Depression and diabetes

the role of syndemics in the social inequality of disability

Diderichsen, Finn; Andersen, Ingelise; Mathisen, Jimmi

Published in:
Journal of Affective Disorders Reports

DOI:
10.1016/j.jadr.2021.100211

Publication date:
2021

Document version
Publisher's PDF, also known as Version of record

Journal of Affective Disorders Reports 6 (2021) 100211

Contents lists available at ScienceDirect

Journal of Affective Disorders Reports

journal homepage: www.sciencedirect.com/journal/journal-of-affective-disorders-reports

Research Paper

Depression and diabetes: The role of syndemics in the social inequality of disability

Finn Diderichsen [a,b,*], Ingelise Andersen [a], Jimmi Mathisen [a]

[a] University of Copenhagen, Department of Public Health, Box 2099, DK-1014. Copenhagen K, Denmark
[b] Fundação Oswaldo Cruz, IAM, 50670-420 Recife/PE, Brazil

A B S T R A C T

Background: Most countries including Brazil have steep social gradients in the prevalence of disability. Many disorders contribute to that, and one individual often suffers from more than one disabling disease. The question is to what extent the syndemics framework that assume clustering and interaction between comorbid disorders influence the inequality in disability.

Methods: We used the National Health Survey of Brazil (PNS 2013 $N = 60.202$ aged 18+ years), and studied prevalent self-reported disability, diabetes and depression. We estimated age- and sex-adjusted prevalence differences across levels of education and interactions as departure from additivity with linear probability models.

Results: The Brazilian population shows social inequalities in the prevalence of both diabetes and depression, and the impact of the disorders on disability is differential, i.e. stronger among the low educated. There is both clustering and interaction between the two disorders, but the two mechanisms seem to play a negligible role in explaining the inequality in disability, whereas the most important mechanism is the differential impact the two disorders have on disability. A majority of patients suffering from both disorders has however a precarious position on the labor market with a combination of disability and only primary school or less education.

Conclusion: The syndemics framework is helpful in understanding how comorbidities impact people's lives in a specific context of social inequality, and the interaction between clustering disorders are very visible on the population level. Clustering and interaction between diabetes and depression does not however contribute much to the social disparities in disability, but the group suffering from this comorbidity represent a significant need for vocational rehabilitation.

1. Introduction

Disability, limitations of daily activities and restrictions in participation, are strongly patterned along socioeconomic lines (Hosseinpoor et al., 2013). Typically, we assume that this disparity is due to a disparity in an underlying disease or injury. It is part of the disabling process (Verbrugge and Jette 1994) that a disease or impairment interacts with the context in which patients live, and the impact on disability is a result of this interaction. The result might be social inequality in the impact of a given morbidity on disability (Klijs et al., 2014) or participation (Burström et al., 2000). More often than not, disability is not due to one disorder only, but to combinations of disorders i.e. multimorbidity (Ryan et al., 2015). Multimorbidity is often measured simply as the occurrence of 2 or more disorders in the same patient, but different typologies of comorbidity have gained increasing interest (McLean et al., 2014; Rzewuska et al., 2017). Management of more "concordant" cardio-metabolic multimorbidity with shared causal mechanisms like hypertension, diabetes and coronary heart disease represent challenges different from a more "discordant" multimorbidity including combination of physical and mental illnesses (Smith et al., 2012; McLean et al., 2014). The latter type of multimorbidity is more often associated with socioeconomic deprivation, but is also characterized by causal relationships where one disorder influences the occurrence of the others (Momen et al., 2020), and/or modifies their consequences (Liu et al., 2017; Scott et al., 2009). The impact on population health of this interaction between disorders depends on how often they cluster to the same individuals.

The framework of syndemics has brought all these different aspects together to create a better understanding of how the burden of disease impact people's daily lives (Singer et al., 2017). When living in a context of structural inequalities driving the occurrence and consequences of multiple morbidities the impact of one disease cannot be seen in isolation, but can only be understood together with other clustering and interacting disorders (Singer et al., 2017). It has, in accordance with this understanding been suggested that syndemics play an important role in generating inequalities in disease burden (Willen et al., 2017). That assumption has however not been subject to much empirical testing.

Interactions between disorders are particularly challenging to handle

* Corresponding author.
E-mail address: fidi@sund.ku.dk (F. Diderichsen).

https://doi.org/10.1016/j.jadr.2021.100211
Received 6 January 2021; Received in revised form 20 August 2021; Accepted 25 August 2021
Available online 28 August 2021

clinically (Smith et al., 2012), but might also be so for public health staff who work to tackle social disparities in disease burden. In countries, like Brazil, with large social inequalities and a health care system where "the inverse care law" is still prevailing (Junior et al., 2019), this is more important than elsewhere. We shall in this paper take diabetes and depression as an example of a prevalent comorbidity, and explore the role syndemic clustering and interaction play in the pathways driving the socioeconomic disparity in disability.

1.1. The framework of syndemics

The concept of "syndemics" (i.e. synergistic epidemics) was introduced by Merrill Singer in the 1990s. In a context of poverty and large inequalities the etiology and course of single disease can only be understood by studying the multiple health problems that tend to cluster in such an environment. Many comorbidities tend to influence both the occurrence and course of each other (Singer et al., 2017). Syndemics thus have three components: (1) co-occurring or clustering diseases; (2) adverse biological interactions between those diseases and (3) a socio-political context that cause or modify the consequences of disease. The occurrence of both the disease*disease and the disease*context interactions are a distinguishing feature of syndemics (Singer et al., 2020).

Most studies on syndemics apply ethnographic or epidemiological methods focusing on small populations living and interacting in particular contexts. We have earlier shown – even in the large heterogenous population of Brazil – that depression and diabetes are clustering an interacting. (Diderichsen and Andersen, 2019). From an anthropological point of view large population studies might however miss an important point of context specificity. Most of the empirical studies have dealt with communicable comorbidities like TBC, HIV, CMV, H1N1 etc. where a biological interaction is more obvious. For most non-communicable diseases, the biological interactions may be more complicated. The diabetes/depression comorbidity has however been studied as a case of non-communicable syndemics of growing relevance in many both high- and middle-income populations (Mendenhall et al., 2017; Diderichsen 2020). Syndemic mechanisms have also recently been identified as important for understanding the unequal burden of COVID-19 (Bambra et al., 2020).

1.2. The diabetes-depression comorbidity

The diabetes/depression comorbidity and clustering have important clinical implications (Petrak et al., 2015), and the literature on the subject is extensive (Roy and Lloyd 2012). Three causal mechanisms might all contribute to the observed clustering: Firstly, depression and diabetes may share common causes such as age, short education, poverty, long term stress, physical inactivity and obesity (Tabak et al., 2014). Some studies have indicated that dysregulation of the HPA-axis and innate immunity and inflammation is involved in the etiology of both type 2 diabetes and depression (Joseph and Golden 2017), and mediate the effect on both conditions of adverse social conditions and behaviours. Secondly, studies have indicated that diagnosed type 2 diabetes might increase risk of depression and vice versa (Nouwen et al., 2019; Chireh et al., 2019).

Living with a chronic disorder like diabetes might increase the risk of depression (Chireh et al., 2019), and depression has a negative influence on self-care and treatment adherence among diabetics (Petrak et al., 2015). That means that depression and diabetes might *interact* in their effects on course and consequences of each disease. A few studies have made a more formal interaction analysis of the effect on mortality (Naicker et al., 2017) and disability (Scott et al., 2009).

1.3. The framework of health inequality

Today socioeconomic inequalities are observed in almost all aspects of somatic and mental health, whereby people living in more socioeconomically disadvantaged conditions experience higher incidence and worse consequences of disease than their more advantaged peers. Health inequalities are observed across rich and poor countries and across socioeconomic groups within both rich and poor countries (Arcaya et al., 2015). Inequalities in disability have been described in both high- and low-income countries and their determinants have been analyzed both in terms of exposures (Perez-Hernández et al. 2019) and disorders (Klijs et al., 2014). As mentioned above the distinction between the differential morbidity and differential disability impact is potentially important. This distinction is parallel to the distinction between differential exposure and differential susceptibility to exposures driving inequalities in disease incidence (Diderichsen et al., 2019).

1.4. Syndemics within the health inequality framework

The starting point for the analysis in this paper is the existing social disparities in disability in Brazil. Brazil is middle-income country characterized by huge socioeconomic inequalities. The Gini-coefficient is 0.629 and the monthly income of richest 10% is 20 times higher than of poorest 50%. In Europe the same ratio is 8 (Piketty, 2020). There has in the last 30 years been large improvements in child health, while the health development among adults have been more problematic with growing prevalence and inequality of NCD's including diabetes (Beltrán-Sanchez et al., 2016). Brazil has a much younger population, but taking that into account, the burden from NCDs is higher and the burden from infections and injuries is more than twice the European levels.

The social disparity in disability will, as mentioned above, mainly be due to social disparities in prevalence of the diseases causing disability - in our example: diabetes and depression (see arrow I in the model shown in Fig. 1). It also depends on how much each disease impacts on disability and whether that impact is modified by socioeconomic position and context (II). It might also be modified by comorbid conditions when two diseases interact (III). The importance of this in a given population will depend on the degree of clustering of diabetes and depression (IV). By clustering we mean the excess occurrence beyond co-occurrence by chance. Without co-occurrence there can be no interaction, and without the interaction the amount of clustering will have no impact on the inequality of disability. We have earlier shown the existence of both clustering and interaction between the two disorders in Brazil (Diderichsen and Andersen, 2019).

The disparity in disability will - for mathematical reasons – depend on these four mechanisms (I-IV in Fig. 1), but how much each of them impacts on disparities in a real population is what we are going to examine here. More specifically, we aim to answer the following five

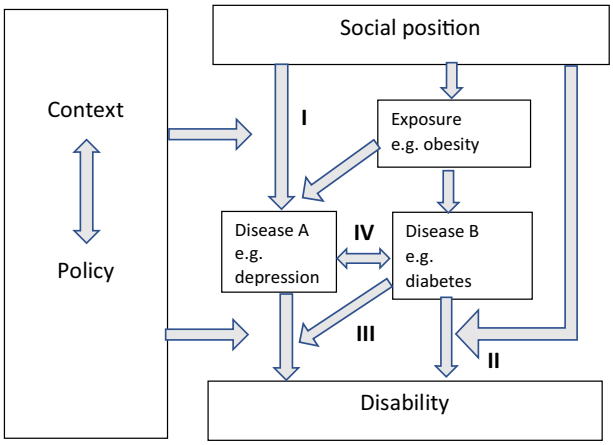

Fig. 1. Model illustrating the four mechanisms of syndemics: Social inequality in disease occurence (I), Differential impact of disease on disability (II), Interaction between diseases (III), clustering of diseases (IV)

questions:

* To what extent is diabetes and depression associated with education? (I)

* To what extent does their impact on disability differ across educational groups? (II)

* To what extent is there interaction between diabetes and depression and does it vary across educational groups? (III)

* To what extent is there clustering between diabetes and depression and does it vary across educational groups? (IV)

* How much does each of these mechanisms influence the educational disparity in disability?

2. Material and methods

The analysis is based on the Brazilian National Health Survey PNS 2013 (Szwarcwald et al., 2014), which has already been used in studies of the prevalence of diabetes, depression and multimorbidity (Rzewuska et al., 2017; Diderichsen and Andersen, 2019; Malta et al., 2019). It is a cross-sectional household survey designed with a three-stage random sampling procedure. The census tracts are the primary units, the households are the second-stage units, and one resident per household aged 18 years or older is the third-stage units. The sample includes 81,357 households. 8.1% did not want to participate or could not be contacted. Interviews on health issues were carried out with 60,202 individuals. The survey was approved by the *Comissão Nacional de Ética em Pesquisa* (CONEP – National Commission of Ethics in Research - no. 328,159).

PNS 2013 is thus a survey with sufficient sample size for the often very power-demanding comorbidity and interaction analyses, but it is cross-sectional which limits any attempt to draw causal inferences. The two disorders analysed are prevalent cases of self-reported diabetes and depressive symptoms. The first is based on an affirmative answer to the question "Has a doctor ever told you that you have diabetes?" The second is based on the PHQ-9 scale with a sum-score ranging from 0 to 27. Having moderate or severe depressive symptoms ("Depression") is defined as scoring 10 or higher (Kroenke et al., 2001). The measure of disability is based on a question raised for each of 13 different chronic disorders: to what degree the disease or its complications limit daily activities including work. Those who answer "moderate, serious or very serious" to at least one of these questions are classified as having disability i.e. limiting activities due to illness. "High education" is defined as having secondary school or more, "Short education" is primary school or less. Age is classified in four age intervals (18–24,25–44, 45–64,65+).

For an analysis of syndemics it would be ideal to have contextual data on local community level, but that is not available in this dataset. As a contextual measure of socioeconomic development, we have used the Human Development Index (HDI) of the Brazilian states. It is a composite index including measures of education, income and longevity. In 2010 HDI varied from 0.631 in Alagoas in the North East region to 0.783 in São Paulo and 0.824 in the District Federal (IBGE, 2017). These differences in HDI corresponds to nearly 20 years of development in Brazil. States with high HDI tend also to be more urbanized and industrialized, with higher average income, much lower poverty rates, and in average smaller income inequalities. We have divided the population according to HDI level of the state in two groups: High-HDI states with HDI $\geq$ 0.750 (Federal District, São Paulo, Rio de Janeiro, Santa Catarina with 37% of the sample), and other states in a group of low-medium-HDI with HDI<0.750.

The mechanism's studied in this paper includes mediation (of the effect of social position on disability), and interaction (between diseases and between disease and social position). The methodologies developed for handling mediation and interaction simultaneously (VanderWeele 2015), cannot be used here since this is a cross-sectional study and we want also to identify effects of clustering and interaction between mediating disorders. We will therefor apply a more simple calculation, as described in the results section, where only one mechanism at a time can be estimated. Associations in absolute terms (rate differences) are in general more policy relevant than relative measures (Harper et al., 2010), and syndemic interactions will be calculated as departure from additivity as proposed by other authors (Tsai and Venkatarmani 2016; Scott et al., 2009). We have therefore estimated age and sex-adjusted prevalence of disability, diabetes and depression by using linear probability models (Battey et al., 2019). We have used IBM SPSS© v25 Generalized Linear Models with robust Huber-White estimations of 95% confidence intervals to take into account heteroscedasticity. We have applied weights to adjust for sampling methods and non-response (Szwarcwald et al., 2014).

3. Results

Prevalence rates and absolute numbers of cases in the sample used is shown in Table 1. The overall prevalence of disability is 13.7% strongly associated with higher age and short education. The same is true for diabetes and depression with an overall prevalence of 6.2% and 7.9% respectively.

The starting point for our analysis is the educational disparity in disability. In the first row of Table 2 it can be seen that age- and sex adjusted prevalence for high educated is 11.5% and for low educated 18.0, which means a difference 6.5 percentage units (95% CI 5.9;7.1). The impact of diabetes and depression on disability is also shown in Table 2. Among those with high education the impact of diabetes without depression is 19.3–9.0 = 10.3 percentage units and of depression without diabetes 34.7–9.0 = 25.7. If there was no interaction between the two disorders the disability rate among the comorbid would be 10.3 + 25.7 + 9.0 = 45.0%. It was however estimated to 65.0, which means there is an interaction of 20.0 (95% CI 11.6;28.5) percentage units. This interaction is stronger among high educated in low-medium-HDI-states - 33.8 (22.9;44.6).

For those with only short education or less the disability impact is stronger – particularly from depression. The differential disability impact i.e. the interaction between short education and depression is in high-HDI states estimated to 13.7 (9.0;18.4) percentage units. There are otherwise small differences between states.

In Table 3 the estimated prevalence of diabetes and depression and their comorbid combination is shown adjusted for age and sex. If the comorbidity only occurred by chance the prevalence would be (6.4%+ 0.9%) * (5.2%+0.9%) = 0.4% among high educated and 0.8% among low educated. In reality there is a clustering that increases the

Table 1
Material: Prevalence rate (weighted) and absolute numbers (unweighted) of people with disability, diabetes or depression across sociodemographic groups in the sample. Brazil PNS 2013.

	Disability	Diabetes	Depression	Total
18–14 years	4.0% (312)	0.5% (34)	5.7% (529)	7,823
25–44 years	8.9% (2,324)	1.8% (495)	7.0% (2,142)	26,740
45–64 years	20.0% (3,543)	9.6% (1,722)	9.5% (1,706)	17,927
65+ years	26.7% (1,995)	19.8% (1,385)	9.8% (674)	7,712
Men	11.1% (2,839)	5.4% (1,281)	4.7% (1,268)	25,920
Women	16.1% (5,335)	7.0% (2,355)	10.7% (3,783)	34,282
High education	8.8% (2,828)	3.7% (1,144)	6.2% (2,276)	31,199
Short education	19.1% (5,346)	9.0% (2,492)	9.7% (2,725)	29,003
High-HDI states	12.8% (1,551)	7.1% (877)	7.8% (1,050)	12,225
Low-Med.-HDI states	14.3% (6,623)	5.7% (2,759)	8.0% (4,001)	47,977
Total	13.7% (8,174)	6.2% (3,636)	7.9% (5,051)	60,202

Table 2
Interaction: Estimated prevalence of disability (% with 95% CI)) across education, diabetes and depression and their interactions with each other. Adjusted for age and sex. Brazil. PNS 2013.

	High education	Short education
Disability (total)	11.5 (11.1;11.9)	18.0 (17.5;18.5)
a. Diabetes 0; Depression 0	9.0 (8.6;9.4)	13.1 (12.6;13.5)
b. Diabetes +; Depression 0	19.3 (16.6;22.0)	27.1 (25.1;29.1)
c. Diabetes 0; Depression +	34.7 (32.5;37.0)	51.5 (49.5;53.5)
d. Diabetes +; Depression +	65.0 (57.4;72;6)	75.7 (71.7;79.8)
Interaction: diabetes*depression (d-a) - ((b-a) + (c-a))	20.0 (11.6;28.5)	10.2 (5.3;15.2)
Interaction diabetes*depression. High-HDI states	9.1 (−3.2;21.4)	9.8 (0.2;17.6)
Interaction diabetes*depression. Low-Med.-HDI states	33.8 (22.9;44.6)	10.0 (3.6;16.4)
Interaction: diab.* short education. High-HDI states		4.3 (−0.6;9.2)
Interaction: diab.* short education. Low/Med.-HDI states		1.6 (−3.1;6.3)
Interaction: depr.* short education. High-HDI states		13.7 (9.0;18.4)
Interaction: depr.* short education. Low-Med.-HDI states		12.9 (9.2;16.5)

Table 3
Clustering. Estimated prevalence rates (% with 95% CI) with and without diabetes and/or depression across levels of education and clustering between the two disorders. Adjusted for age and sex.

	High education	Short education
Diabetes 0; Depression 0	87.5 (87.1;88.0)	83.2 (82.7;83.6)
Diabetes +; Depression 0	6.4 (6.1;6.7)	7.4 (7.1;7.7)
Diabetes 0; Depression +	5.2 (4.9;5.5)	8.1 (7.8;8.5)
Diabetes +; Depression +	0.9 (0.7;1.0)	1.3 (1.2;1.4)
Clustering (all)	0.4 (0.3;0.5)	0.5 (0.4;0.6)
Clustering in High HDI states	0.6 (0.4;0.9)	0.6 (0.3;0.8)
Clustering in Low-Med.-HDI states	0.3 (0.2;0.5)	0.5 (0.4;0.7)

prevalence of co-occurrence to 0.8% and 1.3% respectively. Which means that the clustering i.e. the increase in prevalence compared to co-occurrence by chance, is 0.4% and 0.5% respectively. The clustering is thus slightly higher among those with short education and in the high-HDI states (see Table 3).

The question now is how much each of the four mechanisms (I-IV) contribute to the existing disparity in disability? Let us assume that we have a population where the two disorders occur with the observed prevalence rates across educational groups as shown in Table 3. In the first scenario we apply the disease prevalence from Table 3 and disability impact from Table 2. The estimated prevalence of disability among high educated will then be $100*(0.875\times0.090 + 0.064\times0.193 + 0.052\times0.347 + 0.009\times0.650) = 11.5\%$ and with a similar calculation among short educated 18.1%. That gives an educational disparity of 6.6 percentage units (see Table 4). If we then keep the same overall disease prevalence, but assume that there is no clustering and the co-occurrence only is by chance, as estimated above, there is only marginal change of the inequality of disability, and it is still 6.6. The same is true if we remove the interaction between diseases. It changes hardly anything. If we then take away the differential disability impact and assume that low educated has the same disability impact as well educated the inequality it reduces the inequality substantially to 1.0 percentage unit.

4. Discussion

Referring to the five questions mentioned above we find a clear social disparity in disability. It is partly due to educational disparities in the prevalence of both diabetes and depression, but also to a very unequal

Table 4
Decomposition: Estimated educational inequality in disability (prevalence difference in percentage units). Given the observed educational inequality in prevalence of diabetes and depression, but with and without differential disability impact, clustering or interaction.

	Without differential disability impact	With differential disability impact
No clustering: No interaction	1.01	6.63
With clustering, No interaction	1.01	6.63
No clustering, with interaction	1.00	6.62
With clustering, with interaction	0.97	6.59

disability impact of in particular depression. There is a clear clustering and interaction between diabetes and depression which means that all three elements in the syndemic exist in the Brazilian adult population with a potential to influence the inequality in disability. By stepwise removing the three elements from the calculations it can be seen that most of inequality in disability is due to differential disability impact, while clustering and interaction hardly have any impact at all. That could be because the clustering and interaction is very weak in this population, but that is not the case compared to other findings (Scott et al., 2009; Leone et al., 2012). Applying the stronger interaction found in low-medium-HDI states does not change the conclusion. Other disease combinations or another context could of course yield different results. The population impact of the diabetes/depression syndemic is strongly limited by the fact that in spite of clustering the prevalence of having both disorders is only 0.91%. The clinical relevance is however significant. While, according to PNS 2013, only 9% of the Brazilian population have the labor market disadvantage of both disability and short education, this is true for 56% of patients with both diabetes and depression, and illustrates their need for rehabilitation.

It is a limitation that we do not have data from more contrasting contextual environments. Brazilian states are large heterogenous populations, but they are all characterized with huge socioeconomic inequalities. It might also be the explanation behind the unexpected finding that interaction is stronger among more privileged groups. That is not accordance with qualitative findings (Mendenhall et al., 2017). The fact that all variables are self- reported in this survey may entail a degree of misclassification that lead to an underestimation of the interactions, in particular among low educated groups (Lundberg et al., 1999).

The simplified method by which we stepwise calculate the role played by the different mechanisms in generating inequality in disability is limited in its inability to estimate simultaneous effects and the relevant statistics.

It can be noted that the overall age/sex adjusted disparity in disability was estimated to 6.5 percentage units which includes the impact of many other disorders with social inequalities in their occurrence and disability impact – such as musculoskeletal disorders. The existing disease*education and disease*disease interactions, of which we have seen some here, however means that the sum of proportions of disability attributable to each disorder will sum up to more than 100%.

Does the syndemic framework contribute to a better understanding of disparities in disability? Multimorbidity with both clustering and disease-disease interaction is highly relevant clinically and for population health in general, but as mechanisms driving the size of socioeconomic inequalities in disability it seems less important.

5. Limitations

The cross-sectional design of this study implies strong limitations for making any causal inference since there is no temporal order between

exposures and outcome. All parameters are self-reported and there is made no distinction between type-1 and type 2 diabetes. A validity study on a subsample of the PNS-2013 where the self-reported diagnosis of diabetes is compared to HbA1c levels >6.5%, or use of diabetes medication indicates a slight underreporting of diabetes when self-reported, but it is unclear to what extent that underreporting is differential across social groups (Malta et al., 2019).

The syndemics framework assumes a strong impact of social context. We have in this material only access to very crude and heterogenous indicators such as HDI-level of state and individual social position, here measured as education. Education strongly modifies the impact of disease on disability, but the levels of clustering and interaction varies only slightly between social positions and contexts.

We have adjusted all estimates for age and sex. Race and health insurance status are also potential confounders but including them in the models does not change any estimates reported here.

Declaration of Competing Interest

None.

Contributors

FD made the analysis and the first draft of this paper, IA and JM made several further additions and improvements. All authors have approved the final article.

Role of funding sources

No specific funding was provided for the work with this paper.

Acknowledgements

None.

References

Arcaya, M.C., Arcaya, A.L., Subramanian, S.V, 2015. Inequalities in health: definitions, concepts, and theories. *Glob. Health Action* 8, 27106. https://doi.org/10.3402/gha.v8.27106.

Bambra, C., Riordan, R., Ford, J., Matthews, F, 2020. The COVID-19 pandemic and health inequalities. J. Epidemiol. Community Health 74 (11), 964–968. https://doi.org/10.1136/jech-2020-214401.

Battey, H.S., Cox, D.R., Jackson, M.V, 2019. On the linear in probability model for binary data. R. Soc. Open Sci. 6 (5), 190067 https://doi.org/10.1098/rsos.190067, 2019.

Beltrán-Sánchez, H., Andrade, F.C.D., 2016. Time trends in adult chronic disease inequalities by education in Brazil: 1998–2013. Int. J. Equity Health 15, 139. https://doi.org/10.1186/s12939-016-0426-5.

Burström, B., Diderichsen, F., Whitehead, M., et al., 2000. Inequality in the social consequences of illness. Int. J. Health Serv. 30 (3), 435–451. https://doi.org/10.2190/6PP1-TDEQ-H44D-4LJQ.

Chireh, B., Li, M., D'Arcy, C., 2019. Diabetes increases the risk of depression: a systematic review, meta-analysis and estimates of population attributable fractions based on prospective studies. Prev. Med. Rep. 14, 100822 https://doi.org/10.1016/j.pmedr.2019.100822.

Diderichsen, F., Andersen, I, 2019. The syndemics of diabetes and depression in Brazil – an epidemiological analysis. Soc. Sci Med – Population Health 7, 100318. https://doi.org/10.1016/j.ssmph.2018.11.002.

Diderichsen, F., Hallqvist, J., Whitehead, M, 2019. Differential vulnerability and : how to make use of recent development in our understanding of mediation and interaction to tackle health inequalities. Int. J. Epidemiol. 48 (1), 268–274. https://doi.org/10.1093/ije/dyy167.

Diderichsen, F., 2020. The epidemiology of the diabetes:depression comorbidity in Brazil—Inequality and interaction. In: Faintuch, J., Faintuch, S. (Eds.), Obesity and Diabetes – Scientific Advances and Best Practices, 2nd ed. Springer, Cham, pp. 457–470. https://doi.org/10.1007/978-3-030-53370-0_33.

Harper, S., King, N.B., Meersman, S.C., et al., 2010. Implicit Value Judgments in the Measurement of Health Inequalities. Milbank Q. 88 (1), 4–29. https://doi.org/10.1111/j.1468-0009.2010.00587.x.

Hosseinpoor, A.R., Stewart Williams, J.A., Gautam, J., et al., 2013. Socioeconomic inequality in disability among adults: a multicountry study using the World Health Survey. Am. J. Public Health 103 (7), 1278–1286. https://doi.org/10.2105/AJPH.2012.301115.

IBGE, 2017. *Síntese De Indicadores sociais*: Uma Análise Das Condições De Vida Da População Brasileira 2017. IBGE, Rio de Janeiro. https://www.ibge.gov.br/estatisticas/sociais/populacao/9221-sintese-de-indicadores-sociais.html?edicao=18830&t=publicacoes.

Joseph, J.J., Golden, S.H, 2017. Cortisol dysregulation: the bidirectional link between stress, depression, and type 2 diabetes mellitus. Ann. N. Y. Acad. Sci. 1391, 20–34. https://doi.org/10.1111/nyas.13217.

Junior, G.D.G., Leal, E.M.M., Diderichsen, F., et al., 2019. Resource allocation for equity in Brazilian health care. Saúde Debate 43 (121), 329–340. https://doi.org/10.1590/0103-1104201912103.

Klijs, B., Nusselder, W.J., Looman, C.W., et al., 2014. Educational disparities in the burden of disability: contributions of disease prevalence and disabling impact. Am. J. Publ. Health 104 (8), e141–e148. https://doi.org/10.2105/AJPH.2014.301924.

Kroenke, K., Spitzer, R.L., Williams, J.B., 2001. The PHQ-9: validity of a brief depression severity measure. J. Gen. Intern. Med. 16 (9), 606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x.

Leone, T., Coast, E., Narayanan, S., Aikins, A.G, 2012. Diabetes and depression comorbidity and socioeconomic status in low and middle-income countries (LMICs): a mapping of the evidence. Glob. Health 8, 39. https://doi.org/10.1186/1744-8603-8-39.

Liu, N.H., Daumit, G.L., Dua, T., et al., 2017. Excess mortality in persons with severe mental disorders: a multilevel intervention framework and priorities for clinical practice, policy and research agendas. World Psychiatry 16 (1), 30–40. https://doi.org/10.1002/wps.20384.

Lundberg, M., Hallqvist, J., Diderichsen, F, 1999. Exposure-dependent misclassification of exposure in interaction analyses. Epidemiology 10 (5), 545–549.

Malta, D.C., Duncan, B.B., Schmidt, M.I., et al., 2019. Prevalence of diabetes mellitus as determined by glycated haemoglobin in the Brazilian adult population, National Health Survey. Rev. Bras Epidemiol. 22 (Suppl 2) https://doi.org/10.1590/1980-549720190006.supl.2. E190006.SUPL.2.

McLean, G., Gunn, J., Wyke, S., et al., 2014. The influence of socioeconomic deprivation on multimorbidity at different ages: a cross-sectional study. Br. J. Gen. Pract. 64 (624), e440–e447. https://doi.org/10.3399/bjgp14X680545.

Mendenhall, E., Kohrt, B.A., Norris, S.A., et al., 2017. Noncommunicable disease syndemics: poverty, depression, and diabetes among low-income populations. Lancet 389, 953–963. https://doi.org/10.1016/S0140-6736(17)30402-6.

Momen, N.C., Plana-Ripoll, O., Agerbo, E., et al., 2020. Association between mental disorders and subsequent medical conditions. N. Engl. J. Med. 382 (18), 1721–1731. https://doi.org/10.1056/NEJMoa1915784.

Naicker, K., Johnson, J.A., Skogen, J.C., et al., 2017. Type 2 diabetes and comorbid symptoms of depression and anxiety: longitudinal associations with mortality risk. Diabetes Care 40 (3), 352–358. https://doi.org/10.2337/dc16-2018.

Nouwen, A., Adriaanse, M.C., van Dam, K., et al., 2019. Systematic review or meta-analysis longitudinal associations between depression and diabetes complications: a systematic review and meta-analysis. Diabet. Med. 36 (12), 1562–1572. https://doi.org/10.1111/dme.14054.

Pérez-Hernández, B., Rubio-Valverde, J.R., Nusselder, W.J., et al., 2019. Socioeconomic inequalities in disability in Europe: contribution of behavioral, work-related and living conditions. Eur. J. Publ. Health 29 (4), 640–647. https://doi.org/10.1093/eurpub/ckz009.

Petrak, F., Baumesiter, H., Skinner, T.C., Brown, A., Holt, R.I.G, 2015. Depression and diabetes: treatment and health-care delivery. Lancet Diabetes Endocrinol. 3, 472–485. https://doi.org/10.1016/S2213-8587(15)00045-5.

Piketty, T., 2020. Capital and Ideology. Harvard University Press, Cambridge MA.

Roy, T., Lloyd, C.E, 2012. Epidemiology of depression and diabetes: a systematic review. J. Affect. Disord. 142 (Suppl), S8–S21. https://doi.org/10.1016/S0165-0327(12)70004-6.

Ryan, A., Wallace, E., O'Hara, P., Smith, S.M., 2015. Multimorbidity and functional decline in community-dwelling adults: a systematic review. Health Qual. Life Outcomes 13, 168. https://doi.org/10.1186/s12955-015-0355-9.

Rzewuska, M., de Azevedo-Marques, J.M., Coxon, D., et al., 2017. Epidemiology of multimorbidity within the Brazilian adult general population: evidence from the 2013 National Health Survey (PNS 2013). PLoS One 12 (2), e0171813. https://doi.org/10.1371/journal.pone.0171813.

Scott, K.M., Von Koff, M., Alonso, J., Angermeyer, M.C., 2009. Mental–physical comorbidity and its relationship with disability: results from the World Mental Health Surveys. Psychol. Med. 39 (1), 33–43. https://doi.org/10.1017/S0033291708003188.

Singer, M., Bulled, N., Ostrach, B., Mendenhall, E., 2017. Syndemics and the biosocial conception of health. Lancet North Am. Ed. 389, 941–950. https://doi.org/10.1016/S0140-6736(17)30003-X.

Singer, M., Bulled, N., Ostrach, B, 2020. Whither syndemics? Trends in syndemics research, a review 2015–2019. Glob. Public Health 15 (7), 943–955. https://doi.org/10.1080/17441692.2020.1724317.

Smith, S.M., Soubhi, H., Fortin, M., et al., 2012. Managing patients with multimorbidity: systematic review of interventions in primary care and community settings. BMJ 345, e5205. https://doi.org/10.1136/bmj.e5205.

Szwarcwald, C.L., Malta, D.C., Pereira, C.A., et al., 2014. Pesquisa Nacional de Saude no Brasil: concepcao e metodologia de aplicacao. Ciência Saúde Coletiva 19 (2), 333–342. https://doi.org/10.1590/1413-81232014192.14072012.

Tabak, A.G.T., Akbaraly, T.N., Batty, D., Kivimaki, M, 2014. Depression and type 2 diabetes: a causal association? Lancet Diabetes Endocrinol. 2 (3), 236–245. https://doi.org/10.1016/S2213-8587(13)70139-6.

Tsai, A.C., Venkataramani, A.S., 2016. Syndemics and health disparities: a methodological note. AIDS Behav. 20 (2), 423–430. https://doi.org/10.1007/s10461-015-1260-2.

VanderWeele, T.J., 2015. Explanation in Causal Inference: Methods for Mediation and Interaction. OUP NYC.
Verbrugge, L.M., Jette, A.M, 1994. The disablement process. Soc. Sci. Med. 38 (1), l–14. https://doi.org/10.1016/0277-9536(94)90294-1.
Willen, S., Knipper, M., Abadía-Barrero, C.E., Davidovitch, N., 2017. Syndemic vulnerability and the right to health. Lancet North Am. Ed. 389, 964–977. https://doi.org/10.1016/S0140-6736(17)30261-1.