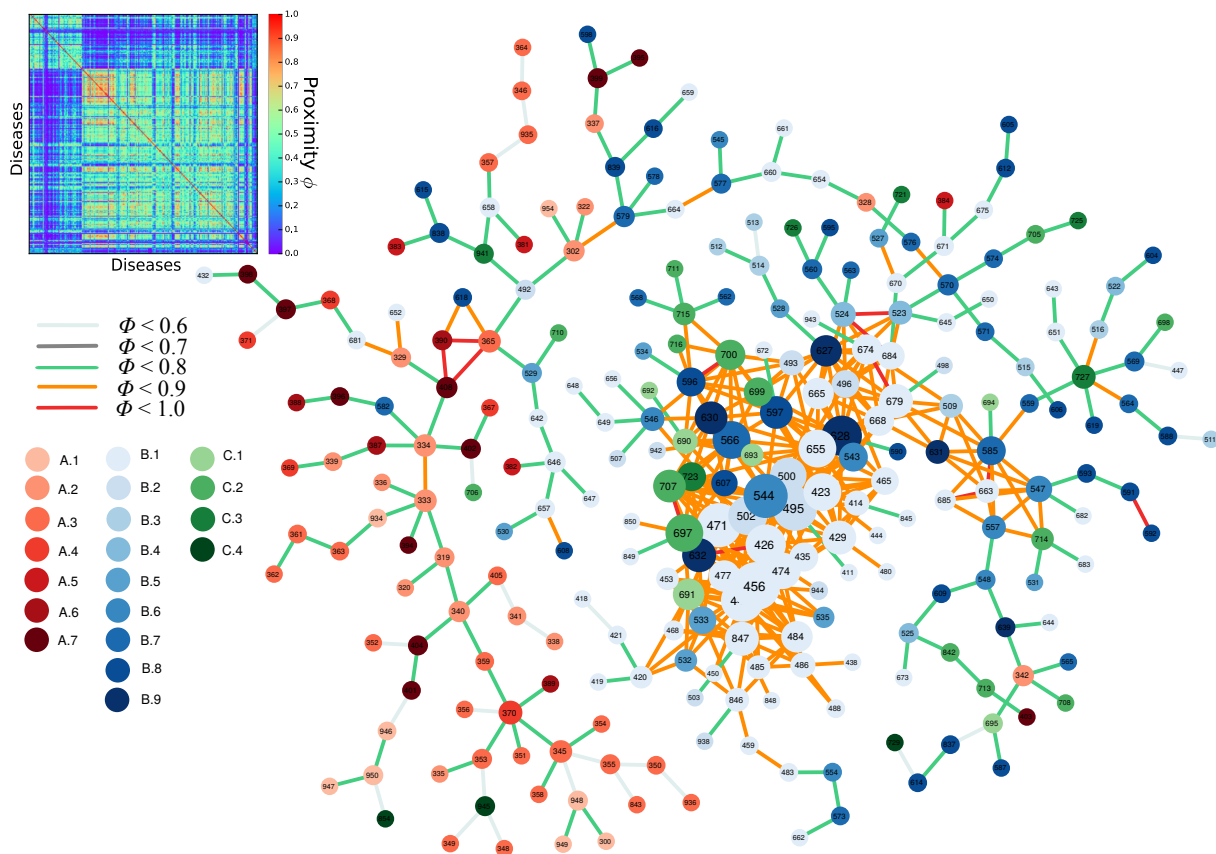


Figure 3: The proximity matrix and the resulting disease space. The size of the nodes is proportional to their degree, i.e., the number of links. Disease colors cover the following categories: [A. 'Communicable, maternal, neonatal, and nutritional diseases'] A.1 'HIV/AIDS and tuberculosis', A.2 'Diarrhea, lower respiratory, and other common infectious diseases', A.3 'Neglected tropical diseases and malaria', A.4 'Maternal disorders', A.5 'Neonatal disorders', A.6 'Nutritional deficiencies', A.7 'Other communicable, maternal, neonatal, and nutritional diseases'; [B. 'Non-communicable diseases'] B.1 'Neoplasms', B.2 'Cardiovascular diseases', B.3 'Chronic respiratory diseases', B.4 'Cirrhosis and other chronic liver diseases', B.5 'Digestive diseases', B.6 'Neurological disorders', B.7 'Mental and substance use disorders', B.8 'Diabetes, urogenital, blood, and endocrine diseases', B.9 'Musculoskeletal disorders'; [C. 'Injuries'] C.1 'Transport injuries', C.2 'Unintentional injuries', C.3 'Self-harm and interpersonal violence', C.4 'Forces of nature, conflict and terrorism, and executions and police conflict'. Data for 2016. Annex 2 reports the correspondence table between the disease number and the disease name.

in many other countries have relatively low health complexity scores, while more health-complex countries have a high prevalence of non-ubiquitous diseases. In other words, a country has a complex disease composition, i.e., it is health-complex, if its diseases have high prevalence in only a few other countries. The HCI is higher for countries with diseases located at the core of the 'disease-space' and lower for countries with diseases located at the periphery of the 'disease-space'.

As discussed in Section 2.1, the HCI is computed using in X_{cd} the number of prevalent cases of a disease (according to cause levels 3 or 4) per 100,000 population for 195 countries and for 196 diseases. The time-period covered is from 1990 to 2016. With the age-standardized data (see the discussion in Section 2.1), we also calculate the age-standardized health complexity index (AHCI) following the same formulas. We use the two indices as alternative measures when checking the robustness of our results. It should be noted here that the computation of the indices is based only on diseases for which a country has a RDD in terms of disease prevalence (the incidence matrix of the bipartite network linking countries to diseases, \mathbf{M} , reflects whether or not a country has a RDD in a specific disease; see Figure 2).

4 The geography of complex diseases

As shown in Figure 4, the localisation of diseases in different income-regions of the world is also observable in Figure 5, where we map the spatial variation in complex diseases. This figure shows the repartition of the HCI across countries when taking average values for the period 1990-2016. We see rather clearly that disease complexity is unevenly distributed in the world and that the most complex countries in terms of diseases seem to be located in Europe, North America, and Australia – European countries, Australia, the US, and Canada belong to the set of countries with the highest HCI (>80%). In contrast, most countries in Africa have much lower HCIs on average.

Regarding the evolution of HCI scores over time, figures 6 and 7 depict how health complexity in our sample of countries has changed from 1990-1996 to 2010-2016. Cambodia, Myanmar, Nepal, Vietnam, Saint Lucia, and Cameroon have registered significant increases in the complexity of their diseases. On the other hand, the diseases of countries like Vanuatu, Kiribati, Palestine, Tajikistan, and Gabon are now less complex than in the early 1990s. Figure 7 depicts the same information in a world map. Blue and light blue colors depict a decrease in HCI score, while orange and red colors denote countries with an increase in HCI score from 1990-1996 to 2010-2016. From these figures, it can be observed that changes over time are rather small. Hence, it seems that a country's HCI score tends to persist through time, which is to be expected for a metric of prevalent cases of diseases aggregated at the country level. This motivates the inclusion of the lagged value of HCI in the set of explanatory variables when estimating the effect of economic development on health complexity in the next section.

5 The effect of economic development on health complexity

We study the effect of economic development on health complexity using data on GDP per capita (from the World Bank's World Development Indicators) and the HCI (see Section 3). Given the availability of controls, the sample covers a minimum of 168 developed and developing countries over the period of 1992-2015.³

5.1 Regression analysis

Previous research shows that there is a strong association between income and indicators of population health such as life expectancy and child mortality. There are various channels through which economic development can stimulate health improvements, for example, via its effect on nutrition (which in turn leads to better resistance to bacterial diseases and faster recovery from illnesses), as well as through greater labor market participation, worker productivity, investment in human capital, investment in public and private health services, savings, fertility, transportation infrastructure, and lifestyle habits. (Preston, 1975, Smith, 1999, Bloom et al., 1998, Gallup and Sachs, 2001, Alleyne and Cohen, 2002, Bloom et al., 2005, Lorentzen et al., 2008, Easterlin, 1999, Hamoudi et al., 1999).⁴ The term 'diseases of affluence' refers to selected diseases and health conditions that are more prevalent in wealthy nations. Examples include mostly non-communicable diseases such as cardiovascular diseases and their nutritional risk factors (overweight and obesity,

³Afghanistan, Albania, Algeria, Angola, Antigua and Barbuda, Argentina, Armenia, Australia, Austria, Azerbaijan, Bahamas, Bahrain, Bangladesh, Barbados, Belarus, Belgium, Belize, Benin, Bhutan, Bolivia, Bosnia and Herzegovina, Botswana, Brazil, Brunei, Darussalam, Bulgaria, Burkina Faso, Burundi, Cabo Verde, Cambodia, Cameroon, Canada, Central African Republic, Chad, Chile, China, Colombia, Comoros, Rep. of the Congo, Costa Rica, Cote d'Ivoire, Croatia, Cyprus, Czech Republic, Denmark, Dominican Republic, Ecuador, Arab Rep. of Egypt, El Salvador, Equatorial Guinea, Estonia, Eswatini, Ethiopia, Fiji, Finland, France, Gabon, Gambia, Georgia, Germany, Ghana, Greece, Grenada, Guatemala, Guinea, Guinea-Bissau, Guyana, Haiti, Honduras, Hungary, Iceland, India, Indonesia, Islamic Rep. of Iran, Iraq, Ireland, Israel, Italy, Jamaica, Japan, Jordan, Kazakhstan, Kenya, Kiribati, Rep. of Korea, Kuwait, Kyrgyz Republic, Lao PDR, Latvia, Lebanon, Lesotho, Liberia, Libya, Lithuania, Luxembourg, Macedonia FYR, Madagascar, Malawi, Malaysia, Maldives, Malta, Mauritania, Mauritius, Mexico, Moldova, Mongolia, Montenegro, Morocco, Mozambique, Myanmar, Namibia, Nepal, Netherlands, New Zealand, Nicaragua, Niger, Nigeria, Norway, Oman, Pakistan, Panama, Papua New Guinea, Paraguay, Peru, Philippines, Poland, Portugal, Qatar, Russian Federation, Rwanda, Samoa, Sao Tome and Principe, Saudi Arabia, Senegal, Serbia, Seychelles, Sierra Leone, Singapore, Slovak Republic, Slovenia, South Africa, Spain, Sri Lanka, St. Lucia, St. Vincent and the Grenadines, Sudan, Suriname, Sweden, Switzerland, Tajikistan, Tanzania, Thailand, Togo, Tonga, Trinidad and Tobago, Tunisia, Turkey, Uganda, Ukraine, United Arab Emirates, United Kingdom, United States, Uruguay, Vanuatu, Venezuela RB, Vietnam, Rep. of Yemen, Zambia, Zimbabwe.

⁴For a review of the empirical evidence see (Lange and Vollmer, 2017).

elevated blood pressure and cholesterol). It has been shown that economic development is a robust predictor of 'diseases of affluence' (Ezzati et al., 2005, Gupta, 2006, Murray et al., 1996, Reddy and Yusuf, 1998, Yusuf et al., 2001). However, there is also a large and growing literature that investigates the reverse channel, i.e., that better population health leads to economic development (Acemoglu and Johnson, 2007, Bleakley, 2010). The argument is that improved health conditions increase population size, which – in the medium term – leads to more people entering the labor force, higher capital accumulation, and higher income per capita.

In order to estimate the effect of economic development on the health complexity of countries we follow a fixed-effects two-stage least squares/instrumental variables (FE 2SLS/IV) strategy, complemented with a difference Generalized Method of Moments (diff-GMM) approach. We regress the baseline specification described by the following equation:

$$HCI_{i,t} = \rho HCI_{i,t-1} + \beta_1 GDPpc_{i,t} + \beta_k controls_{i,t} + \gamma_i + \delta_t + u_{i,t}. \quad (5)$$

Here, the health complexity of country i in period t ($HCI_{i,t}$) depends on the country's level of economic development in per capita terms (in logs), $GDPpc_{i,t}$. The lagged value of the dependent variable on the right-hand side is included to capture persistence in health complexity. The main variable of interest is $GDPpc$. The parameter β_1 therefore measures the effect of income per capita on health complexity.⁵ Additional potential covariates are included in the vector $controls_{i,t}$. The γ_i 's denote a full set of country dummies and the δ_t 's denote a full set of time effects that capture common shocks to the health complexity scores of all countries. The error term $u_{i,t}$ captures all other omitted factors, with $E(u_{i,t}) = 0$ for all i and t . To examine the robustness of our results and to generalize our findings, we replicate our analysis for additional/alternative control variables and substitute the HCI with the AHCI, finding qualitatively similar results (see subsection 5.2).

5.1.1 Control Variables

We include in the estimated equation a number of control variables that are likely related to health complexity.

The proportion of nations' populations over the age of 65 has been increasing in recent years and will continue to rise in future as a result of longer life expectancy. Population age-structure is a significant determinant of a nation's health status, due to age-related diseases (i.e., illnesses and conditions that occur more frequently in people as they get older). Examples of age-related diseases include cardiovascular and cerebrovascular diseases, hypertension, cancer, Parkinson's disease, Alzheimer's disease, osteoarthritis and osteoporosis. Demographic factors such as age and sex are considered key covariates in the study of human health and well-being, hence the percentage of *old* population (aged 65 and above, in logs) and the percentage of *female* population (in logs) are included in the set of control variables.

It has previously been shown that sex interacts with social, economic and biological determinants to create different health outcomes for males and females. For example, (Vlassoff, 2007) reviews a large number of studies on the interaction between sex and the determinants and consequences of chronic diseases, showing how these interactions result in different approaches to prevention, treatment, and coping with illness.

In our analysis, we also control for the (log) percentage of urban population, *urban*. According to the World Health Organization (WHO), a large proportion of non-communicable diseases is linked to risks related to the urban environment, such as physical inactivity and obesity, cardiovascular and pulmonary diseases from transport-generated urban air pollution, ischemic heart disease and cancers from household biomass energy use, asthma from indoor air pollution, and heat-related strokes and illnesses. In addition, communicable diseases such as tuberculosis, dengue fever, and many respiratory and diarrheal diseases result from unhealthy urban environments (e.g. lack of adequate ventilation, unsafe water storage and poor waste management, indoor air pollution, moldy housing interiors, poor sanitation).⁶

⁵In order to account for possible changes in the relation between economic development and health complexity over the process of economic development, we have experimented with the inclusion of the quadratic specification of GDP per capita in the estimated equation. Our baseline results (which are available upon request) do not confirm a U-shaped relationship between economic development and health complexity.

⁶See WHO, Health and sustainable development: About health risks in cities, <https://www.who.int/sustainable-development/cities/health-risks/about/en/>

Table 1: Variable definitions, sources and summary statistics

Variable	Definition	Source	Mean	Std. Dev.
HCI	Health Complexity Index.	Authors' calculations	-0.006	1.004
HCI+	age-standardized Health Complexity Index.	Authors' calculations	-0.008	1.008
GDPpc	(log) GDP per capita, PPP (constant 2011 international \$)	World Development Indicators	8.342	1.521
old	(log) Population aged 65 and above (% of total)	World Development Indicators	1.764	0.667
female	(log) Female population (% of total)	World Development Indicators	3.912	0.067
urban	(log) Urban population (% of total)	World Development Indicators	3.871	0.519
agriculture	(log) Agriculture, value added (% of GDP)	World Development Indicators	2.054	1.228
manufacturing	(log) Manufacturing, value added (% of GDP)	World Development Indicators	2.407	0.591
education	(log) Enrollment in secondary education, both sexes (total)	World Development Indicators	4.229	0.587
population density	(log) Population density (people per sq. km of land area)	World Development Indicators	4.123	1.398
CO ₂	(log) CO2 emissions (kg per 2010 \$US of GDP)	World Bank	-0.930	0.704
health expenditure	(log) Total health spending, PPP (thousands of 2017 \$US)	Global Health Spending 1995-2015, IHME	15.071	2.239
economic globalization	Actual flows (trade, foreign direct investment, stocks, portfolio investment, income payments to foreign nationals), restrictions (hidden import barriers, mean tariff rate, taxes on international trade, capital account restrictions). Higher values reflect greater economic globalization.	KOF Index of Globalization	54.462	16.234
political globalization	Embassies in country, membership in international organizations, participation in UN security council missions, international treaties. Higher values reflect greater political globalization.	KOF Index of Globalization	62.283	21.985

Industrialization, i.e., the structural transformation from agricultural to industrial production also has a range of significant health implications (McNeill, 1998, Chaudhuri, 1985, Steckel and Rose, 2002, Szreter, 2004, Steckel, 1999). We capture these implications in our analysis by including the (log) value added of *agriculture* (% of GDP) and the (log) value added of *manufacturing* (% of GDP) in the estimated equation.

To check the robustness of our baseline results, we replicate our analysis controlling also for the human capital of the population by utilizing total enrolment in secondary *education* (in logs). It is well established in the relevant literature that through education, people gain the ability to be effective in their lives. They adopt healthier lifestyles and inspire their offspring to do as well (Mirowsky and Ross, 1998). Individuals with higher levels of education also tend to have better socioeconomic resources for a healthy lifestyle and a higher probability of living and working in healthy environments (Adler and Newman, 2002, Braveman et al., 2010). In addition, educated individuals tend to have lower exposure to chronic stress (Pampel et al., 2010). Low educational attainment, on the other hand, is associated with a shorter life expectancy, poor self-reported health, and a high prevalence of infectious and chronic non-infectious diseases (Feldman et al., 1989, Guralnik and Kaplan, 1989, Liu et al., 1982, Woodward et al., 1992).⁷ Furthermore, we re-estimate the baseline model by substituting *urban* with *population density* (people per square km of land, in logs).

The variable CO_2 (log of CO_2 emissions in kg per 2010 \$US of GDP) captures the effect of air pollution on health, which has been the subject of numerous studies in recent years (for an extensive review, see (Brunekreef and Holgate, 2002)).

Finally, *health expenditure* (log of total health spending in thousands of purchasing power parity (PPP)-adjusted 2017 \$US) is also included in the set of explanatory variables controlling for the association between healthcare spending and health outcomes (Werblow et al., 2007, Barlow and Vissandjee, 1999, Crémieux et al., 1999, Wolfe, 1986, Mackenbach, 1991, Seshamani and Gray, 2004, Zweifel et al., 1999, Nixon and Ulmann, 2006)

Data definitions, sources and summary statistics for the variables included in the analysis are given in Table 1.

5.1.2 Instrumental variables

We estimate equation (5) using different econometric methods. First, we use fixed-effects OLS. However, fixed effects estimators do not necessarily identify the effect of economic development on health complexity. The estimation of causal effects requires exogenous sources of variation. While we do not have an ideal source of exogenous variation recognized by previous studies, there are two promising potential instruments of economic development that we adopt in our fixed-effects 2SLS/IV and diff-GMM analyses.

First, we use the KOF Swiss Economic Institute's *economic globalization* index, characterized as the flows of goods, capital, and services, as well as information and perceptions that accompany market exchanges (Dreher, 2006). Higher values reflect greater economic globalization.

The second instrument considered is the KOF Swiss Economic Institute's *political globalization* index, characterized by the number of embassies in a country, its membership in international organizations, its participation in UN security council missions and international treaties. Higher values reflect greater political globalization.

There is extensive research documenting the positive relationship between globalization and economic development and growth (Dreher, 2006, Gözgor and Can, 2017, Duttagupta et al., 2018, Gurgul and Lach, 2014, Chang and Lee, 2010). While we do not have a precise theory to support the prediction, it is expected that changes in the *economic globalization* and *political globalization* indices have no direct effect on a country's disease structure and impact health complexity only indirectly, through the channel of economic development. The tests performed and described in the next section (Section 5.2) strongly confirm the relevance of the use of these instruments.

5.2 Regression results

In this section, we discuss the results of estimating equation (5) with different econometric techniques. Table 2 reports the results of fixed-effects ordinary least squares (FE-OLS)

⁷(Grossman, 2006) and (Ross and Wu, 1995) review the relationships between education and a wide variety of health measures.

Table 2: The effect of economic development on health complexity: Fixed-effects OLS

	(1)	(2)	(3)	(4)	(5)	(6)
HCI_{t-1}	0.938*** (0.009)	0.938*** (0.009)	0.938*** (0.010)	0.933*** (0.010)	0.929*** (0.010)	0.929*** (0.010)
GDP_{pc}	0.013*** (0.003)	0.013*** (0.003)	0.013*** (0.003)	0.012*** (0.003)	0.009** (0.003)	0.011*** (0.004)
<i>old</i>		-0.001 (0.006)	-0.001 (0.006)	0.002 (0.006)	0.000 (0.007)	0.002 (0.007)
<i>female</i>			-0.014 (0.024)	-0.013 (0.024)	0.002 (0.023)	-0.006 (0.024)
<i>urban</i>				0.020** (0.008)	0.025*** (0.008)	0.021** (0.009)
<i>agriculture</i>					-0.006*** (0.002)	-0.006*** (0.002)
<i>manufacturing</i>						0.001 (0.002)
Observations	4,750	4,593	4,593	4,593	4,377	4,181
Countries	190	183	183	183	180	177
R-squared	0.873	0.874	0.874	0.875	0.872	0.872

Note: Dependent variable: Health Complexity Index (HCI). Main independent variable: GDP per capita in logs (GDP_{pc}). Country and time fixed-effects are included in all regressions. Robust standard errors are in parentheses. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

with time dummies, adding an additional variable from the set of controls in each step (column). In all specifications, economic development has a positive relationship with health complexity, and the control variables enter with the expected sign. The *agriculture* coefficient is negative, and countries with a higher proportion of *urban* population exhibit greater health complexity.

The results depicted in Table 2 could only be interpreted as correlations. For a robust analysis accounting for the potential endogeneity problem in the relationship under consideration (discussed above), we use fixed-effects 2SLS/IV estimation techniques complemented with diff-GMM estimations à la Arellano-Bond (Arellano and Bond, 1991). Table 3 presents our baseline results.

In columns (1)-(8), we estimate equation (5) with FE 2SLS/IV regressions. We use time dummies and robust standard errors (in parentheses). In all cases, GDP_{pc} is a positive and statistically significant predictor of health complexity. In fact, we find that an increase in *GDP per capita* of 10% is associated with an improvement of about 0.003 in the HCI (standard deviation: 1.004). This positive impact of economic development on health complexity is robust to the inclusion of control measures discussed in subsection 5.1.1. The statistically significant *urban* coefficient implies that a higher proportion of urban population is associated with more complex diseases.

In the fixed effects 2SLS/IV estimations we report: (a) the *F-test* for the joint significance of the instruments in the first stage: the rule of thumb is to exceed 10, hence the test implies no weak significance (Stock and Yogo, 2005); (b) the Durbin-Wu-Hausmann (*DWH*) test for the endogeneity of regressors: the null hypothesis that the IV regression is not required is rejected; (c) the Cragg-Donald F-statistic (*Weak-*id**), testing the relevance of the instruments in the first-stage regression: no evidence of a low correlation between instruments and the endogenous regressor is found after controlling for the exogenous regressors; (d) the Kleibergen-Paap Wald test (*LM-weak*id**) of weak identification: the null hypothesis that the model is weakly identified is rejected; (e) the p-value for Hansen's test of overidentification: the acceptance of the null indicates that the overidentifying restrictions cannot be rejected.

In column (9) of Table 3 we report the diff-GMM estimations including year fixed effects and robust standard errors. The results verify the previous findings both qualitatively and quantitatively, i.e., the estimated coefficient of GDP_{pc} implies an improvement of 0.003 in the HCI with a *GDP per capita* increase of 10%. Among the control variables, only the *urban* variable has a statistically significant and positive sign. The values reported for AR(1) and AR(2) are the p-values for first- and second-order autocorrelated disturbances. As expected, there is high first-order autocorrelation and no evidence for significant second-order autocorrelation. Hence, our test statistics hint at a proper specification.

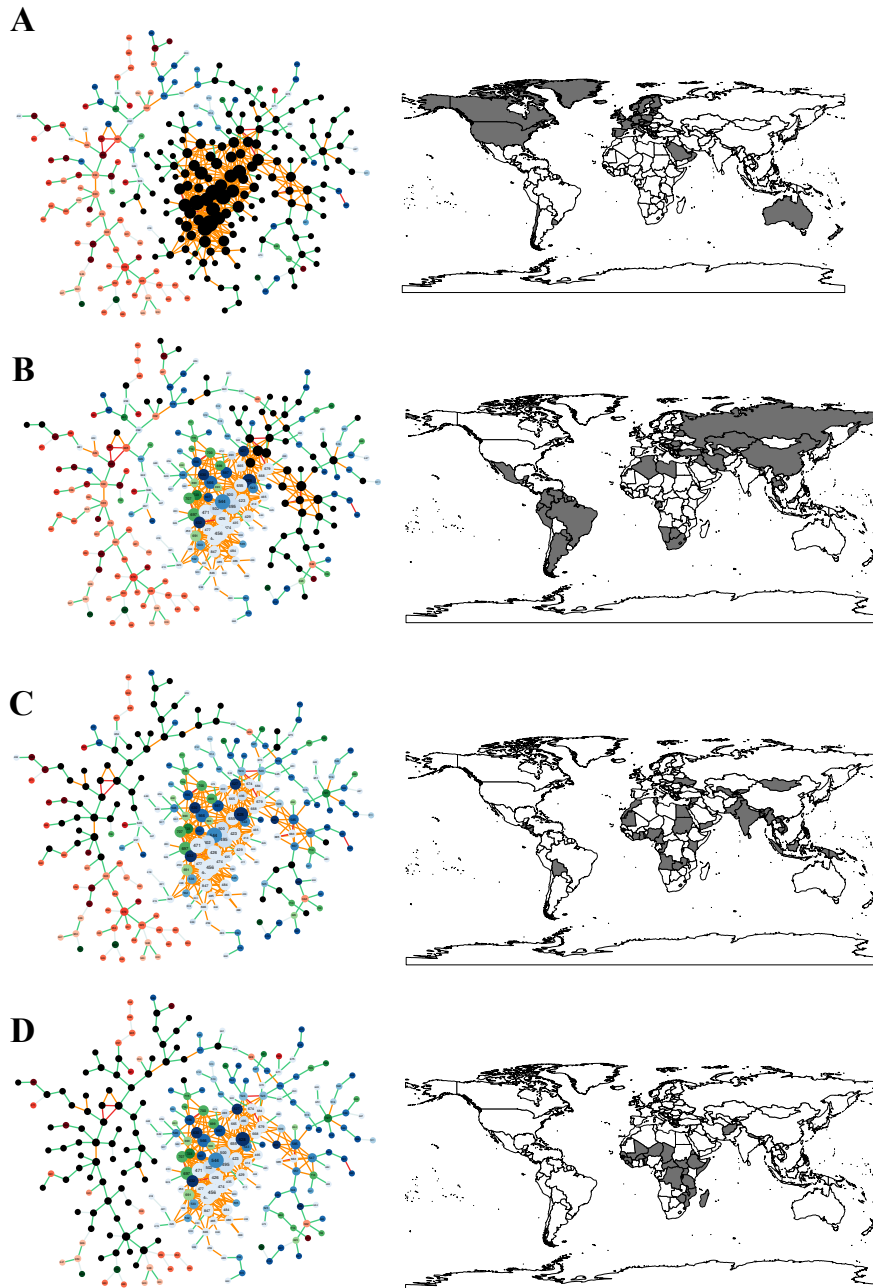


Figure 4: Localisation of diseases for different income-regions of the world. A: High income, B: Upper-middle income, C: Lower-middle income, D: Low income. Diseases in an income-region where more than half of the countries belonging to this region have a $RDD > 1$ are shown with black nodes in the disease space network. Data for 2016.

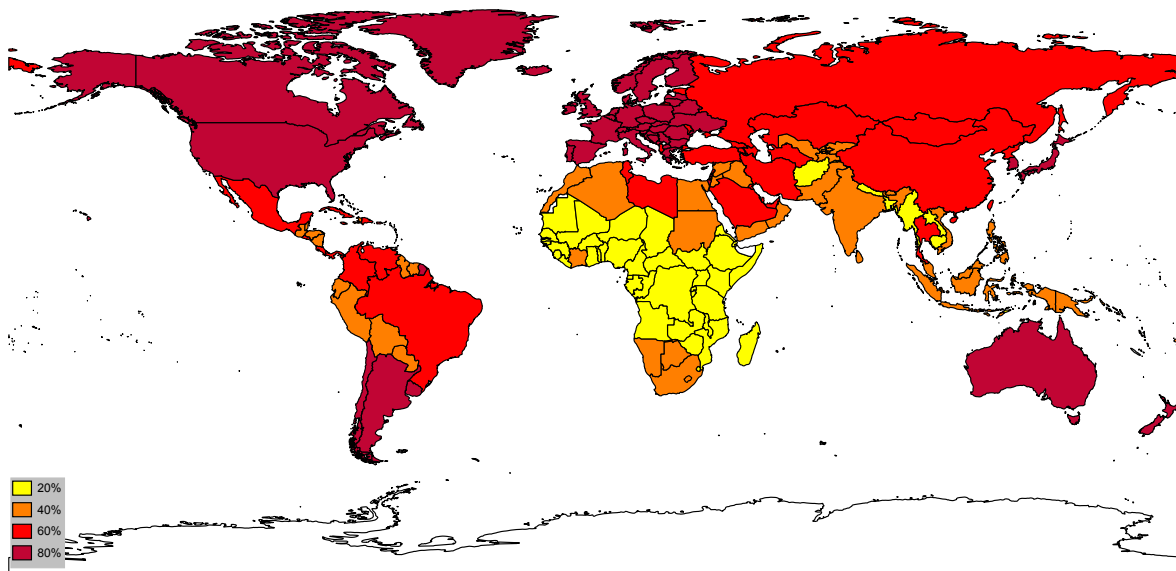


Figure 5: Health complexity index across the world. Mean values for the period 1990-2016: percentile repartition. Countries depicted in dark red have a mean value above the 80th percentile.

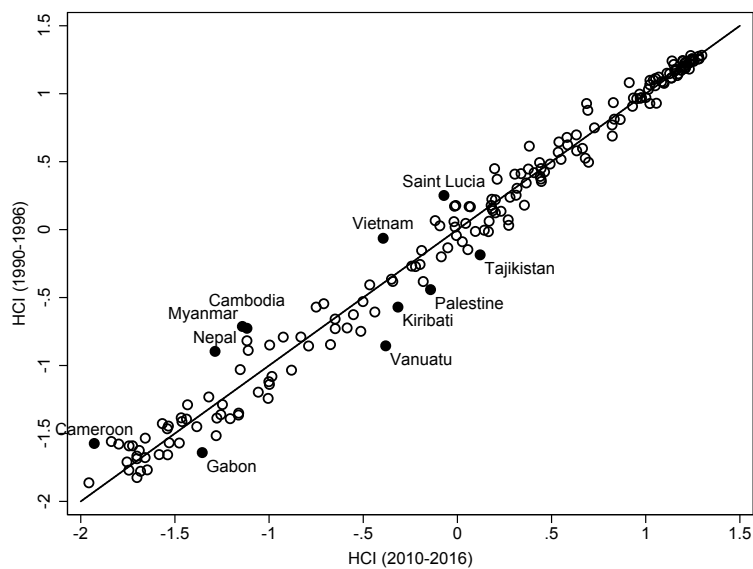


Figure 6: Evolution of the health complexity index over time. Changes in the health complexity index from 1990-1996 to 2010-2016. The labelled black dots are the 10 countries with the largest changes over time.

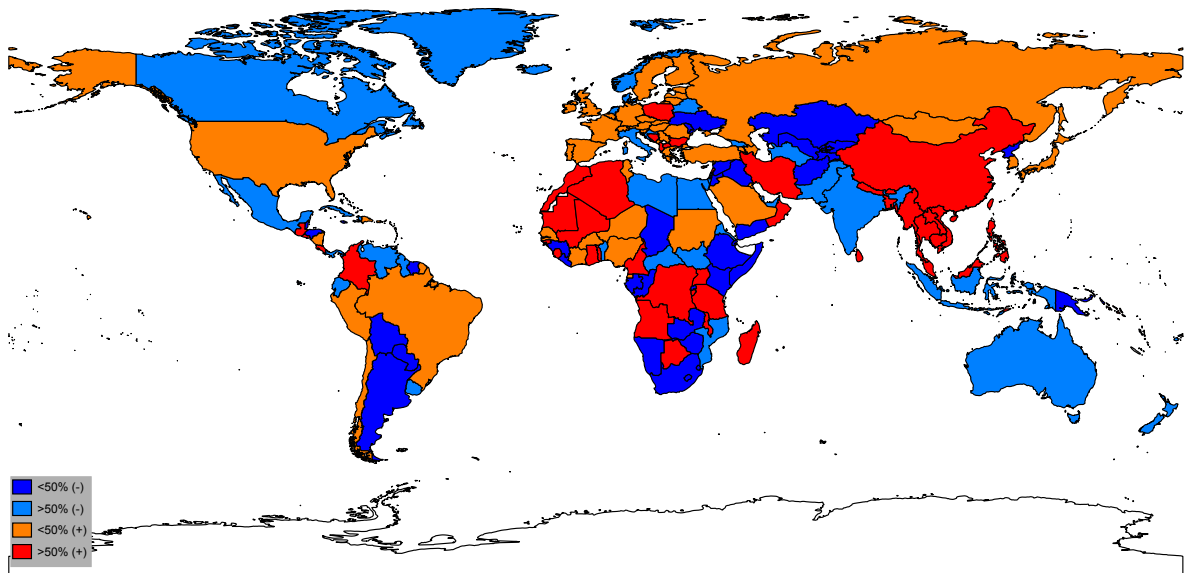


Figure 7: Changes in the health complexity index across the world. Changes in HCI scores (percentile repartition) from the period 1990-1996 to 2010-2016. Countries depicted in light blue and blue (orange and red) have experienced a decrease (increase) in HCI score below and above the median decrease (increase), respectively.

Table 3: The effect of economic development on health complexity: baseline results

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
	FE 2SLS/IV	FE 2SLS/IV	FE 2SLS/IV	FE 2SLS/IV	FE 2SLS/IV	FE 2SLS/IV	FE 2SLS/IV	FE 2SLS/IV	diff-GMM
<i>HCI_{t-1}</i>	0.926*** (0.010)	0.927*** (0.010)	0.927*** (0.010)	0.923*** (0.010)	0.923*** (0.010)	0.922*** (0.010)	0.922*** (0.011)	0.921*** (0.010)	0.814*** (0.061)
<i>GDP_{pc}</i>	0.031*** (0.011)	0.031*** (0.011)	0.031*** (0.011)	0.031*** (0.011)	0.026** (0.011)	0.029*** (0.011)	0.030* (0.017)	0.027** (0.013)	0.032** (0.013)
<i>old</i>		-0.003 (0.005)	-0.002 (0.005)	-0.001 (0.005)	-0.003 (0.006)	-0.001 (0.006)	-0.002 (0.006)	-0.001 (0.006)	-0.005 (0.017)
<i>female</i>			-0.015 (0.023)	-0.015 (0.023)	-0.019 (0.027)	-0.029 (0.028)	-0.031 (0.033)	-0.026 (0.029)	0.029 (0.044)
<i>urban</i>				0.013 (0.008)	0.020*** (0.008)	0.017** (0.008)	0.017** (0.009)	0.017** (0.008)	0.031* (0.018)
<i>agriculture</i>					-0.003 (0.003)	-0.003 (0.003)	-0.002 (0.004)	-0.003 (0.003)	-0.002 (0.008)
<i>manufacturing</i>						0.002 (0.002)	0.002 (0.002)	0.002 (0.002)	-0.003 (0.012)
Fist-stage results									
<i>economic globalization</i>	0.003*** (0.001)	0.003*** (0.001)	0.003*** (0.001)	0.003*** (0.001)	0.004*** (0.000)	0.003*** (0.000)	0.005*** (0.000)		
<i>political globalization</i>	0.004*** (0.001)	0.004*** (0.001)	0.004*** (0.001)	0.004*** (0.001)	0.004*** (0.000)	0.005*** (0.000)		0.006*** (0.000)	
Observations	4,168	4,143	4,143	4,143	3,976	3,826	3,826	3,926	3,652
Countries	171	170	170	170	170	168	168	173	168
F-test	37.24	37.05	36.31	39.93	56.26	61.41	79.18	76.56	
DWH-test	2.978	2.911	2.785	3.073	2.500	2.646	1.304	1.523	
Weak-id	59.73	54.25	54.88	56.82	97.43	107.0	104.3	152.6	
LM-weakid	71.12	70.95	69.68	75.01	109.7	116.3	72.90	73.98	
Hansen (p-value)	0.590	0.699	0.676	0.897	1.000	0.904			
AR(1)									0.000
AR(2)									0.475

Note: Dependent variable: Health Complexity Index (HCI). Main independent variable: GDP per capita in logs (*GDP_{pc}*). Columns (1)-(8): Fixed-effects 2SLS/IV; HCI is instrumented: To save space, we only include the first-stage estimated coefficients of the instruments. The results for the rest of the variables are available upon request. Column (9): One-step diff-GMM. All regressions include time dummies. Robust standard errors are in parentheses. F-test gives the F-statistic for the joint significance of the instruments in the first stage. DWH-test is the Durbin-Wu-Hausman test of endogeneity of the regressors. Weak-id gives the Cragg-Donald F-statistic for weak identification. LM-weakid gives the Kleibergen-Paap Wald test of weak identification. Hansen (p-value) gives the p-value of the Hansen test of overidentification. AR(1) and AR(2) are the p-values for first- and second-order autocorrelated disturbances. * p<0.10, ** p<0.05, *** p<0.01

Table 4: The effect of economic development on health complexity: AHCI

	(1) FE 2SLS/IV	(2) FE 2SLS/IV	(3) FE 2SLS/IV	(4) diff-GMM
<i>AHCI</i> _{<i>t</i>-1}	0.923*** (0.011)	0.925*** (0.012)	0.919*** (0.011)	0.828*** (0.114)
<i>GDP</i> _{<i>pc</i>}	0.037*** (0.011)	0.033** (0.015)	0.041*** (0.014)	0.024* (0.013)
<i>female</i>	-0.028 (0.027)	-0.021 (0.034)	-0.037 (0.031)	0.030 (0.040)
<i>urban</i>	0.009 (0.007)	0.010 (0.008)	0.007 (0.008)	0.011 (0.023)
<i>agriculture</i>	0.002 (0.003)	0.001 (0.004)	0.003 (0.004)	0.008 (0.010)
<i>manufacturing</i>	0.002 (0.002)	0.002 (0.002)	0.003 (0.002)	-0.013 (0.011)
Fist-stage results				
<i>economic globalization</i>	0.004*** (0.000)	0.005*** (0.000)		
<i>political globalization</i>	0.004*** (0.000)		0.005*** (0.000)	
Observations	3,826	3,826	3926	3,652
Countries	168	168	173	168
F-test	67.39	101.5	71.22	
DWH-test	6.055	2.200	4.548	
Weak-id	116.2	136.4	138.9	
LM-weakid	125.8	92.43	67.20	
Hansen (p-value)	0.681			
AR(1)				0.000
AR(2)				0.158

Note: Dependent variable: Age-standardized Health Complexity Index (AHCI). Main independent variable: GDP per capita in logs (*GDP*_{*pc*}). Columns (1)-(3): Fixed-effects 2SLS/IV; *AHCI* is instrumented: To save space, we only include the first-stage estimated coefficients of the instruments. The results for the rest of the variables are available upon request. Column (4): One-stage diff-GMM. All regressions include time dummies. Robust standard errors are in parentheses. F-test gives the F-statistic for the joint significance of the instruments in the first stage. DWH-test is the Durbin-Wu-Hausman test of endogeneity of the regressors. Weak-id gives the Cragg-Donald F-statistic for weak identification. LM-weakid gives the Kleibergen-Paap Wald test of weak identification. Hansen (p-value) gives the p-value of the Hansen test of overidentification. AR(1) and AR(2) are the p-values for first- and second-order autocorrelated disturbances. * p<0.10, ** p<0.05, *** p<0.01

Table 5: The effect of economic development on health complexity: robustness checks

	(1)	(2)	(3)	(4)	(5)
	diff-GMM	diff-GMM	diff-GMM	diff-GMM	diff-GMM
HCI_{t-1}	0.752*** (0.059)	0.871*** (0.046)	0.812*** (0.063)	0.920*** (0.040)	0.666*** (0.062)
GDP_{pc}	0.031* (0.016)	0.031*** (0.011)	0.024* (0.013)	0.042*** (0.016)	0.038* (0.020)
<i>old</i>	-0.022 (0.024)	-0.010 (0.017)	0.004 (0.018)	-0.002 (0.016)	-0.005 (0.029)
<i>female</i>	0.053 (0.050)	0.018 (0.051)	0.053 (0.045)	-0.068 (0.047)	-0.170 (0.124)
<i>urban</i>	0.055 (0.035)		0.013 (0.017)	0.022 (0.023)	
<i>agriculture</i>	0.007 (0.009)	-0.001 (0.006)	0.003 (0.009)	0.001 (0.008)	0.015 (0.011)
<i>manufacturing</i>	0.008 (0.012)	-0.003 (0.011)	-0.015 (0.010)	0.014 (0.011)	0.020 (0.014)
<i>education</i>	-0.003 (0.011)				0.026 (0.017)
<i>population density</i>		0.000 (0.016)			-0.073 (0.049)
CO_2			0.013* (0.007)		-0.003 (0.015)
<i>health expenditure</i>				-0.006 (0.012)	-0.012 (0.018)
Observations	2,347	3,642	3,470	3,158	1,936
Countries	161	168	168	168	158
AR(1)	0.000	0.000	0.000	0.000	0.000
AR(2)	0.395	0.505	0.621	0.525	0.274

Note: Dependent variable: Health Complexity Index (HCI). Main independent variable: GDP per capita in logs (GDP_{pc}). Regression analysis: One-step diff-GMM. All regressions include time dummies. Robust standard errors are in parentheses. AR(1) and AR(2) are the p-values for first- and second-order autocorrelated disturbances. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

In Tables 4 and 5, we investigate the robustness of our baseline findings. First, we substitute the HCI with the age-standardized health complexity index (AHCI) maintaining the same set of controls (and time dummies) as in the baseline specification. Second, we investigate whether the positive impact of economic development on health complexity persists under additional and/or alternative control measures (including time dummies). In all cases, the baseline results remain qualitatively intact. In particular, the coefficient of GDP_{pc} is positive and statistically significant in the instrumented regressions (see Table 4; to save space, we only include the first-stage estimated coefficients of the instruments – the results for the rest of the variables are available upon request).

Table 5 starts from the baseline specification with the full set of controls [column (9) in Table 3] and introduces additional variables or alternative measures for some of the previous controls. Specifically, in column (1), we add *education* (enrolment in secondary education in logs). In column (2), we substitute the *urban* population variable with *population density* (people per sq. km of land in logs). In columns (3) and (4), we employ (log) CO_2 emissions (CO_2 emissions, kg per 2010 \$US of GDP) and (log) *health expenditure* (total health spending, thousands of 2017 PPP adjusted \$US), respectively. Finally, in column (5), we consider all of the above variables together. Adding these controls in our estimations leaves the findings qualitatively and quantitatively intact.

The above analysis suggests that economically developed countries tend to exhibit more complex disease structures. Furthermore, exploiting the temporal variation in the data, the fixed-effects 2SLS/IV analysis and the difference GMM estimators reveal a positive, statistically significant, and robust impact of economic development on health complexity.

6 Economic development and disease complexity

The economic complexity methodology provides a useful toolbox that allows us to compute indices that quantify the complexity of both countries and diseases. For example, using the same methodology that computes the HCI, we can calculate the DCI (see Section 3). This index quantifies the complexity of countries' diseases according to their prevalent cases worldwide.

6.1 The disease complexity index

In a similar manner, but placing the spotlight on diseases rather than countries, we calculate the *Disease Complexity Index* (DCI) in which the $k \times k$ matrix $\tilde{\mathbf{M}}$ provides information about links connecting two diseases d and d' , based on the number of countries in which both diseases are present⁸. Therefore, the matrix elements $\tilde{M}_{dd'}$ are computed as

$$\tilde{M}_{dd'} = \frac{1}{k_{d,0}} \sum_c \frac{M_{cd}M_{cd'}}{k_{c,0}}, \quad (6)$$

and if \mathbf{Q} is the eigenvector of $\tilde{\mathbf{M}}$ associated with the second largest eigenvalue,

$$\text{DCI} = \frac{\mathbf{Q} - \langle \mathbf{Q} \rangle}{\text{std}(\mathbf{Q})}. \quad (7)$$

Table 6 lists the five diseases with the highest and lowest DCI scores averaged over the period of 1990-2016.

Table 6: List of the five diseases with the highest and lowest DCI values during the period of 1990-2016

Code	Disease name	Disease section	DCI
<i>Highest DCI</i>			
459	Malignant skin melanoma	Neoplasms	1.210
441	Colon and rectal cancer	Neoplasms	1.170
502	Peripheral artery disease	Cardiovascular diseases	1.169
456	Pancreatic cancer	Neoplasms	1.159
533	Vascular intestinal disorders	Digestive diseases	1.152
<i>Lowest DCI</i>			
345	Malaria	Neglected tropical diseases and malaria	-2.045
350	African trypanosomiasis	Neglected tropical diseases and malaria	-1.978
370	Maternal obstructed labor and uterine rupture	Maternal and neonatal disorders	-1.957
358	Yellow fever	Neglected tropical diseases and malaria	-1.893
340	Tetanus	Other infectious diseases	-1.883

Notes: DCI: Disease Complexity Index; Average values for 1990-2016.

⁸As discussed in 2.1, the DCI is computed using in X_{cd} the number of prevalent cases of a disease (according to cause levels 3 or 4) per 100,000 population for 195 countries and for 196 diseases. The time-period covered is from 1990 to 2016. With the age-standardized data (see the discussion in Section 2.1), we also calculate the age-standardized disease complexity index (ADCI) following the same formulas.

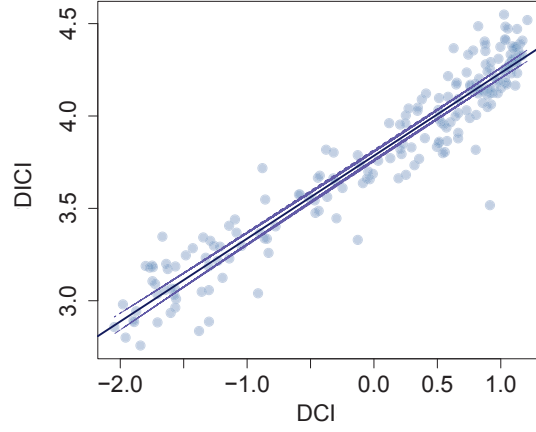


Figure 8: DICI against DCI. The solid line represents the fit of a linear model and the dashed line a 95% prediction interval based on the fitted linear model.

6.2 The disease-income complexity index

Using the economic complexity methodology, (Hartmann et al., 2017) recently introduced a measure that associates products with income inequality and showed how the development of new products is associated with changes in income inequality. Here, to decompose economic development at the disease level, we introduce a measure that links a disease to the average income per capita of the countries for which they have a relative disease disadvantage i.e., an estimate of the expected income per capita related to different diseases. In this way, we illustrate how disease complexity is being affected by the level of economic development and quantify the relationship between countries' income per capita and the complexity of their diseases.

Following the methodology in (Hartmann et al., 2017), we define the *Disease-Income Complexity Index* (DICI), and decompose the relationship between the DCI and the DICI for the diseases in our sample of countries.⁹

Assuming that we have information for l countries and k diseases, we can fill the $(l \times k)$ matrix \mathbf{M} so that its matrix element $M_{cd} = 1$ if country c has a RDD in disease d , and zero otherwise (see Section 3.1). Our dataset contains information for 195 developed and developing countries and for 196 diseases from 1990 to 2016. A visualization of the matrix \mathbf{M} that is used to calculate the HCI and the DCI for this dataset is shown in Figure 2.

Every disease d can have prevalent cases in a country c . For every disease d , we can calculate the fraction s_{cd} :

$$s_{cd} = \frac{X_{cd}}{\sum_{d'} X_{cd'}}, \quad (8)$$

where X_{cd} is the number of prevalent cases per 100,000 population for disease d in country c , while $\sum_{d'} X_{cd'}$ is the number of prevalent cases of all diseases in country c . If GDP_c is the (log) *GDP per capita* of country c , we can calculate the $DICI_d$ for every disease d as:

$$DICI_d = \frac{1}{N_d} \sum_c M_{cd} s_{cd} GDP_c, \quad (9)$$

where $N_d = \sum_c M_{cd} s_{cd}$ is a normalization factor.

The DICI is defined at the disease level as the average level of (log) *GDP per capita* of the countries that have a RDD in disease d , weighted by the disease's importance in each country's pool of diseases. Utilizing the (log) PPP *GDP per capita* (constant 2011 international \$) from the World Bank's World Development Indicators for the countries in our sample, we calculate the above index for every year in the period of 1990-2016.

Table 7 lists the five diseases with the highest and lowest average DICI values during the period of 1990-2016. It is evident that higher economic development is associated with more complex diseases such as motor neuron disease and malignant skin melanoma. At the other end of the spectrum, less complex diseases such as acute hepatitis E and malaria are associated with low levels of income per capita.

⁹We also computed the ADICI and investigated its relationship with the ADCI, finding similar results.

Table 7: List of the five diseases with the highest and lowest DICl values during the period of 1990-2016

code	disease name	disease section	DICI	DCI
<i>Highest DICl</i>				
554	Motor neuron disease	Neurological disorders	4.55	1.025
459	Malignant skin melanoma	Neoplasms	4.52	1.210
573	Anorexia nervosa	Mental disorders	4.49	0.818
483	Mesothelioma	Neoplasms	4.49	1.041
485	Non-Hodgkin's lymphoma	Neoplasms	4.48	1.057
<i>Lowest DICl</i>				
404	Acute hepatitis E	Other infectious diseases	2.89	-1.707
345	Malaria	Neglected tropical diseases and malaria	2.86	-2.045
353	Cystic echinococcosis	Neglected tropical diseases and malaria	2.84	-1.383
370	Maternal obstructed labor and uterine rupture	Maternal and neonatal disorders	2.80	-1.957
359	Rabies	Neglected tropical diseases and malaria	2.76	-1.840

Notes: DICl: Disease-Income Complexity Index; DCI: Disease Complexity Index; Average values for 1990-2016

6.3 Linking disease complexity and economic development

In this subsection, we test the existence of a bivariate relationship between the DCI and the DICl. Thus, we calculate Pearson's correlation coefficient for DICl against DCI. If such an association exists, it should allow us to derive expectations about whether disease complexity can be associated with economic development and verify, with disease-level data, the statistically significant and positive relationship between health complexity and economic development that we found above (Section 5.2). The correlation coefficient for the relationship between the average values of the DICl and the DCI for the period of 1990-2016 is $\rho = 0.96 \pm 0.01$ with a p-value $< 2.2 \times 10^{-16}$. In Figure 8, we present the scatter-plot of the relationship between the DICl and the DCI for the 196 diseases in our dataset (average values for 1990-2016), together with the fitted linear model. The slope of the linear fit is the corresponding correlation coefficient.

The statistically significant positive correlation between the DICl and the DCI indicates that more complex diseases are associated with more developed countries, as measured by the (log) *GDP per capita*. This allows us to understand which sets of diseases are linked to better overall economic performance, based on their complexity.

In Table 8, we run panel regressions between the DCI and DICl. The results show that the relationship between the DCI and the DICl is the outcome of the correlations both *between* diseases (regression on group means) and *within* diseases (fixed-effects regression with time dummies and standard errors adjusted for disease clusters). This suggests that the positive effect of economic development on the complexity of diseases is due to both changes in the structure of the disease space towards more complex diseases and increases in the complexity of existing diseases.

Table 8: Disease-income complexity index and the complexity of diseases

	(1)	(2)
	DCI	DCI
	Within Estimation	Between Estimation
DICI	0.479*** (0.149)	2.041*** (0.045)
Observations	5,211	5,211
Diseases	193	193
R-square	0.90	0.88

Notes: DICl: Disease-Income Complexity Index; DCI: Disease Complexity Index. Time dummies are included in the within regression. Standard errors are in parentheses. * p<0.10, ** p<0.05, *** p<0.01

7 Conclusions

Our analysis illustrates that a country's level of development determines the structure of its disease space. Following the economic complexity methodology, we developed the HCI, which quantifies the network representation of the relatedness and proximity of diseases. In a dynamic panel data setting, we showed that there is a robust positive effect of a country's economic development, measured by GDP per capita, on its level of health complexity, i.e., on the 'structural' composition of its pool of diseases. The evidence presented here suggests that the economic development of nations conditions the disease space. Specifically, more complex diseases tend to be relatively more prevalent in populations with a higher income per capita. Explicitly, it seems that when an economy accelerates, the impact on health complexity is positive.

In addition, we build the DICI, which links a disease to the average level of income per capita of the countries in which they have a relative disease disadvantage and illustrate how disease complexity is related to economic development. Specifically, we show how changes in GDP per capita are associated with more complex diseases. The temporal variation of the above indices is important from a policy perspective. Using the HCI and DCI, it is possible to design policies aimed at improving the recognition, visibility, and traceability of complex diseases across the globe and through time (e.g., by developing a classification system for all health information systems). These indices can also be used as tools for the development of national plans for complex diseases and the establishment of knowledge networks on complex diseases, so as to improve their diagnosis, treatment, and cure. Furthermore, the DICI could be used to design a health expenditure reallocation policy promoting health activities and services associated with the prevention of complex diseases.

This study employs the economic complexity methodology to compute two new metrics that quantify the disease space of countries. These can be valuable tools for estimating the effect of economic development on the health status of nations. The topic of economic complexity is a rather new one, and its use in economics is rather limited so far. By focusing on the topic of disease complexity, our contribution lies in bridging the health economics literature with the literature that highlights economic complexity as a powerful paradigm in understanding key issues in economics, geography, innovation studies, and other social sciences.

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List of figures

Figure 1. Maximum Spanning Tree of the country-disease bipartite network	7
Figure 2. Matrix representation of the links between countries and diseases	8
Figure 3. The proximity matrix and the resulting disease space	10
Figure 4. Localisation of diseases for different income-regions of the world	16
Figure 5. Health complexity index across the world	17
Figure 6. Evolution of the health complexity index over time	17
Figure 7. Changes in the health complexity index across the world	18
Figure 8. DICI against DCI	23

List of tables

Table 1. Variable definitions, sources and summary statistics 13

Table 2. The effect of economic development on health complexity: Fixed-effects OLS 15

Table 3. The effect of economic development on health complexity: baseline results 19

Table 4. The effect of economic development on health complexity: AHCI 20

Table 5. The effect of economic development on health complexity: robustness checks 21

Table 6. List of the five diseases with the highest and lowest DCI values during the period of 1990-2016 22

Table 7. List of the five diseases with the highest and lowest DICI values during the period of 1990-2016 24

Table 8. Disease-income complexity index and the complexity of diseases 24

Table 9. List of countries 45

Table 10. List of diseases and injuries 46

Annexes

Annex 1. List of countries

Table 9: List of countries

Country id	Country name	Region	World Bank group
6	China	East Asia	World Bank Upper Middle Income
7	North Korea	East Asia	World Bank Low Income
8	Taiwan	East Asia	World Bank High Income
10	Cambodia	Southeast Asia	World Bank Lower Middle Income
11	Indonesia	Southeast Asia	World Bank Lower Middle Income
12	Laos	Southeast Asia	World Bank Lower Middle Income
13	Malaysia	Southeast Asia	World Bank Upper Middle Income
14	Maldives	Southeast Asia	World Bank Upper Middle Income
15	Myanmar	Southeast Asia	World Bank Lower Middle Income
16	Philippines	Southeast Asia	World Bank Lower Middle Income
17	Sri Lanka	Southeast Asia	World Bank Lower Middle Income
18	Thailand	Southeast Asia	World Bank Upper Middle Income
19	Timor-Leste	Southeast Asia	World Bank Lower Middle Income
20	Vietnam	Southeast Asia	World Bank Lower Middle Income
22	Fiji	Oceania	World Bank Upper Middle Income
23	Kiribati	Oceania	World Bank Lower Middle Income
24	Marshall Islands	Oceania	World Bank Upper Middle Income
25	Federated States of Micronesia	Oceania	World Bank Lower Middle Income
26	Papua New Guinea	Oceania	World Bank Lower Middle Income
27	Samoa	Oceania	World Bank Upper Middle Income
28	Solomon Islands	Oceania	World Bank Lower Middle Income
29	Tonga	Oceania	World Bank Upper Middle Income
30	Vanuatu	Oceania	World Bank Lower Middle Income
33	Armenia	Central Asia	World Bank Lower Middle Income
34	Azerbaijan	Central Asia	World Bank Upper Middle Income
35	Georgia	Central Asia	World Bank Lower Middle Income
36	Kazakhstan	Central Asia	World Bank Upper Middle Income
37	Kyrgyzstan	Central Asia	World Bank Lower Middle Income
38	Mongolia	Central Asia	World Bank Lower Middle Income
39	Tajikistan	Central Asia	World Bank Lower Middle Income
40	Turkmenistan	Central Asia	World Bank Upper Middle Income
41	Uzbekistan	Central Asia	World Bank Lower Middle Income
43	Albania	Central Europe	World Bank Upper Middle Income
44	Bosnia and Herzegovina	Central Europe	World Bank Upper Middle Income
45	Bulgaria	Central Europe	World Bank Upper Middle Income
46	Croatia	Central Europe	World Bank Upper Middle Income
47	Czech Republic	Central Europe	World Bank High Income
48	Hungary	Central Europe	World Bank High Income
49	Macedonia	Central Europe	World Bank Upper Middle Income
50	Montenegro	Central Europe	World Bank Upper Middle Income
51	Poland	Central Europe	World Bank High Income
52	Romania	Central Europe	World Bank Upper Middle Income
53	Serbia	Central Europe	World Bank Upper Middle Income
54	Slovakia	Central Europe	World Bank High Income
55	Slovenia	Central Europe	World Bank High Income
57	Belarus	Eastern Europe	World Bank Upper Middle Income
58	Estonia	Eastern Europe	World Bank High Income
59	Latvia	Eastern Europe	World Bank High Income
60	Lithuania	Eastern Europe	World Bank High Income
61	Moldova	Eastern Europe	World Bank Lower Middle Income
62	Russian Federation	Eastern Europe	World Bank Upper Middle Income
63	Ukraine	Eastern Europe	World Bank Lower Middle Income
66	Brunei	High-income Asia Pacific	World Bank High Income
67	Japan	High-income Asia Pacific	World Bank High Income
68	South Korea	High-income Asia Pacific	World Bank High Income
69	Singapore	High-income Asia Pacific	World Bank High Income
71	Australia	Australasia	World Bank High Income
72	New Zealand	Australasia	World Bank High Income
74	Andorra	Western Europe	World Bank High Income
75	Austria	Western Europe	World Bank High Income
76	Belgium	Western Europe	World Bank High Income
77	Cyprus	Western Europe	World Bank High Income
78	Denmark	Western Europe	World Bank High Income
79	Finland	Western Europe	World Bank High Income
80	France	Western Europe	World Bank High Income
81	Germany	Western Europe	World Bank High Income
82	Greece	Western Europe	World Bank High Income
83	Iceland	Western Europe	World Bank High Income
84	Ireland	Western Europe	World Bank High Income
85	Israel	Western Europe	World Bank High Income
86	Italy	Western Europe	World Bank High Income
87	Luxembourg	Western Europe	World Bank High Income
88	Malta	Western Europe	World Bank High Income
89	Netherlands	Western Europe	World Bank High Income
90	Norway	Western Europe	World Bank High Income
91	Portugal	Western Europe	World Bank High Income
92	Spain	Western Europe	World Bank High Income
93	Sweden	Western Europe	World Bank High Income
94	Switzerland	Western Europe	World Bank High Income
95	United Kingdom	Western Europe	World Bank High Income
97	Argentina	Southern Latin America	World Bank Upper Middle Income
98	Chile	Southern Latin America	World Bank High Income
99	Uruguay	Southern Latin America	World Bank High Income
101	Canada	High-income North America	World Bank High Income
102	United States	High-income North America	World Bank High Income
105	Antigua and Barbuda	Caribbean	World Bank High Income
106	The Bahamas	Caribbean	World Bank High Income
107	Barbados	Caribbean	World Bank High Income
108	Belize	Caribbean	World Bank Upper Middle Income
109	Cuba	Caribbean	World Bank Upper Middle Income
110	Dominica	Caribbean	World Bank Upper Middle Income
111	Dominican Republic	Caribbean	World Bank Upper Middle Income
112	Grenada	Caribbean	World Bank Upper Middle Income
113	Guyana	Caribbean	World Bank Upper Middle Income
114	Haiti	Caribbean	World Bank Low Income
115	Jamaica	Caribbean	World Bank Upper Middle Income
116	Saint Lucia	Caribbean	World Bank Upper Middle Income
117	Saint Vincent and the Grenadines	Caribbean	World Bank Upper Middle Income
118	Suriname	Caribbean	World Bank Upper Middle Income
119	Trinidad and Tobago	Caribbean	World Bank High Income
121	Bolivia	Andean Latin America	World Bank Lower Middle Income
122	Ecuador	Andean Latin America	World Bank Upper Middle Income
123	Peru	Andean Latin America	World Bank Upper Middle Income
125	Colombia	Central Latin America	World Bank Upper Middle Income
126	Costa Rica	Central Latin America	World Bank Upper Middle Income
127	El Salvador	Central Latin America	World Bank Lower Middle Income
128	Guatemala	Central Latin America	World Bank Lower Middle Income
129	Honduras	Central Latin America	World Bank Lower Middle Income
130	Mexico	Central Latin America	World Bank Upper Middle Income

Continuation of Table 10			
Country id	Country name	Region	World Bank group
131	Nicaragua	Central Latin America	World Bank Lower Middle Income
132	Panama	Central Latin America	World Bank Upper Middle Income
133	Venezuela	Central Latin America	World Bank Upper Middle Income
135	Brazil	Tropical Latin America	World Bank Upper Middle Income
136	Paraguay	Tropical Latin America	World Bank Upper Middle Income
139	Algeria	North Africa and Middle East	World Bank Upper Middle Income
140	Bahrain	North Africa and Middle East	World Bank High Income
141	Egypt	North Africa and Middle East	World Bank Lower Middle Income
142	Iran	North Africa and Middle East	World Bank Upper Middle Income
143	Iraq	North Africa and Middle East	World Bank Upper Middle Income
144	Jordan	North Africa and Middle East	World Bank Lower Middle Income
145	Kuwait	North Africa and Middle East	World Bank High Income
146	Lebanon	North Africa and Middle East	World Bank Upper Middle Income
147	Libya	North Africa and Middle East	World Bank Upper Middle Income
148	Morocco	North Africa and Middle East	World Bank Lower Middle Income
149	Palestine	North Africa and Middle East	World Bank Lower Middle Income
150	Oman	North Africa and Middle East	World Bank High Income
151	Qatar	North Africa and Middle East	World Bank High Income
152	Saudi Arabia	North Africa and Middle East	World Bank High Income
153	Syria	North Africa and Middle East	World Bank Lower Middle Income
154	Tunisia	North Africa and Middle East	World Bank Lower Middle Income
155	Turkey	North Africa and Middle East	World Bank Upper Middle Income
156	United Arab Emirates	North Africa and Middle East	World Bank High Income
157	Yemen	North Africa and Middle East	World Bank Lower Middle Income
160	Afghanistan	North Africa and Middle East	World Bank Low Income
161	Bangladesh	South Asia	World Bank Lower Middle Income
162	Bhutan	South Asia	World Bank Lower Middle Income
163	India	South Asia	World Bank Lower Middle Income
164	Nepal	South Asia	World Bank Low Income
165	Pakistan	South Asia	World Bank Lower Middle Income
168	Angola	Central Sub-Saharan Africa	World Bank Lower Middle Income
169	Central African Republic	Central Sub-Saharan Africa	World Bank Low Income
170	Congo	Central Sub-Saharan Africa	World Bank Lower Middle Income
171	Democratic Republic of the Congo	Central Sub-Saharan Africa	World Bank Low Income
172	Equatorial Guinea	Central Sub-Saharan Africa	World Bank Upper Middle Income
173	Gabon	Central Sub-Saharan Africa	World Bank Upper Middle Income
175	Burundi	Eastern Sub-Saharan Africa	World Bank Low Income
176	Comoros	Eastern Sub-Saharan Africa	World Bank Low Income
177	Djibouti	Eastern Sub-Saharan Africa	World Bank Lower Middle Income
178	Eritrea	Eastern Sub-Saharan Africa	World Bank Low Income
179	Ethiopia	Eastern Sub-Saharan Africa	World Bank Low Income
180	Kenya	Eastern Sub-Saharan Africa	World Bank Lower Middle Income
181	Madagascar	Eastern Sub-Saharan Africa	World Bank Low Income
182	Malawi	Eastern Sub-Saharan Africa	World Bank Low Income
183	Mauritius	Southeast Asia	World Bank Upper Middle Income
184	Mozambique	Eastern Sub-Saharan Africa	World Bank Low Income
185	Rwanda	Eastern Sub-Saharan Africa	World Bank Low Income
186	Seychelles	Southeast Asia	World Bank High Income
187	Somalia	Eastern Sub-Saharan Africa	World Bank Low Income
189	Tanzania	Eastern Sub-Saharan Africa	World Bank Low Income
190	Uganda	Eastern Sub-Saharan Africa	World Bank Low Income
191	Zambia	Eastern Sub-Saharan Africa	World Bank Lower Middle Income
193	Botswana	Southern Sub-Saharan Africa	World Bank Upper Middle Income
194	Lesotho	Southern Sub-Saharan Africa	World Bank Lower Middle Income
195	Namibia	Southern Sub-Saharan Africa	World Bank Upper Middle Income
196	South Africa	Southern Sub-Saharan Africa	World Bank Upper Middle Income
197	Swaziland	Southern Sub-Saharan Africa	World Bank Lower Middle Income
198	Zimbabwe	Southern Sub-Saharan Africa	World Bank Low Income
200	Benin	Western Sub-Saharan Africa	World Bank Low Income
201	Burkina Faso	Western Sub-Saharan Africa	World Bank Low Income
202	Cameroon	Western Sub-Saharan Africa	World Bank Lower Middle Income
203	Cape Verde	Western Sub-Saharan Africa	World Bank Lower Middle Income
204	Chad	Western Sub-Saharan Africa	World Bank Low Income
205	Cote d'Ivoire	Western Sub-Saharan Africa	World Bank Lower Middle Income
206	The Gambia	Western Sub-Saharan Africa	World Bank Low Income
207	Ghana	Western Sub-Saharan Africa	World Bank Lower Middle Income
208	Guinea	Western Sub-Saharan Africa	World Bank Low Income
209	Guinea-Bissau	Western Sub-Saharan Africa	World Bank Low Income
210	Liberia	Western Sub-Saharan Africa	World Bank Low Income
211	Mali	Western Sub-Saharan Africa	World Bank Low Income
212	Mauritania	Western Sub-Saharan Africa	World Bank Lower Middle Income
213	Niger	Western Sub-Saharan Africa	World Bank Low Income
214	Nigeria	Western Sub-Saharan Africa	World Bank Lower Middle Income
215	Sao Tome and Principe	Western Sub-Saharan Africa	World Bank Lower Middle Income
216	Senegal	Western Sub-Saharan Africa	World Bank Low Income
217	Sierra Leone	Western Sub-Saharan Africa	World Bank Low Income
218	Togo	Western Sub-Saharan Africa	World Bank Low Income
298	American Samoa	Oceania	World Bank Upper Middle Income
305	Bermuda	Caribbean	World Bank High Income
349	Greenland	High-income North America	World Bank High Income
351	Guam	Oceania	World Bank High Income
376	Northern Mariana Islands	Oceania	World Bank High Income
385	Puerto Rico	Caribbean	World Bank High Income
422	Virgin Islands, U.S.	Caribbean	World Bank High Income
435	South Sudan	Eastern Sub-Saharan Africa	World Bank Low Income
522	Sudan	North Africa and Middle East	World Bank Lower Middle Income

Notes: Global Burden of Disease Study 2016

Annex 2. List of diseases and injuries

Table 10: List of diseases and injuries

Disease id	Disease name	Parent dis- ease	Outline
294	All causes	294	Total
295	Communicable, maternal, neonatal, and nutritional diseases	294	A
296	HIV/AIDS and tuberculosis	295	A.1
297	Tuberculosis	296	A.1.1
934	Drug-susceptible tuberculosis	297	A.1.1.1
946	Multidrug-resistant tuberculosis without extensive drug resistance	297	A.1.1.2
947	Extensively drug-resistant tuberculosis	297	A.1.1.3
954	Latent tuberculosis infection	297	A.1.1.4
298	HIV/AIDS	296	A.1.2
948	Drug-susceptible HIV/AIDS - Tuberculosis	298	A.1.2.1
949	Multidrug-resistant HIV/AIDS - Tuberculosis without extensive drug resistance	298	A.1.2.2
950	Extensively drug-resistant HIV/AIDS - Tuberculosis	298	A.1.2.3
300	HIV/AIDS resulting in other diseases	298	A.1.2.4

Continuation of Table 10			
Disease id	Disease name	Parent dis- ease	Outline
301	Diarrhea, lower respiratory, and other common infectious diseases	295	A.2
302	Diarrheal diseases	301	A.2.1
318	Intestinal infectious diseases	301	A.2.2
319	Typhoid fever	318	A.2.2.1
320	Paratyphoid fever	318	A.2.2.2
321	Other intestinal infectious diseases	318	A.2.2.3
322	Lower respiratory infections	301	A.2.3
328	Upper respiratory infections	301	A.2.4
329	Otitis media	301	A.2.5
332	Meningitis	301	A.2.6
333	Pneumococcal meningitis	332	A.2.6.1
334	H influenzae type B meningitis	332	A.2.6.2
335	Meningococcal meningitis	332	A.2.6.3
336	Other meningitis	332	A.2.6.4
337	Encephalitis	301	A.2.7
338	Diphtheria	301	A.2.8
339	Whooping cough	301	A.2.9
340	Tetanus	301	A.2.10
341	Measles	301	A.2.11
342	Varicella and herpes zoster	301	A.2.12
344	Neglected tropical diseases and malaria	295	A.3
345	Malaria	344	A.3.1
346	Chagas disease	344	A.3.2
347	Leishmaniasis	344	A.3.3
348	Visceral leishmaniasis	347	A.3.3.1
349	Cutaneous and mucocutaneous leishmaniasis	347	A.3.3.2
350	African trypanosomiasis	344	A.3.4
351	Schistosomiasis	344	A.3.5
352	Cysticercosis	344	A.3.6
353	Cystic echinococcosis	344	A.3.7
354	Lymphatic filariasis	344	A.3.8
355	Onchocerciasis	344	A.3.9
356	Trachoma	344	A.3.10
357	Dengue	344	A.3.11
358	Yellow fever	344	A.3.12
359	Rabies	344	A.3.13
360	Intestinal nematode infections	344	A.3.14
361	Ascariasis	360	A.3.14.1
362	Trichuriasis	360	A.3.14.2
363	Hookworm disease	360	A.3.14.3
364	Food-borne trematodiasis	344	A.3.15
405	Leprosy	344	A.3.16
843	Ebola	344	A.3.17
935	Zika virus	344	A.3.18
936	Guinea worm disease	344	A.3.19
365	Other neglected tropical diseases	344	A.3.20
366	Maternal disorders	295	A.4
367	Maternal hemorrhage	366	A.4.1
368	Maternal sepsis and other maternal infections	366	A.4.2
369	Maternal hypertensive disorders	366	A.4.3
370	Maternal obstructed labor and uterine rupture	366	A.4.4
371	Maternal abortion, miscarriage, and ectopic pregnancy	366	A.4.5
375	Indirect maternal deaths	366	A.4.6
376	Late maternal deaths	366	A.4.7
741	Maternal deaths aggravated by HIV/AIDS	366	A.4.8
379	Other maternal disorders	366	A.4.9
380	Neonatal disorders	295	A.5
381	Neonatal preterm birth complications	380	A.5.1
382	Neonatal encephalopathy due to birth asphyxia and trauma	380	A.5.2
383	Neonatal sepsis and other neonatal infections	380	A.5.3
384	Hemolytic disease and other neonatal jaundice	380	A.5.4
385	Other neonatal disorders	380	A.5.5
386	Nutritional deficiencies	295	A.6
387	Protein-energy malnutrition	386	A.6.1
388	Iodine deficiency	386	A.6.2
389	Vitamin A deficiency	386	A.6.3
390	Iron-deficiency anemia	386	A.6.4
391	Other nutritional deficiencies	386	A.6.5
392	Other communicable, maternal, neonatal, and nutritional diseases	295	A.7
393	Sexually transmitted diseases excluding HIV	392	A.7.1
394	Syphilis	393	A.7.1.1
395	Chlamydial infection	393	A.7.1.2
396	Gonococcal infection	393	A.7.1.3
397	Trichomoniasis	393	A.7.1.4
398	Genital herpes	393	A.7.1.5
399	Other sexually transmitted diseases	393	A.7.1.6
400	Hepatitis	392	A.7.2
401	Acute hepatitis A	400	A.7.2.1
402	Hepatitis B	400	A.7.2.2
403	Hepatitis C	400	A.7.2.3
404	Acute hepatitis E	400	A.7.2.4
408	Other infectious diseases	392	A.7.3
409	Non-communicable diseases	294	B
410	Neoplasms	409	B.1
444	Lip and oral cavity cancer	410	B.1.1
447	Nasopharynx cancer	410	B.1.2
450	Other pharynx cancer	410	B.1.3
411	Esophageal cancer	410	B.1.4
414	Stomach cancer	410	B.1.5
441	Colon and rectum cancer	410	B.1.6
417	Liver cancer	410	B.1.7
418	Liver cancer due to hepatitis B	417	B.1.7.1
419	Liver cancer due to hepatitis C	417	B.1.7.2
420	Liver cancer due to alcohol use	417	B.1.7.3
421	Liver cancer due to other causes	417	B.1.7.4
453	Gallbladder and biliary tract cancer	410	B.1.8
456	Pancreatic cancer	410	B.1.9
423	Larynx cancer	410	B.1.10
426	Tracheal, bronchus, and lung cancer	410	B.1.11
459	Malignant skin melanoma	410	B.1.12
462	Non-melanoma skin cancer	410	B.1.13
849	Non-melanoma skin cancer (squamous-cell carcinoma)	462	B.1.13.1
850	Non-melanoma skin cancer (basal-cell carcinoma)	462	B.1.13.2
429	Breast cancer	410	B.1.14
432	Cervical cancer	410	B.1.15
435	Uterine cancer	410	B.1.16
465	Ovarian cancer	410	B.1.17
438	Prostate cancer	410	B.1.18
468	Testicular cancer	410	B.1.19
471	Kidney cancer	410	B.1.20
474	Bladder cancer	410	B.1.21
477	Brain and nervous system cancer	410	B.1.22
480	Thyroid cancer	410	B.1.23
483	Mesothelioma	410	B.1.24
484	Hodgkin lymphoma	410	B.1.25
485	Non-Hodgkin lymphoma	410	B.1.26
486	Multiple myeloma	410	B.1.27
487	Leukemia	410	B.1.28

Continuation of Table 10			
Disease id	Disease name	Parent disease	Outline
845	Acute lymphoid leukemia	487	B.1.28.1
846	Chronic lymphoid leukemia	487	B.1.28.2
847	Acute myeloid leukemia	487	B.1.28.3
848	Chronic myeloid leukemia	487	B.1.28.4
943	Other leukemia	487	B.1.28.5
488	Other neoplasms	410	B.1.29
491	Cardiovascular diseases	409	B.2
492	Rheumatic heart disease	491	B.2.1
493	Ischemic heart disease	491	B.2.2
494	Cerebrovascular disease	491	B.2.3
495	Ischemic stroke	494	B.2.3.1
496	Hemorrhagic stroke	494	B.2.3.2
498	Hypertensive heart disease	491	B.2.4
499	Cardiomyopathy and myocarditis	491	B.2.5
942	Myocarditis	499	B.2.5.1
938	Alcoholic cardiomyopathy	499	B.2.5.2
944	Other cardiomyopathy	499	B.2.5.3
500	Atrial fibrillation and flutter	491	B.2.6
501	Aortic aneurysm	491	B.2.7
502	Peripheral artery disease	491	B.2.8
503	Endocarditis	491	B.2.9
507	Other cardiovascular and circulatory diseases	491	B.2.10
508	Chronic respiratory diseases	409	B.3
509	Chronic obstructive pulmonary disease	508	B.3.1
510	Pneumoconiosis	508	B.3.2
511	Silicosis	510	B.3.2.1
512	Asbestosis	510	B.3.2.2
513	Coal workers pneumoconiosis	510	B.3.2.3
514	Other pneumoconiosis	510	B.3.2.4
515	Asthma	508	B.3.3
516	Interstitial lung disease and pulmonary sarcoidosis	508	B.3.4
520	Other chronic respiratory diseases	508	B.3.5
521	Cirrhosis and other chronic liver diseases	409	B.4
522	Cirrhosis and other chronic liver diseases due to hepatitis B	521	B.4.1
523	Cirrhosis and other chronic liver diseases due to hepatitis C	521	B.4.2
524	Cirrhosis and other chronic liver diseases due to alcohol use	521	B.4.3
525	Cirrhosis and other chronic liver diseases due to other causes	521	B.4.4
526	Digestive diseases	409	B.5
527	Peptic ulcer disease	526	B.5.1
528	Gastritis and duodenitis	526	B.5.2
529	Appendicitis	526	B.5.3
530	Paralytic ileus and intestinal obstruction	526	B.5.4
531	Inguinal, femoral, and abdominal hernia	526	B.5.5
532	Inflammatory bowel disease	526	B.5.6
533	Vascular intestinal disorders	526	B.5.7
534	Gallbladder and biliary diseases	526	B.5.8
535	Pancreatitis	526	B.5.9
541	Other digestive diseases	526	B.5.10
542	Neurological disorders	409	B.6
543	Alzheimer disease and other dementias	542	B.6.1
544	Parkinson disease	542	B.6.2
545	Epilepsy	542	B.6.3
546	Multiple sclerosis	542	B.6.4
554	Motor neuron disease	542	B.6.5
547	Migraine	542	B.6.6
548	Tension-type headache	542	B.6.7
557	Other neurological disorders	542	B.6.8
558	Mental and substance use disorders	409	B.7
559	Schizophrenia	558	B.7.1
560	Alcohol use disorders	558	B.7.2
561	Drug use disorders	558	B.7.3
562	Opioid use disorders	561	B.7.3.1
563	Cocaine use disorders	561	B.7.3.2
564	Amphetamine use disorders	561	B.7.3.3
565	Cannabis use disorders	561	B.7.3.4
566	Other drug use disorders	561	B.7.3.5
567	Depressive disorders	558	B.7.4
568	Major depressive disorder	567	B.7.4.1
569	Dysthymia	567	B.7.4.2
570	Bipolar disorder	558	B.7.5
571	Anxiety disorders	558	B.7.6
572	Eating disorders	558	B.7.7
573	Anorexia nervosa	572	B.7.7.1
574	Bulimia nervosa	572	B.7.7.2
575	Autistic spectrum disorders	558	B.7.8
576	Autism	575	B.7.8.1
577	Asperger syndrome and other autistic spectrum disorders	575	B.7.8.2
578	Attention-deficit/hyperactivity disorder	558	B.7.9
579	Conduct disorder	558	B.7.10
582	Idiopathic developmental intellectual disability	558	B.7.11
585	Other mental and substance use disorders	558	B.7.12
586	Diabetes, urogenital, blood, and endocrine diseases	409	B.8
587	Diabetes mellitus	586	B.8.1
588	Acute glomerulonephritis	586	B.8.2
589	Chronic kidney disease	586	B.8.3
590	Chronic kidney disease due to diabetes mellitus	589	B.8.3.1
591	Chronic kidney disease due to hypertension	589	B.8.3.2
592	Chronic kidney disease due to glomerulonephritis	589	B.8.3.3
593	Chronic kidney disease due to other causes	589	B.8.3.4
594	Urinary diseases and male infertility	586	B.8.4
595	Interstitial nephritis and urinary tract infections	594	B.8.4.1
596	Urolithiasis	594	B.8.4.2
597	Benign prostatic hyperplasia	594	B.8.4.3
598	Male infertility	594	B.8.4.4
602	Other urinary diseases	594	B.8.4.5
603	Gynecological diseases	586	B.8.5
604	Uterine fibroids	603	B.8.5.1
605	Polycystic ovarian syndrome	603	B.8.5.2
606	Female infertility	603	B.8.5.3
607	Endometriosis	603	B.8.5.4
608	Genital prolapse	603	B.8.5.5
609	Premenstrual syndrome	603	B.8.5.6
612	Other gynecological diseases	603	B.8.5.7
613	Hemoglobinopathies and hemolytic anemias	586	B.8.6
614	Thalassemias	613	B.8.6.1
837	Thalassemias trait	613	B.8.6.2
615	Sickle cell disorders	613	B.8.6.3
838	Sickle cell trait	613	B.8.6.4
616	G6PD deficiency	613	B.8.6.5
839	G6PD trait	613	B.8.6.6
618	Other hemoglobinopathies and hemolytic anemias	613	B.8.6.7
619	Endocrine, metabolic, blood, and immune disorders	586	B.8.7
626	Musculoskeletal disorders	409	B.9
627	Rheumatoid arthritis	626	B.9.1
628	Osteoarthritis	626	B.9.2
629	Low back and neck pain	626	B.9.3
630	Low back pain	629	B.9.3.1
631	Neck pain	629	B.9.3.2

Continuation of Table 10			
Disease id	Disease name	Parent disease	Outline
632	Gout	626	B.9.4
639	Other musculoskeletal disorders	626	B.9.5
640	Other non-communicable diseases	409	B.10
641	Congenital birth defects	640	B.10.1
642	Neural tube defects	641	B.10.1.1
643	Congenital heart anomalies	641	B.10.1.2
644	Orofacial clefts	641	B.10.1.3
645	Down syndrome	641	B.10.1.4
646	Turner syndrome	641	B.10.1.5
647	Klinefelter syndrome	641	B.10.1.6
648	Other chromosomal abnormalities	641	B.10.1.7
649	Congenital musculoskeletal and limb anomalies	641	B.10.1.8
650	Urogenital congenital anomalies	641	B.10.1.9
651	Digestive congenital anomalies	641	B.10.1.10
652	Other congenital birth defects	641	B.10.1.11
653	Skin and subcutaneous diseases	640	B.10.2
654	Dermatitis	653	B.10.2.1
655	Psoriasis	653	B.10.2.2
656	Cellulitis	653	B.10.2.3
657	Pyoderma	653	B.10.2.4
658	Scabies	653	B.10.2.5
659	Fungal skin diseases	653	B.10.2.6
660	Viral skin diseases	653	B.10.2.7
661	Acne vulgaris	653	B.10.2.8
662	Alopecia areata	653	B.10.2.9
663	Pruritus	653	B.10.2.10
664	Urticaria	653	B.10.2.11
665	Decubitus ulcer	653	B.10.2.12
668	Other skin and subcutaneous diseases	653	B.10.2.13
669	Sense organ diseases	640	B.10.3
670	Glaucoma	669	B.10.3.1
671	Cataract	669	B.10.3.2
672	Macular degeneration	669	B.10.3.3
673	Refraction and accommodation disorders	669	B.10.3.4
674	Age-related and other hearing loss	669	B.10.3.5
675	Other vision loss	669	B.10.3.6
679	Other sense organ diseases	669	B.10.3.7
680	Oral disorders	640	B.10.4
681	Caries of deciduous teeth	680	B.10.4.1
682	Caries of permanent teeth	680	B.10.4.2
683	Periodontal diseases	680	B.10.4.3
684	Edentulism and severe tooth loss	680	B.10.4.4
685	Other oral disorders	680	B.10.4.5
686	Sudden infant death syndrome	640	B.10.5
687	Injuries	294	C
688	Transport injuries	687	C.1
689	Road injuries	688	C.1.1
690	Pedestrian road injuries	689	C.1.1.1
691	Cyclist road injuries	689	C.1.1.2
692	Motorcyclist road injuries	689	C.1.1.3
693	Motor vehicle road injuries	689	C.1.1.4
694	Other road injuries	689	C.1.1.5
695	Other transport injuries	688	C.1.2
696	Unintentional injuries	687	C.2
697	Falls	696	C.2.1
698	Drowning	696	C.2.2
699	Fire, heat, and hot substances	696	C.2.3
700	Poisonings	696	C.2.4
704	Exposure to mechanical forces	696	C.2.5
705	Unintentional firearm injuries	704	C.2.5.1
706	Unintentional suffocation	704	C.2.5.2
707	Other exposure to mechanical forces	704	C.2.5.3
708	Adverse effects of medical treatment	696	C.2.6
709	Animal contact	696	C.2.7
710	Venomous animal contact	709	C.2.7.1
711	Non-venomous animal contact	709	C.2.7.2
712	Foreign body	696	C.2.8
713	Pulmonary aspiration and foreign body in airway	712	C.2.8.1
714	Foreign body in eyes	712	C.2.8.2
715	Foreign body in other body part	712	C.2.8.3
842	Environmental heat and cold exposure	696	C.2.9
716	Other unintentional injuries	696	C.2.10
717	Self-harm and interpersonal violence	687	C.3
718	Self-harm	717	C.3.1
721	Self-harm by firearm	718	C.3.1.1
723	Self-harm by other specified means	718	C.3.1.2
724	Interpersonal violence	717	C.3.2
725	Physical violence by firearm	724	C.3.2.1
726	Physical violence by sharp object	724	C.3.2.2
941	Sexual violence	724	C.3.2.3
727	Physical violence by other means	724	C.3.2.4
728	Forces of nature, conflict and terrorism, and executions and police conflict	687	C.4
729	Exposure to forces of nature	728	C.4.1
945	Conflict and terrorism	728	C.4.3
854	Executions and police conflict	728	C.4.2

Notes: Global Burden of Disease Study 2016

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Publications Office

doi:10.2760/793876

ISBN 978-92-76-02924-3