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Consequences of childhood disadvantage on later-life health among older Brazilians

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Consequences of childhood disadvantage on later-life health among older Brazilians

A dissertation submitted in partial satisfaction

of the requirements for the degree Doctor of Philosophy

in Health Policy and Management

by

Brayan Viegas Seixas

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ABSTRACT OF THE DISSERTATION

Consequences of childhood disadvantage on later-life health among older Brazilians

by

Brayan Viegas Seixas

Doctor of Philosophy in Health Policy and Management

University of California, Los Angeles, 2023

Professor James A Macinko Jr, Chair

A growing literature has explored the relationship between life course factors and health in later life. In particular, childhood circumstances have been shown to be associated with several health outcomes many decades later. Most of this literature has focused on high-income countries and on associations between single events or exposure variables in childhood and individual health outcomes among older adults. Less is known about the combined effect of harmful exposure in childhood on later-life health outcomes and, especially, in lower- and middle-income countries. Also, imperfect strategy identifications in observational studies make difficult to assess the robustness of these associations.

This dissertation aims to address this gap in the literature with three separate studies on the relationship between childhood disadvantage and several later-life health outcomes among Brazilians aged 50 and over using data from the baseline assessment of the Brazilian Longitudinal

Study of Aging. The first study sheds light on the associations between several potentially harmful exposures in childhood (separately and combined) and the occurrence of chronic conditions, separately and together (multimorbidity). The second study focuses on the impact on distinct theoretically appropriate domains of childhood disadvantage on three measures of cognitive performance. These first two studies also investigate the potential mediation effect of adulthood socioeconomic status (SES) on these relationships. And the last study discusses the appropriateness of a novel sensitivity framework (SenseMakr) to analyze observational studies by analyzing the robustness of 65 hypothesized associations between individual exposure and outcome variables.

Results from the first study shows that a childhood disadvantage scale was associated with 8 different chronic conditions as well as the total count of chronic conditions. Mediation analyses suggest that part of the effect of childhood disadvantage (10%) on multimorbidity is mediated by higher SES in adulthood, while extensive sensitivity analyses suggest that omitted confounding is very unlikely. In the second study, we found that childhood disadvantage is associated with low performance in memory tests and semantic verbal fluency tests among older Brazilians. Adulthood SES fully mediated the association between all domains of childhood disadvantage and memory performance and only partially mediated its association with verbal fluency. The last study found that out of the 65 possible associations between single exposure and outcome variables, 24 were found to be statistically significant. Although the SenseMakr framework does not provide thresholds to support any mechanistic conclusion as it is not possible to establish universal cutoff values for its robustness measures, this approach can be highly useful in other observational studies of aging and the life course.

The dissertation of Brayan Viegas Seixas is approved.

Jack Stephen Needleman

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University of California, Los Angeles

2023

Dedication Page

A todas as crianças e adolescentes das periferias do mundo, as quais não necessitam nenhuma aprovação do império occidental, seus campeões e sua epistemologia.

Para aqueles já assaltados em sua auto-estima e potência, podem confirar nas palavaras do menino Manoelzinho:

“desaprender oito horas por dia [REALMENTE] ensina os princípios”.

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Acknowledgments

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Chapter 1 – Introduction

Promoting health among older adults has become an increasingly critical topic in the political and public health arenas in (all/most) countries in the world today. Comprising the fastest growing age group, these individuals suffer from chronic conditions at much higher rates, demanding substantial provision of healthcare. Concern with the rapid pace of aging and the inability of most healthcare systems to provide integral care to these populations have led researchers and policymakers to inquire not only better ways to improve their health through cost-effective curative and preventive medicine but also to understand how later-life health is shaped throughout the life course in order to inform long-term preventive efforts.

In particular, the relationship between potentially harmful exposures in childhood and health outcomes much later in life has been object of substantial research efforts in high-income countries. Much of this growth is related to the availability of nationally representative data on demographic factors, health characteristics and life trajectories of older adults from the US with the HRS (Health and Retirement Study), from England with ELSA (English Longitudinal Study of Ageing) and from SHARE (Survey of Health, Ageing and Retirement in Europe, which collects data from 27 European countries and Israel). These cohort studies have been in place for many years and have provided a rich data source for life course investigation. More recently, a series of sister studies have been replicated in several lower and middle-income countries, such as China, Mexico, India, and Brazil. That opened up an exciting realm for life course investigation outside rich Western countries and also created a multiplicity of opportunities for comparative studies.

My doctoral dissertation fits precisely within this investigative space, seeking to understand the relationship between childhood disadvantage and health outcomes in later life

within the context of a middle-income country. Relying on data from the baseline assessment of the Brazilian Longitudinal Study of Aging (ELSI-Brazil) for three separate but related papers, I investigated whether several adverse circumstances in childhood are associated with a series of chronic conditions and cognitive performance among older Brazilians. Two other main aspects were also explored in this work: (a) how an individual's level of socio-economic status in early adulthood can whether mitigate or exacerbate the impact of childhood disadvantage in later-life health and how such life course associations can be properly assessed using observational data.

In the first paper (chapter 2), I conducted an extensive examination of the association between five related exposure variables of childhood disadvantage, separately and combined into a single score, and thirteen chronic conditions, separately and together (multimorbidity). I analyzed the association between early life disadvantage and chronic conditions, its potential mediation by socioeconomic status (SES) in early adulthood, and carry out a series of rigorous sensitivity analyses.

In the second paper (chapter 3), nine childhood exposure variables were grouped into three theoretically appropriate domains (family SES, childhood health, and cultural capital), for which scores were created, and tested for associations with cognitive performance, as measured by immediate memory, late memory, and semantic verbal fluency. Also, mediation analysis assessed whether adulthood socioeconomic status mediated this relationship of interest.

The last paper (chapter 4) assesses the relevance and applicability of a sensitivity analysis framework known as SenseMakr to assess the robustness of a numerous array of life course associations obtained from an observational study under imperfect identification. In addition, given the possibility of randomly picking exposure and outcome variables from existing survey

data on self-reported measures of childhood disadvantage and health outcomes, I also discussed the pertinence and implications of multiple-testing adjustment of p-value thresholds.

Chapter 2 – Childhood disadvantage and chronic conditions in later life: Robust association demonstrated under imperfect identification

ABSTRACT

Background: A growing literature has connected childhood conditions to later-life health, but most studies focus on ad-hoc relationships and do not demonstrate robustness of associations. This study uses baseline (2015/2016) data from the Brazilian Longitudinal Study of Aging (ELSI) to thoroughly assess the relationship between multiple indicators of early childhood disadvantage and several chronic conditions within a nationally representative cohort of 9,412 adults aged 50 and over.

Methods: A series of binomial logistic regression models assessed the relationship between individual/combined measures of childhood disadvantage (poverty, hunger, crowded housing, poor self-rated health, rural residence) and 13 chronic conditions. Ordinary Least Squares regression estimated the effects of individual and combined measures of childhood disadvantage on the number of chronic conditions. Mediation analysis assessed whether adulthood socioeconomic status (SES) mediated this relationship of interest. A novel sensitivity analysis framework was employed to determine the likelihood of potential unobserved confounding.

Results: Individual and combined measures of childhood disadvantage were associated with several diseases and with the total number of chronic conditions, even after controlling for potential confounders. The childhood disadvantage scale was associated with 8 different chronic conditions as well as the total count of chronic conditions. The greater the value of the childhood disadvantage scale, the higher the predicted number of chronic conditions in later life, all else equal. Mediation analyses suggest that part of the effect of childhood disadvantage (10%) is

mediated by higher SES in adulthood, while extensive sensitivity analyses suggest that omitted confounding is very unlikely.

Conclusions: We found extremely robust association between several childhood disadvantage measures and chronic conditions among older Brazilians. Our work shows link between childhood disadvantage and faster aging, partial mitigation by adulthood SES and offers insights to potential life-course mechanisms. Results should inform public policy efforts to improve early childhood development, enhance adult SES and also guide further research avenues.

Keywords: childhood disadvantage, childhood adversity, aging, multimorbidity, chronic conditions.

2.1. Introduction

An increasing literature has suggested that the socioeconomic environment in which individuals are born and raised exerts significant influence on the health characteristics of adults(1–5). Pikhartova et al (6), for instance, found an association between being in a socially disadvantaged position in childhood and increased risk of type 2 diabetes in later adulthood. Similarly, Camelo and colleagues (7) demonstrated that lower socioeconomic position in childhood is associated with carotid intima-media thickness (a risk factor for cardiovascular disease) later in life. A systematic review (8) indicates that various forms of disadvantage in childhood may increase the risk of adult cancer. This literature continues to provide new insights into the importance of early life stressors as an essential determinant of adult health as well as a fundamental cause of the persistence of some health inequalities over time and across generations (9–13).

The mechanisms through which the social environment "gets under our skin" are not completely understood, although substantial knowledge has been gained on some aspects of this process(14–17). Recent work suggests that immune responses, stress-related endocrine pathways, neural processes and epigenetic transformations may all be at work (18). Several conceptual models have been proposed to illustrate the connection between early life socioeconomic conditions and later life health, like the accumulation of risks model (which assumes that pernicious prior exposures interact with adverse events across the life course to increase risk over time), the pathway model (which holds that childhood conditions set people on divergent socioeconomic trajectories with distinct stressors on health) and the social mobility model (that contends that early life exposures can be altered by other socioeconomic environments or interventions later in life)(19). A further explanation, known as the sensitive period model, has

gained a paradigmatic status in the field, suggesting that experiences during critical periods of development (such as gestation, birth, childhood, and adolescence) generate far-reaching and long-lasting biological effects that may not be reversable and, hence, alter later life disease risks (9).

Childhood disadvantage can occur through different processes and events, from stressful conditions caused by poverty (like growing up in an overcrowded home (20,21) and experiencing financial hardship (22,23)) to specific traumatic events, like malnutrition, obesity, or violence (24–26). It is reasonable to hypothesize that particular components of disadvantage in early childhood can impact health later in life and that these different stressors may also have additive or synergistic effects with certain other negative stressors. The present study aims to add to knowledge on the relationship between different aspects of childhood disadvantage and chronic conditions in later life by unpacking this problem through the exploration of four research questions:

(1) Do specific measures of childhood disadvantage increase the risk of developing specific chronic conditions later in life?

    Addressing this question sheds light on whether certain single forms of deprivation trigger biological processes that lead to greater risk of a particular chronic condition related to a specific organ or tissue. For example, does childhood hunger raise the lifetime risk of developing diabetes, but not depression?

(2) Do specific aspects of childhood disadvantage increase overall susceptibility of developing any chronic conditions later in life?

    This question is related to another hypothetical phenomenon, i.e., that a particular harmful exposure in childhood, like malnutrition, is so dangerous that it affects fundamental aspects of growth and development setting people up for many possible chronic conditions – especially those with an underlying etiology.

(3) Does exposure to a set of adverse circumstances and/or events in childhood increase the risk of developing any specific chronic condition later in life?

It is possible that the combination of hardship, disadvantageous conditions and stressful events in childhood make individuals more susceptible to a particular disease. This phenomenon may be related to the specific onset process of a given disease, beyond an overall higher susceptibility to poorer health set into motion by childhood disadvantage.

(4) Does exposure to a set of adverse conditions in childhood increase the overall susceptibility of developing chronic conditions later in life?

It is possible that a combination of childhood disadvantage components primes the body in a way that alters metabolism in general so they can trigger a number of different chronic conditions later in life.

There is a further inquiry related to these research questions: to what extent is the impact of childhood disadvantage mediated by socioeconomic conditions in adulthood? It is important not only to know which aspects or events of childhood disadvantage have effects on later-life health, but also whether or not they may be mitigated by factors experienced later in life.

This study addresses each of these research questions, with particular emphasis on the joint relationships between variables of childhood disadvantage and several chronic conditions. Apart from conducting a formal mediation test for socioeconomic status in adulthood, we also applied a novel formal strategy of sensitivity analysis that has great value under imperfect identification.

2.2. Methods

Data

ELSI is a longitudinal, household survey of Brazilians aged 50 and over, with the goal of understanding the social and biological aspects of aging in a middle-income country setting. Participants were drawn from a multi-stage cluster sample, stratified by municipality, census tract and residence. The baseline assessment took place in 2015-2016 with subsequent data collection scheduled to take place every 3 to 4 years. A total of 9,412 people, across 70 municipalities and all five major geographic regions in Brazil were part of the initial assessment, which included household and individual interviews, physical measurements, and blood tests. A more detailed methodological description can be found elsewhere (27). The ELSI-Brazil study was approved by the Research Ethics Committee of the Oswaldo Cruz Foundation, Minas Gerais (CAAE 34649814.3.0000.509). Participants signed separate informed consent forms for each aspect of the survey. The consent fully clarifies and ensures all the rights and obligations of the participant. All interviewers were trained to answer and explain any potential doubts or queries raised by the participant who is entitled to consult a third party before signing the consent.

Measures

Five binary exposure variables related to different aspects of childhood disadvantage were used: 1) poor financial status in childhood (self-declared as poor from birth to fifteen years of age); 2) poor self-rated health in childhood (coded as “yes” for average, poor and very poor, and “no” for good or very good); 3) raised in an overcrowded home (defined as having four or more people per bedroom when the survey participant was ten years old); 4) hunger in childhood (defined as having experienced lack of food at home and going to bed feeling hungry in the period from birth

to fifteen years of age); 5) residence in a rural area until fifteen years old. We created another exposure variable through polychoric factor analysis of the five aforementioned variables (referred to hereafter as the 'childhood disadvantage scale').

In terms of outcomes, we developed binary variables for self-reported medical diagnosis of hypertension, diabetes, chronic-obstructive pulmonary disease (COPD), any heart disease, stroke, arthritis, osteoporosis, back pain, renal failure, depression, cancer, Alzheimer's disease, and Parkinson's disease, as well as a numeric variable composed of the sum of these conditions. While the former set of variables was used to understand the relationship between childhood disadvantage and specific diseases, the latter was used to capture an individual's overall burden of chronic conditions.

We also included the following covariates in our models: age group (50-59, 60-69, 70-79, and 80 and over); sex, self-reported skin color (white; black; brown or other); educational attainment (less than five years of schooling; between five and eight years; nine or more); occupational status categories that reflect the sociohistorical patterns of SES including intense physical effort, some physical effort, standing or walking most of the time, seated most of the time); household income (expressed in terms of Brazilian monthly minimum wages); residence in an urban area (yes or no); living with a partner (yes or no); poor current self-rated health (yes or no); daily smoking (yes or no); alcohol consumption (never, occasionally, regularly); and body mass index (BMI) (normal weight, overweight, or obese; very few individuals were underweight and were grouped under normal weight). Because of the high correlation among adult SES measures, we created a variable (referred to hereafter as 'adult SES scale") through polychoric factor analysis of educational attainment, occupational status and current household income.

Statistical Analysis

Univariate and bivariate analyses were conducted and presented as descriptive statistics. Statistical significance for the bivariate analyses was obtained through the design-based F test (28). Age-adjusted prevalence rates were calculated using Poisson regression. For multivariate analysis involving binary outcome variables for individual chronic diseases, we employed binomial logistic regression models and estimated odds ratios. For multivariate analysis involving the combined burden of chronic conditions, ordinary least squares (OLS) regression models were applied. The statistical significance of the associations between childhood disadvantage variables and the outcomes of interest was assessed through the adjusted version of the Wald test (necessary for complex survey data).(28) A formal mediation analysis based on the Baron and Kenny approach was conducted using a system of seemingly unrelated regressions (SUR) and 1000 bootstrap samples to calculate confidence intervals of indirect and direct effects (REF).

To evaluate robustness, several analyses were performed. First, in order to check the impact of missing data, we estimated multivariate regression models both with complete cases using listwise deletion and with imputed values using multiple imputation by chained equations (MICE). Second, given that the outcome variable for the number of chronic conditions could be interpreted as a count rather than a continuous variable, we compare results from OLS to Poisson models Third, we applied a formal framework of sensitivity analysis developed for OLS regression, SenseMakr (29), which allows for quantifying the potential influence of unobserved confounders.

All analyses were conducted in Stata 15 using the ‘svy’ command to account for the complex survey design and survey weights. Data visualization was performed in R using ggplot2.

2.3. Results

Table 1 presents descriptive statistics on participants' sociodemographic characteristics, stratified by the number of chronic conditions. Less than one fifth of Brazilians aged 50 and over report having none of the considered diseases and approximately 30% have three or more. Age is significantly associated with chronic conditions and the number of diseases increases with age. Among people aged 50-59 there is a higher fraction of those with one condition (29.9%) than with two (22.1%) or three or more (23.1%), but by age 60 and above, the highest fraction is observed among those with three or more conditions. The percentage of women with three or more chronic conditions (38%) is nearly double that of men (20%). The number of chronic conditions did not vary significantly across different race groups. Clear gradients are found for education and income, as the number of schooling years or income grows the number of chronic conditions decreases. Although occupational status is correlated with education and income, it is not significantly associated with the number of chronic conditions. Regional disparities were found to be statistically significant, with higher multimorbidity in the North and Northeast. Those who lived with a partner are found to be generally healthier. Those who report drinking regularly have lower rates of chronic disease than those who drink occasionally, which in turn are healthier than those who never drink. In terms of body mass index, 70% of Brazilians aged 50 and over are either overweight or obese. Also, there are age-related gradients for rural residence until the age of 15 years, poor childhood health (both less common among younger cohorts) and hunger (more common among younger cohorts), but no statistically significant difference regarding poor childhood SES and no clear pattern regarding overcrowded home (data not shown).

Age-adjusted prevalence rates of each chronic condition, stratified by number of childhood disadvantage experiences, are shown in table 2. The most prevalent conditions are hypertension (51.5%), back pain (40.8%), arthritis (20.7%), diabetes (15.5%) and osteoporosis (15.1). Overall, there is a tendency towards higher prevalence among individuals that have experienced more numerous aspects of childhood disadvantage. The difference in the age-adjusted prevalence rate between having zero and having two or more experiences of childhood disadvantage is statistically significant for hypertension, arthritis, osteoporosis, back pain, and depression.

To assess research question one, we ran two types (partially and fully adjusted) of logistic regressions for all binary variables corresponding to the presence of any of the thirteen chronic conditions and all five early childhood exposure variables. Partially adjusted models contained relevant covariates but not the variables hypothesized as mediators and fully adjusted models additionally included potential mediators. All 130 partially and fully adjusted odds ratios are shown in supplementary table 1.

Poor socioeconomic status in childhood was found to be associated with higher likelihood of having hypertension, diabetes, osteoporosis, back pain and depression in later life in the partially adjusted model (supplementary table 1). After the inclusion of mediators, the associations with hypertension and osteoporosis were no longer statistically significant. Being raised in an overcrowded home was found to be significantly associated with arthritis and osteoporosis, in both partially and fully adjusted models. Poor self-rated health in childhood was the exposure variable significantly associated with the highest number of chronic conditions (COPD, heart disease, stroke, arthritis, osteoporosis, back pain, renal failure, depression and cancer). All odds ratios remain statistically significant even after the inclusion of mediator variables. Hunger in childhood had statistically significant associations with hypertension, diabetes, COPD, arthritis, osteoporosis,

back pain, renal failure, depression and Parkinson's disease. The association with hypertension was not statistically significant in the fully adjusted model. Lastly, being raised in a rural residence was found associated with hypertension, arthritis, osteoporosis, and back pain in the partially adjusted models but only with arthritis and osteoporosis in the fully adjusted ones. Overall, no evident pattern was identified. Out of 65 possible associations between the five exposure variables and the thirteen chronic conditions, 29 were found to be statistically significant in the partially adjusted models and only five of those completely disappeared after the inclusion of potential mediator as covariates in the fully adjusted models. Figure 1 illustrates results of both partially and fully adjusted odds ratios of hunger in childhood and poor childhood health for each chronic condition. Among all exposure variables, these two were found to be significantly associated with the largest number of individual outcomes of chronic conditions. The odds ratios of poor childhood health on COPD, heart disease, arthritis, renal failure, and depression in the fully adjusted model indicate an increase of at least 70% in the odds for these five outcomes.

In addressing research question 2 (whether specific aspects or events of childhood disadvantage increase overall susceptibility of developing chronic conditions later in life), we regressed the sum of chronic conditions on the individual exposure variables of childhood disadvantage. Supplementary table 2 presents the results of this analysis. We ran both OLS and Poisson regressions and found that OLS coefficients are nearly identical to the average marginal effects predicted by the Poisson models. All five exposure variables were found to be significantly associated with the number of chronic conditions in partially adjusted models. Estimated coefficients were similar in fully adjusted models, with the exception of rural residence, whose effect became no longer statistically significant. The highest effect size was observed for poor

childhood health (OLS coefficient: 0.450, 95% CI: 0.358-0.542) followed by hunger in childhood (OLS coefficient: 0.292, 95% CI: 0.206-0.377).

Next, in exploring research question three, we addressed whether exposure to a set of adverse circumstances and/or events in childhood increases the risk of developing specific chronic conditions later in life by carrying out logistic regressions for each chronic condition on the combined childhood disadvantage scale. Supplementary table 3 presents odds ratios and confidence intervals from partially and fully adjusted models. The variable for combined childhood disadvantage was significantly associated with hypertension (OR = 1.307, 95% CI: 1.098-1.555), diabetes (OR = 1.395, 95% CI: 1.110-1.753), COPD (OR = 1.585, 95% CI: 1.167-2.152), arthritis (OR = 1.671, 95% CI: 1.341-2.082), osteoporosis (OR = 1.840, 95% CI: 1.434-2.361), back pain (OR = 1.623, 95% CI: 1.407-1.872), renal failure (OR = 1.667, 95% CI: 1.162-2.390), and depression (OR = 1.849, 95% CI: 1.422-2.404) in the partially adjusted model. The inclusion of potential mediator variables of adulthood socioeconomic status in the fully adjusted model eliminated the statistical significance of the association with renal failure (OR = 1.442, 95% CI: 0.976-2.131) but only marginally changed the odds ratios for the other outcome variables.

Lastly, to answer research question 4, we assessed whether exposure to a set of adverse conditions in childhood increases the overall susceptibility of developing any chronic condition later in life (table 3). Model 1 presents the unadjusted coefficient, without additional covariates. Model 2 presents the coefficient adjusted for all relevant covariates that are not potential mediators, i.e., age, sex, race, macrogeographic region, urban residence, living with a partner, daily smoking, and drinking. Model 3 includes BMI as a covariate to test whether or not BMI could be in the pathway between childhood disadvantage and burden of chronic condition in later life. Model 4 includes the adulthood socioeconomic status scale expressed in the three measurable mediator

variables (educational attainment, occupational status, and income) and the control variables, except BMI. Model 5 is the most complete model, including sociodemographic covariates, adult SES and BMI. As we can see in table 3, the inclusion of BMI in model 3 does not decrease the coefficient for the exposure variable of childhood disadvantage. Conversely, including the variable for adult SES decreased the coefficient estimate by about 10%, suggesting some level of mediation. Supplementary table 4 compares the OLS estimates for the main explanatory variable to Poisson regression estimates in all models shown in table 3 from the main text.

Figure 2 presents the predicted number of chronic conditions by percentiles of the exposure variable representing the childhood disadvantage scale, the mediator variable (adult SES) and age groups based on model 5 in table 3. Overall, being in the highest tertile of childhood disadvantage (i.e., more hardship) is associated with substantially higher number of chronic diseases in comparison to those in the lowest tertiles of childhood disadvantage. For those in the highest tertile of childhood disadvantage, the predicted number of chronic diseases for those aged 50-59 was similar to that of individuals aged 70-79 who were in the lowest tertile of childhood disadvantage. Those aged 60-69 in the middle tertile of childhood disadvantage had a predicted number of chronic conditions similar to that of those aged 80 or over in the lowest childhood disadvantage tertile. We also see that the predicted number of chronic diseases decreases as adult SES increases, suggesting that part of the effect of childhood adversity appears to be mediated by better life conditions in adulthood, although this mediation effect is not linear throughout levels of adulthood SES.

To further investigate the potential mediating role of adulthood socioeconomic status in the relationship between childhood disadvantage and later-life health, we conducted a formal mediation analysis using a system of seemingly unrelated regressions (SUR) and bootstrap with

1000 simulations. We found that only 9.90% (95% bias-corrected confidence interval: 4.54, 14.07) of the association between childhood disadvantage and number of chronic conditions is mediated by adult SES. In other words, the vast majority (over 90%) of the observed effect is direct.

Lastly, we employed a formal framework for sensitivity analysis called SenseMakr (29), which is presented in the appendix. This analytical framework helps to evaluate how much unobserved confounding would be necessary to eliminate the statistical significance of the associations found here. Using age and body mass index as benchmark covariates, we found that only a hypothetical confounder with an impact on the residual variances of the exposure variable and outcome variable that is more than five times the impact that age has in the full model would eliminate the statistical significance of the association between childhood disadvantage and number of chronic conditions. Similarly, using body mass index as a benchmark covariate, a confounder would have to explain more than 30 times what that variable already explains in model 5 to completely eliminate the statistical significance observed. Thus, these tests increase confidence that the associations between measures of childhood disadvantage and number of chronic conditions in later life are not due to unmeasured confounding.

2.4. Discussion

The present work sheds light on the relationship between childhood disadvantage and chronic conditions in later life through various lenses. Overall, results revealed that the specific elements composing childhood disadvantage may both increase individuals' likelihood of developing certain chronic diseases and having multiple chronic conditions, but more importantly it also showed that the greater the level of disadvantage in early life, the higher the likelihood of

living with chronic conditions in later life. In addition, we found that the two most impactful types of childhood disadvantage are poor health and hunger, as they are not only robustly associated with a larger set of chronic conditions and with multimorbidity but also that the magnitudes of these associations are quite substantial. It suggests that exposures directly related to biological changes in childhood seem to have more impact on later-life health than the domains of childhood disadvantage that put individuals on pathways of socioeconomic hardship in their life course.

We observed that out of 65 possible associations between the five exposure variables and the thirteen chronic conditions, 24 were found to be statistically significant in the fully adjusted models. Poor self-rated health in childhood and hunger were found to be the most important factors, having the highest number of statistically significant associations with chronic conditions. Previous research has shown that hunger in childhood is associated with increased risk of depression (30), lower self-rated health status (31), worse subjective-wellbeing (32), faster aging (33) and being overweight after the age of 50 years (34). Similarly, other studies have revealed the association between childhood poor health and several type of chronic conditions, like depression (35), cardiovascular disease (36) and physical functioning (37).

Second, we investigated the relationship between each measure of childhood disadvantage and the sum of chronic conditions. While the first finding sheds light on how early disadvantage may set up or exacerbate specific biological pathways that ultimately increase the likelihood of certain chronic conditions, this research question provides evidence on a different phenomenon: whether or not negative stimuli early in life put individuals on a pathway of overall increased susceptibility for chronic diseases. That is important throughout the life course, but it is particularly critical in the population of older adults that present multimorbidities. We found that all five exposure variables (poor childhood socioeconomic status, overcrowded home, poor childhood

health, hunger in childhood, and rural residence) were associated with an increased number of chronic diseases, although the association with rural residence was no longer significant after adjustment for adult SES. Pavela and Latham (38) also found that lower childhood SES and poor childhood health are associated with higher multimorbidity after the age of 50. Similarly, Humphreys et al (39) found evidence that higher rates of childhood illnesses are associated with increased future multimorbidity. Williams et al (40) have shown that several domains of childhood misfortune decrease the likelihood of being disease free in later life.

Among the five measures of childhood disadvantage, hunger and poor self-rated health were most strongly associated with more types of chronic conditions and increased overall number of diseases. The third most impactful variable was poor childhood SES. This seems reasonable considering that hunger and poor health in childhood constitute factors more directly related to biological pathways that impact health status (41–43). Childhood SES represents a broad proxy for childhood disadvantage and often overlaps these other domains of disadvantage. The other two variables (overcrowded home and rural residence until the age of 15 years) also matter, although they were found to be associated with fewer types of chronic condition and had a lower effect size on multimorbidity. These findings confirm previous studies that have shown the importance of the physical space where children are raised for good health later in life (21,44). Also, the distinction between urban and rural residence during childhood has been found to matter, especially in low- and middle-income countries (45). Migration from rural to urban areas represented an important phenomenon of social mobility and transformation in Brazil during the twentieth century, particularly affecting the cohorts involved in the ELSI study (46,47).

Studying how specific adverse events or domain of misfortune affects later-life health is important both to understand the biological mechanisms underlying the statistical associations

revealed and to develop tailored interventions to protect individuals from poor health in the future and tackle disparities. Yet, these factors of childhood disadvantage rarely occur in isolation and may have an overall combined/cumulative impact via stress, sociobiological underdevelopment, and weakening of health functions. That is why we decided to combine all five exposures variables into a single factor variable that reflects a theoretical latent variable of childhood disadvantage and investigate its relationship with specific chronic conditions as well as the overall number of conditions.

Tackling our third research question, we investigated the impact of overall childhood disadvantage on the likelihood of developing certain disease. We found that childhood disadvantage is robustly associated with increased likelihood of developing the following diseases in later life: hypertension, diabetes, COPD, arthritis, osteoporosis, back pain, renal failure and depression. These associations only marginally decreased after adjusting for the adulthood SES, remaining statistically significant. A direct comparison with findings from the literature might be problematic given the discrepancies around the exposure variable, conceptualized in different ways (referred to as childhood disadvantage, misfortune, hardship or adversity) and operationalized through specific variables (like hunger or SES) or through a variety of scores and constructs for latent variables.

The last research question constituted the central problem of the present paper. Despite an overview of possible associations between multiple variables of childhood disadvantage and various chronic conditions, we wanted to focus on the joint effects, i.e., the latent variable for childhood disadvantage and the number of chronic conditions. The study of the latter through OLS or Poisson models can be both understood as multimorbidity (in the sense of translating the cumulative burden of multiple chronic diseases, analyzed elsewhere through multinomial (38) or

ordinal logistic regression (39)) and as overall susceptibility for chronic disease (as it also captures the occurrence of at least one disease). We found that being in the highest percentiles of childhood disadvantage is positively associated with the number of chronic conditions. The difference between being in the first tertile of childhood disadvantage and the third tertile in terms of predicted number of diseases can be as nearly as one. In other words, being in the highest tertile of childhood disadvantage in comparison to being in the lowest tertile is almost the equivalent of conditioning individuals to have at least one chronic disease in later life. This effect size changes across the percentiles of adulthood SES, which was found to have a small mediating effect. This association was found to be very robust, being extremely unlikely that an omitted variable bias is occurring to the extent of eliminating the observed effect. Moreover, individuals aged 50-59 in the highest tertile of childhood disadvantage experienced an average number of chronic conditions similar to people aged 80+ in the lowest tertile of childhood disadvantage which suggest an early aging among those who experienced the most childhood disadvantage.

Our work has several strengths. First, it constitutes a comprehensive analysis of the phenomenon of interest. To better understand the relationship between disadvantage or adversity in childhood and health in later life, we disentangle four research questions andoffer strong empirical evidence on different possible underlying mechanisms. Second, in using constructs for latent variables of both childhood disadvantage and adulthood SES as well as using the overall number of chronic diseases, we looked at the complex nature of the multifactorial independent, mediator and dependent variables. Third, the use of partially and fully adjusted models to address questions #1, #2, #3 and the multiple nested models to address question #4 allowed us to have a more refined view of possible mediating processes, including a formal mediation analysis. Fourth, we assessed the robustness of the central finding through an explicit and formal framework of

sensitivity analysis that offers concrete measures to evaluate how likely is a possible confounding as big as to eliminate the observed effect. Thus, we showed that the relationship between childhood disadvantage and the number of chronic conditions is extremely robust.

There are some limitations to this study. Relying on cross-sectional data, we were unable to evaluate the longitudinal aspect involved in the phenomenon of interest and thus cannot pinpoint how long early childhood stressors affected an individual nor assess at what age chronic conditions began to develop. Yet, the typical issue of reverse causality is less of a concern here and the problem of unobserved confounding was assessed by the sensitivity analyses. Another important limitation is that we cannot completely eliminate a threat of recall bias, given that individuals were asked to recall conditions that occurred many decades in their past. Also, there is a concern of possible sample selection (survival bias), given that only those who were able to survive at least to age 50 when the interview took place could be included in the study. This may be particularly relevant in the context of Brazil as infant/child mortality was high before the 1970s when survey participants were growing up (48).

2.5. Conclusion

This study has found robust evidence for the relationship between a set of childhood disadvantage measures and chronic conditions among older Brazilian adults. Results should inform efforts to strengthen interventions targeting early childhood development and to enhance other key inputs (such as education) in order to strengthen adult SES and thus lessen the impact of early life stressors on health in older adulthood. It highlights particularly the relevance of nutrition and health promotion among children as a necessary way to achieve healthier adult populations.

2.6. References

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Table 2-1 - Descriptive statistics, by number of chronic conditions.

			Chronic conditions				
			None	*One*	*Two*	*Three or more*	
	Sample Size	*Total*	%	%	%	%	
Total	(n = 9,412)	*%*	19.21	27.82	23.61	29.37	
Age groups							
50-59	3,980	47.62	24.97	29.91	22.05	23.07	***
60-69	2,875	29.66	15.04	27.16	25.48	32.33	
70-79	1,781	15.65	12.55	25.04	23.42	38.99	
80+	776	7.08	12.62	22.72	26.64	38.02	
Sex							
Female	5,314	53.95	13.91	24.44	23.92	37.73	***
Male	4,098	46.05	25.41	31.79	23.23	19.57	
Race/Skin color							
White	3,590	42.71	19.30	26.93	23.10	30.67	.
Black	887	9.69	16.09	28.51	25.24	30.16	
Brown	4,283	44.67	20.26	28.48	23.31	27.95	
Others	310	2.93	15.16	24.98	27.49	32.37	
Education (Years of schooling)							
Less than 5	3,463	32.85	16.07	27.43	23.83	32.67	***
Between 5 and 8	2,845	31.44	18.84	26.62	24.49	30.06	
9 or more	3,042	35.71	22.57	29.23	22.60	25.60	
Household income							
Less than 2 Minimum Wages	3,153	30.47	18.58	28.27	21.13	32.02	***
2-5 Minimum Wages	4,294	48.38	17.87	27.30	25.25	29.57	
5-9 Minimum Wages	1,148	14.16	22.65	27.85	23.96	25.54	
9+ Minimum Wages	546	6.99	23.78	31.26	21.56	23.40	
Occupational status							
Intense physical effort	1,841	19.31	17.00	26.47	24.96	31.57	.
Some physical effort	2,977	32.20	19.67	27.76	23.11	29.46	

Standing or walking most of the time	2,955	32.63	20.00	27.98	23.37	28.64	
Seated most of the time	1,414	15.86	19.45	29.62	23.16	27.77	
Region							
North	743	5.56	23.65	26.95	22.64	26.76	**
Northeast	2,549	24.10	21.61	31.03	22.74	24.62	
Southeast	3,922	47.19	17.93	27.94	23.98	30.15	
South	1,278	16.55	17.74	23.97	23.80	34.50	
Midwest	920	6.60	19.54	25.62	24.41	30.43	
Residence in urban area							
No	1,477	15.31	21.46	29.08	22.10	27.36	.
Yes	7,935	84.69	18.80	27.59	23.88	29.73	
Living with partner							
No partner	3,970	36.53	18.13	25.96	23.37	32.54	***
Living with partner	5,442	63.47	19.83	28.89	23.74	27.54	
Poor self-rated health							
No	3,970	43.71	29.43	32.54	20.82	17.20	***
Yes	5,420	56.29	11.26	24.12	25.79	38.83	
Daily smoking							
No	4,775	50.97	18.21	28.29	23.96	29.54	.
Yes	4,634	49.03	20.26	27.30	23.24	29.20	
Drink							
Never	6,909	70.89	16.63	26.51	23.74	33.12	***
Eventually	544	6.01	22.32	27.95	23.16	26.58	
Regularly	1,952	23.10	26.36	31.89	23.18	18.57	
Body Mass Index							
Normal	2,803	29.18	24.84	29.24	22.60	23.32	***
Overweight	3,561	37.71	19.77	28.08	24.79	27.36	
Obese	3,048	33.12	13.60	26.27	23.14	36.98	

Weighted and survey-adjusted proportions.
Design-corrected F-test *= p<0.05; **=p<0.01; ***p<0.001.
Data source: Brazilian Longitudinal Study of Aging (ELSI-Brazil), baseline assessment (2015-2016).

Table 2-2 – Age-adjusted prevalence rates of chronic conditions among Brazilians aged 50 or over by number of childhood disadvantage components experienced.

		Components of childhood disadvantage[1]		
Disease	Total	None	One	Two or more
Hypertension	51.48%	43.52%	50.39%	53.32%
	(49.83%-53.13%)	(38.68%-48.36%)	(47.70%-53.09%)	(51.57%-55.07%)
Diabetes	15.54%	14.12%	14.95%	16.02%
	(14.28%-16.79%)	(11.76%-16.47%)	(12.79%-17.12%)	(14.71%-17.32%)
COPD	6.02%	4.33%	5.96%	6.35%
	(5.23%-6.82%)	(2.60%-6.07%)	(4.77%-7.15%)	(5.39%-7.30%)
Heart disease	0.80%	0.75%	0.87%	0.79%
	(0.59%-1.01%)	(0.17%-1.34%)	(0.30%-1.43%)	(0.55%-1.03%)
Stroke	4.92%	3.59%	3.69%	5.61%
	(4.30%-5.53%)	(2.22%-4.97%)	(2.70%-4.69%)	(4.84%-6.39%)
Arthritis	20.74%	15.78%	18.78%	22.38%
	(19.13%-22.35%)	(12.93%-18.62%)	(16.93%-20.64%)	(20.44%-24.33%)
Osteoporosis	15.07%	9.29%	14.01%	16.49%
	(13.83%-16.30%)	(6.97%-11.61%)	(11.57%-16.45%)	(15.12%-17.87%)
Back pain	40.77%	32.88%	38.50%	43.08%
	(38.63%-42.91%)	(29.21%-36.54%)	(35.73%-41.28%)	(40.41%-45.75%)
Renal failure	4.45%	3.46%	4.05%	4.70%
	(3.77%-5.12%)	(2.23%-4.69%)	(3.09%-5.01%)	(3.97%-5.44%)
Depression	18.51%	14.90%	16.23%	20.00%
	(16.65%-20.36%)	(12.12%-17.68%)	(13.49%-18.97%)	(17.76%-22.25%)
Cancer	5.00%	4.19%	5.58%	4.89%
	(4.30%-5.70%)	(2.68%-5.70%)	(4.30%-6.86%)	(4.08%-5.69%)
Alzheimer's	0.35%	0.13%	0.37%	0.39%
	(0.22%-0.48%)	(0.02%-0.24%)	(0.09%-0.66%)	(0.21%-0.57%)
Parkinson's	0.67%	0.44%	0.57%	0.74%
	(0.45%-0.90%)	(-0.06%-0.94%)	(0.22%-0.92%)	(0.45%-1.04%)

Weighted and survey- and age-adjusted prevalence rates and 95% confidence intervals in parentheses.
Data source: Brazilian Longitudinal Study of Aging (ELSI-Brazil), baseline assessment (2015-2016).

1. The elements of childhood disadvantage include poverty, hunger, crowded housing, poor self-rated health, rural residence.

Table 2-3 - OLS models for number of chronic conditions.

VARIABLES	Model 1	Model 2	Model 3	Model 4	Model 5
Childhood disadvantage – scale[1]	0.491*** (0.0680)	0.533*** (0.0641)	0.543*** (0.0611)	0.481*** (0.0614)	0.484*** (0.0580)
Covariates	No	Yes	Yes	Yes	Yes
BMI – ref: Normal[+]					
Overweight			0.201*** (0.0476)		0.204*** (0.0522)
Obese			0.497*** (0.0565)		0.499*** (0.0575)
Adult SES – scale				-0.117** (0.0392)	-0.127*** (0.0378)
Constant	1.651*** (0.0455)	1.307*** (0.115)	1.077*** (0.117)	1.494*** (0.130)	1.285*** (0.137)
Observations	9,257	8,792	8,792	8,325	8,325
R-squared	0.011	0.117	0.133	0.120	0.136

Coefficients from survey-adjusted OLS regression.
Standard errors in parentheses.
[+] Includes underweight (BMI < 18.5) because sample size for this group is very small (n = 163)
*** p<0.001, ** p<0.01, * p<0.05.
[1] The childhood disadvantage scale was operationalized through a polychoric factor analysis of the following five measure variables: poor childhood socioeconomic status, overcrowded home, poor childhood health, hunger in childhood, and rural residence.
[2] The adult SES (socioeconomic status) scale was operationalized through a polychoric analysis of the following three variables: educational attainment, family income, and occupational status.
Covariates include age, sex, race, macrogeographic region, urban residence, living with a partner, daily smoking, drinking.
Data source: ELSI-Brazil, 2015-2016.

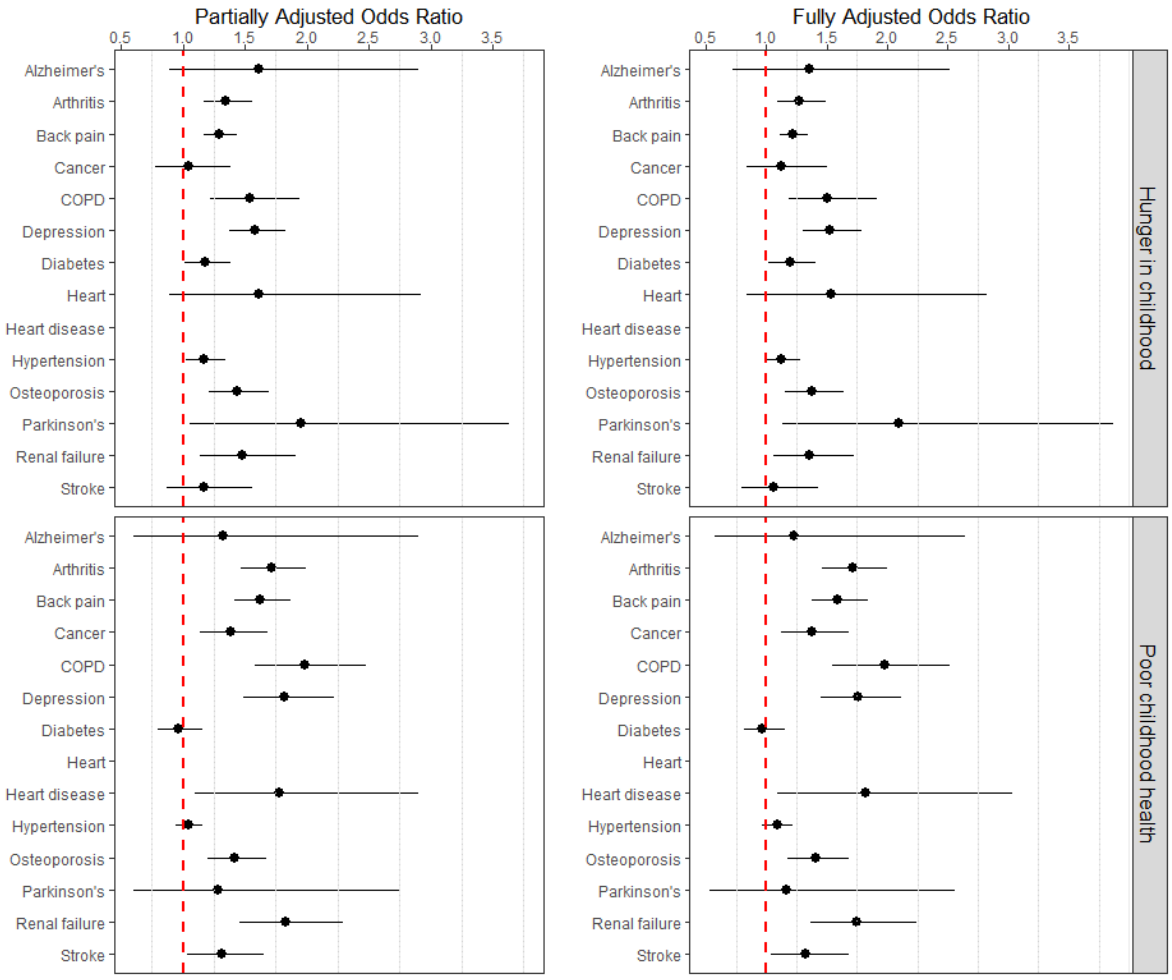


Figure 2-1 - Odds ratios and 95% confidence intervals of childhood hunger and poor childhood health for all studied chronic conditions among Brazilians aged 50 and older.

Partially adjusted odds ratios were obtained from survey-adjusted logistic regressions controlling for age, sex, race, macrogeographic region, urban residence, living with a partner, daily smoking, drinking and body mass index. Fully adjusted models included these covariates plus the following potential mediator variables: educational attainment, household income, occupational status. Data source: ELSI-Brazil, 2015-2016.

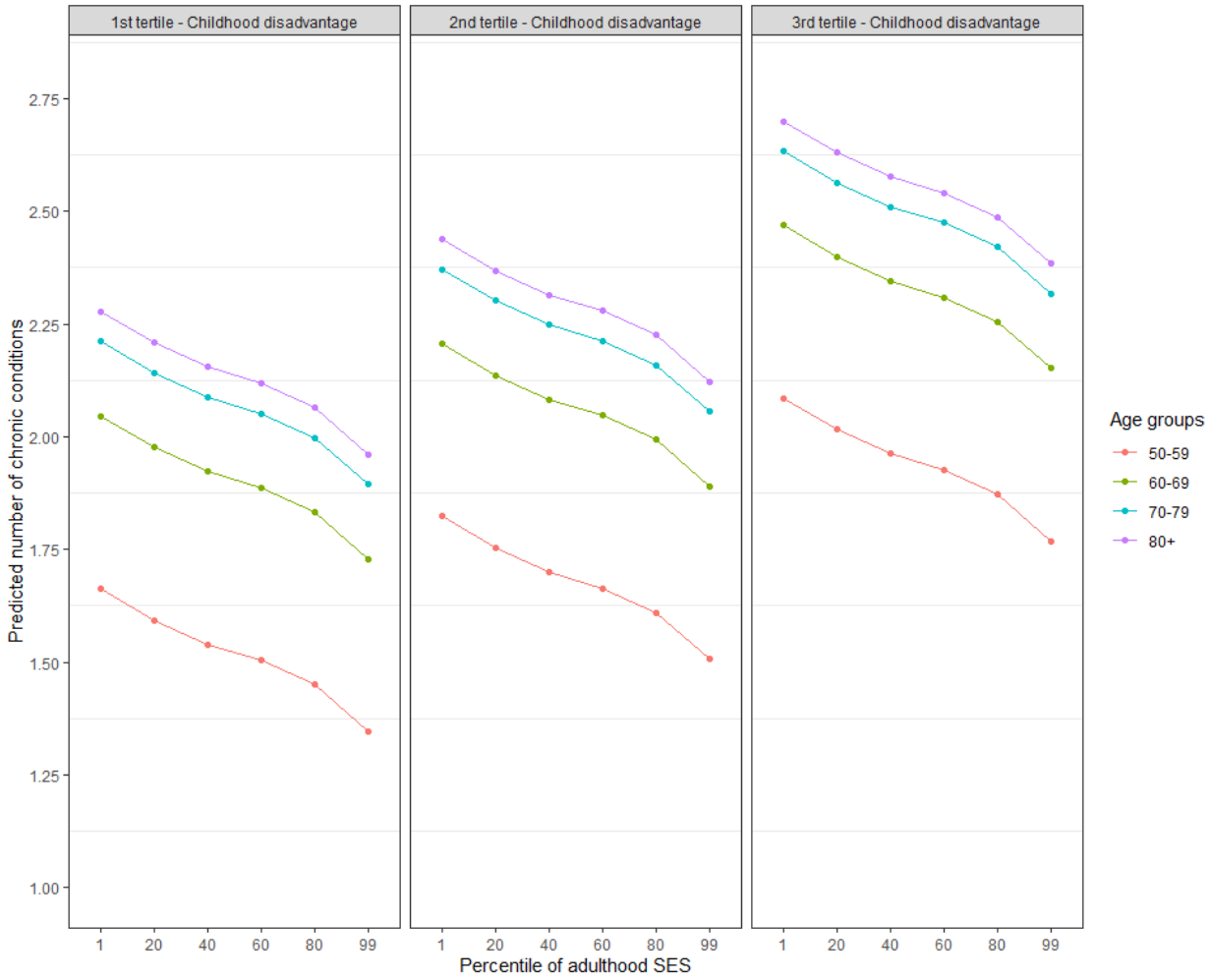


Figure 2-2 - Predicted number of chronic conditions, by percentiles of the childhood disadvantage scale, adult SES scale, and age groups based on model 5 from table 3. Data source: ELSI-Brazil, 2015-2016.

Supplementary table 1 – Associations between exposure variables of childhood disadvantage and occurrence of chronic conditions later in life expressed in odds ratios.

VARIABLES	Poor SES		Overcrowded home		Poor childhood health		Hunger in childhood		Rural residence	
	Partially adjusted	Fully adjusted	Partially adjusted	Fully adjusted	Partially adjusted	Fully adjusted	Partially adjusted	Fully adjusted	Partially adjusted	Fully adjusted
Hypertension	1.130* (1.016 - 1.258)	1.092 (0.966 - 1.236)	1.016 (0.917 - 1.126)	0.988 (0.887 - 1.101)	1.044 (0.938 - 1.162)	1.088 (0.971 - 1.220)	1.173* (1.026 - 1.340)	1.121 (0.983 - 1.279)	1.186** (1.053 - 1.337)	1.110 (0.983 - 1.254)
Diabetes	1.249** (1.065 - 1.464)	1.242* (1.040 - 1.483)	1.103 (0.960 - 1.269)	1.094 (0.944 - 1.268)	0.962 (0.799 - 1.159)	0.971 (0.814 - 1.158)	1.183* (1.014 - 1.381)	1.199* (1.022 - 1.406)	0.897 (0.783 - 1.028)	0.889 (0.756 - 1.046)
COPD	0.997 (0.801 - 1.240)	1.005 (0.819 - 1.233)	1.065 (0.858 - 1.321)	1.054 (0.838 - 1.325)	1.979*** (1.583 - 2.475)	1.976*** (1.552 - 2.515)	1.541*** (1.224 - 1.941)	1.506*** (1.183 - 1.918)	1.022 (0.843 - 1.238)	0.907 (0.728 - 1.131)
Heart	1.038 (0.654 - 1.646)	0.965 (0.610 - 1.527)	1.007 (0.594 - 1.709)	0.983 (0.580 - 1.664)	1.780* (1.094 - 2.897)	1.822* (1.094 - 3.035)	1.614 (0.890 - 2.925)	1.539 (0.840 - 2.819)	0.904 (0.542 - 1.506)	0.892 (0.449 - 1.774)
Stroke	1.187 (0.908 - 1.551)	1.111 (0.830 - 1.488)	1.091 (0.833 - 1.429)	1.076 (0.827 - 1.401)	1.310* (1.039 - 1.651)	1.320* (1.037 - 1.680)	1.167 (0.870 - 1.565)	1.064 (0.793 - 1.428)	1.100 (0.884 - 1.369)	0.992 (0.766 - 1.285)
Arthritis	1.127 (0.982 - 1.293)	1.110 (0.959 - 1.286)	1.229** (1.086 - 1.390)	1.214** (1.067 - 1.382)	1.711*** (1.470 - 1.993)	1.712*** (1.463 - 2.003)	1.349*** (1.165 - 1.561)	1.276** (1.089 - 1.494)	1.232** (1.074 - 1.415)	1.289** (1.105 - 1.504)
Osteoporosis	1.242* (1.030 - 1.497)	1.200 (0.977 - 1.473)	1.164* (1.022 - 1.326)	1.176* (1.025 - 1.349)	1.416*** (1.198 - 1.674)	1.406*** (1.178 - 1.679)	1.433*** (1.214 - 1.692)	1.377*** (1.154 - 1.643)	1.262** (1.082 - 1.471)	1.276** (1.077 - 1.511)
Back pain	1.203*** (1.088 - 1.330)	1.185** (1.070 - 1.312)	1.079 (0.966 - 1.206)	1.057 (0.947 - 1.180)	1.623*** (1.412 - 1.866)	1.593*** (1.379 - 1.840)	1.295*** (1.171 - 1.433)	1.224*** (1.109 - 1.350)	1.192** (1.051 - 1.352)	1.154 (0.998 - 1.334)
Renal failure	1.073 (0.848 - 1.359)	0.994 (0.769 - 1.284)	1.028 (0.819 - 1.291)	1.001 (0.799 - 1.253)	1.828*** (1.455 - 2.297)	1.752*** (1.371 - 2.240)	1.477** (1.143 - 1.910)	1.354* (1.062 - 1.726)	1.158 (0.897 - 1.494)	1.022 (0.749 - 1.395)
Depression	1.178* (1.005 - 1.380)	1.190* (1.007 - 1.407)	1.112 (0.936 - 1.322)	1.144 (0.968 - 1.353)	1.820*** (1.494 - 2.217)	1.757*** (1.455 - 2.122)	1.584*** (1.371 - 1.831)	1.527*** (1.306 - 1.785)	0.993 (0.843 - 1.169)	0.918 (0.775 - 1.086)
Cancer	0.978 (0.790 - 1.211)	1.030 (0.827 - 1.282)	0.977 (0.742 - 1.286)	0.980 (0.744 - 1.290)	1.387** (1.140 - 1.689)	1.381** (1.129 - 1.689)	1.041 (0.779 - 1.391)	1.123 (0.839 - 1.502)	0.968 (0.759 - 1.234)	1.008 (0.777 - 1.308)
Alzheimer	1.186 (0.721 - 1.952)	0.998 (0.565 - 1.763)	0.984 (0.566 - 1.709)	0.864 (0.469 - 1.591)	1.325 (0.604 - 2.905)	1.235 (0.577 - 2.644)	1.611 (0.895 - 2.900)	1.354 (0.728 - 2.517)	1.060 (0.629 - 1.784)	0.934 (0.529 - 1.649)

Parkinson	0.889 (0.517 - 1.529)	0.680 (0.394 - 1.174)	0.998 (0.537 - 1.855)	1.012 (0.559 - 1.833)	1.286 (0.601 - 2.752)	1.169 (0.534 - 2.560)	1.954* (1.051 - 3.635)	2.094* (1.134 - 3.866)	0.663 (0.309 - 1.422)	0.550 (0.214 - 1.414)

*** p<0.001, ** p<0.01, * p<0.05. Partially adjusted odds ratios were obtained from logistic regressions controlling for age, sex, race, macrogeographic region, urban residence, living with a partner, daily smoking, drinking and body mass index. Fully adjusted models included these covariates plus the following potential mediator variables: educational attainment, household income, occupational status. Data source: ELSI-Brazil, 2015-2016.

Supplementary table 2 – Associations between exposure variables of childhood disadvantage and total number of chronic conditions using OLS and Poisson.

	OLS model coefficients (95% confidence interval)		Poisson model average marginal effect (95% confidence interval)	
VARIABLES	Partially adjusted	Fully adjusted	Partially adjusted	Fully adjusted
Poor SES	0.177***	0.151***	0.176***	0.151***
	(0.103 - 0.251)	(0.073 - 0.228)	(0.101 - 0.251)	(0.069 - 0.232)
Overcrowded home	0.111*	0.0992*	0.108*	0.094*
	(0.021 - 0.201)	(0.011 - 0.188)	(0.020 - 0.196)	(0.008 - 0.180)
Poor childhood health	0.456***	0.450***	0.460***	0.452***
	(0.362 - 0.549)	(0.358 - 0.542)	(0.367 - 0.552)	(0.361 - 0.544)
Hunger in childhood	0.342***	0.292***	0.348***	0.293***
	(0.249 - 0.436)	(0.206 - 0.377)	(0.254 - 0.442)	(0.207 - 0.378)
Rural residence	0.133**	0.087	0.131**	0.087
	(0.052 - 0.214)	(-0.001 - 0.176)	(0.050 - 0.212)	(-0.003 - 0.178)

*** p<0.001, ** p<0.01, * p<0.05.

Partially adjusted odds ratios were obtained from OLS and Poisson regressions controlling for age, sex, race, macrogeographic region, urban residence, living with a partner, daily smoking, drinking and body mass index. Fully adjusted models included these covariates plus the following potential mediator variables: educational attainment, household income, occupational status.

Data source: ELSI-Brazil, 2015-2016.

Supplementary table 3 – Associations between a combined childhood disadvantage scale and occurrence of chronic conditions later in life expressed in odds ratios.

	Childhood Disadvantage Latent Variable			
Variables	Partially adjusted Odds Ratio	95% CI	Fully adjusted Odds Ratio	95% CI
Hypertension	1.307**	(1.098 - 1.555)	1.217*	(1.017 - 1.457)
Diabetes	1.395**	(1.110 - 1.753)	1.417**	(1.099 - 1.825)
COPD	1.585**	(1.167 - 2.152)	1.583**	(1.163 - 2.153)
Heart disease	1.685	(0.758 - 3.747)	1.566	(0.713 - 3.443)
Stroke	1.385	(0.923 - 2.080)	1.228	(0.802 - 1.880)
Arthritis	1.671***	(1.341 - 2.082)	1.632***	(1.276 - 2.088)
Osteo	1.840***	(1.434 - 2.361)	1.810***	(1.378 - 2.378)
Back pain	1.623***	(1.407 - 1.872)	1.551***	(1.347 - 1.785)
Renal failure	1.667**	(1.162 - 2.390)	1.442	(0.976 - 2.131)
Depression	1.849***	(1.422 - 2.404)	1.885***	(1.430 - 2.484)
Cancer	1.065	(0.764 - 1.484)	1.199	(0.863 - 1.664)
Alzheimer's	1.653	(0.646 - 4.233)	1.224	(0.400 - 3.743)
Parkinson's	1.461	(0.562 - 3.797)	1.204	(0.411 - 3.522)

*** p<0.001, ** p<0.01, * p<0.05.
Partially adjusted odds ratios were obtained from logistic regressions controlling for age, sex, race, macrogeographic region, urban residence, living with a partner, daily smoking, drinking and body mass index. Fully adjusted models included these covariates plus the following potential mediator variables: educational attainment, household income, occupational status. Data source: ELSI-Brazil, 2015-2016.

Supplementary table 4 – Association between the childhood disadvantage scale and number of chronic conditions for all models shown in table 3 of the main text using OLS and Poisson regression models.

Models shown in table 3	OLS regression Coefficient (95% confidence interval)	Poisson regression Average marginal effect (95% confidence interval)
Model 1	0.491*** (0.357 - 0.624)	0.485*** (0.354 - 0.617)
Model 2	0.533*** (0.407 - 0.659)	0.529*** (0.406 - 0.652)
Model 3	0.543*** (0.422 - 0.663)	0.537*** (0.419 - 0.653)
Model 4	0.481*** (0.359 - 0.601)	0.478*** (0.359 - 0.598)
Model 5	0.484*** (0.370 - 0.598)	0.482*** (0.369 - 0.594)

*** p<0.001, ** p<0.01, * p<0.05
Data source: ELSI-Brazil, 2015-2016

Chapter 1 Appendix – Sensitivity Analysis using the SenseMakr Framework

One of the measures provided by this framework is the Robustness Value, which can be either expressed as the proportion of residual variance in the treatment and outcome variables that a confounder would have to explain in order to bring the estimated effect down to zero (RV_q) or proportion of residual variance in the treatment and outcome variables that a confounder would have to explain in order to eliminate the statistical significance observed ($RV_{q,\alpha}$). Model 5 (table 3) has a $RV_q = 0.093$, which tells us that a confounder capable of explaining at least 9.3% of the residual variance in the number of chronic conditions and at the same time at least 9.3% of the residual variance in the latent variable for childhood disadvantage would completely eliminate the estimated treatment effect. And it has $RV_{q,\ \alpha = 0.05} = 0.074$, which indicates that a hypothetical unobserved confounder capable of explaining at least 7.4% of the residual variance of both exposure and outcome variables is strong enough to make the observed association no longer statistically significant at $\alpha = 0.05$.

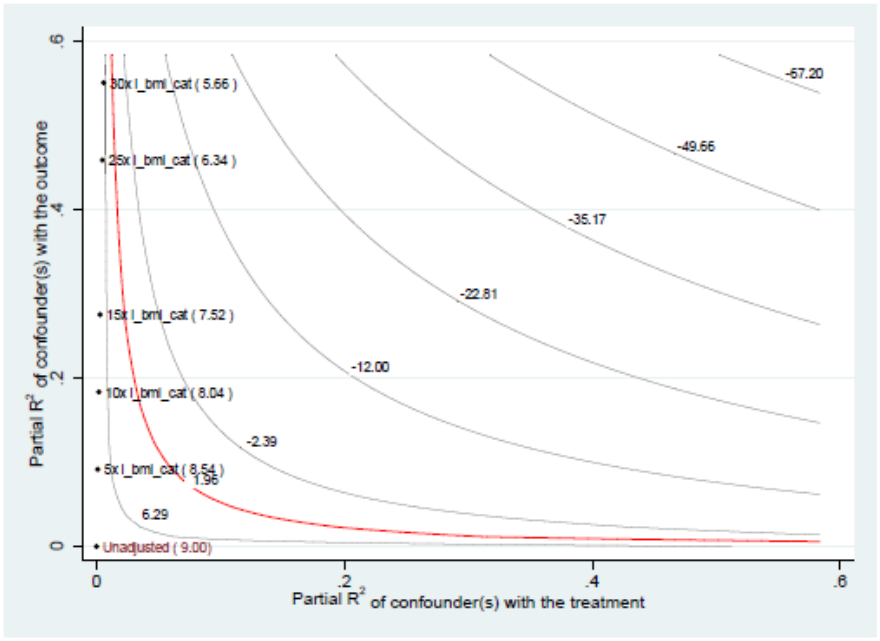
While unlikely, it is possible to imagine a confounder capable of explaining over 7% of residual variance in both exposure and outcome variables. The SenseMakr framework does not provide threshold to support any conclusion because it is not possible to establish universal cutoff values for these measures. For this reason, we rely on the idea of benchmark covariates to inform us about how strong the explanatory power of a possible unobserved confounder would have to be in comparison to the explanatory power of observed variables in order to eliminate the estimated treatment effect. We chose two variables as benchmark covariates: age and body mass index given that it is difficult to imagine observable variables that explain the number of chronic conditions better than them in this population.

Results are presented in appendix figure 1 which plots the the partial R^2 of the hypothesized confounder with the outcome on the y-axis and the partial R^2 of the treatment on the x-axis, these plots allow us to understand how much a potential confounder would have to explain of the residual variance in treatment and outcome in order to change our findings, expressed in terms of the impact of a given benchmark covariate. In one version, the contours depict the t-values that would be obtained for coefficient of interest in the Wald test in the presence of a possible confounder with the hypothesized values of the sensitivity parameters. That allows us to determine if any of that level of confounding is sufficient to eliminate the statistical significance of the association.

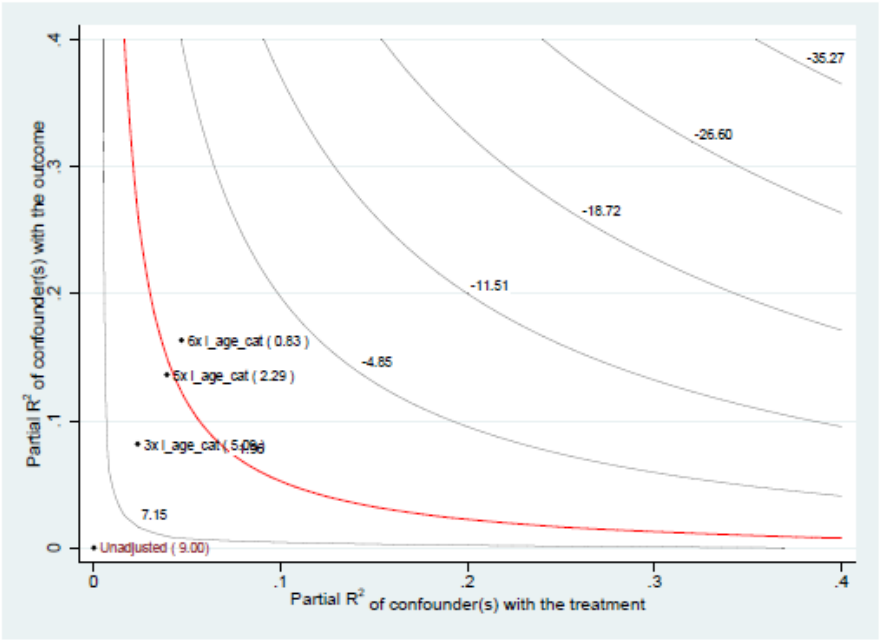
Appendix figure 1 indicates that only a confounder with an impact on the residual variances of the exposure variable and outcome variable that is more than five times the impact that the variable age has in the full model would eliminate the statistical significance of the association between childhood disadvantage and number of chronic conditions. Similarly, using body mass index as a benchmark covariate, a confounder would have to explain more than 30 times what that variable already explains in model 5 to completely eliminate the statistical significance observed.

Another Sensemakr tool is the "extreme scenario" analysis. We considered scenarios in which a confounder explains 25%, 50% and 75% of the remaining variance in the outcome. As can be seen in appendix figure 2, the proportion of the residual variance of the treatment variable (childhood adversity) that a confounder would have to explain to eliminate the estimated effect is arguably very high. For a hypothetical confounder capable of explaining 75% of the residual variance in the outcome, this same unobserved confounder would still have to explain almost 20% of the residual variance in the exposure variable. And given that our model controls for most of the variables known to cause common chronic conditions, it is unlikely that results are due to an unobserved confounder explaining 75% of the residual variance in the outcome. On the other hand,

if we look at the less unreasonable scenario, i.e., a confounder that explains 25% of the residual variance in the outcome (which is still very unlikely), that hypothetical confounder would then also have to explain over 40% of the residual variance in the exposure variable.

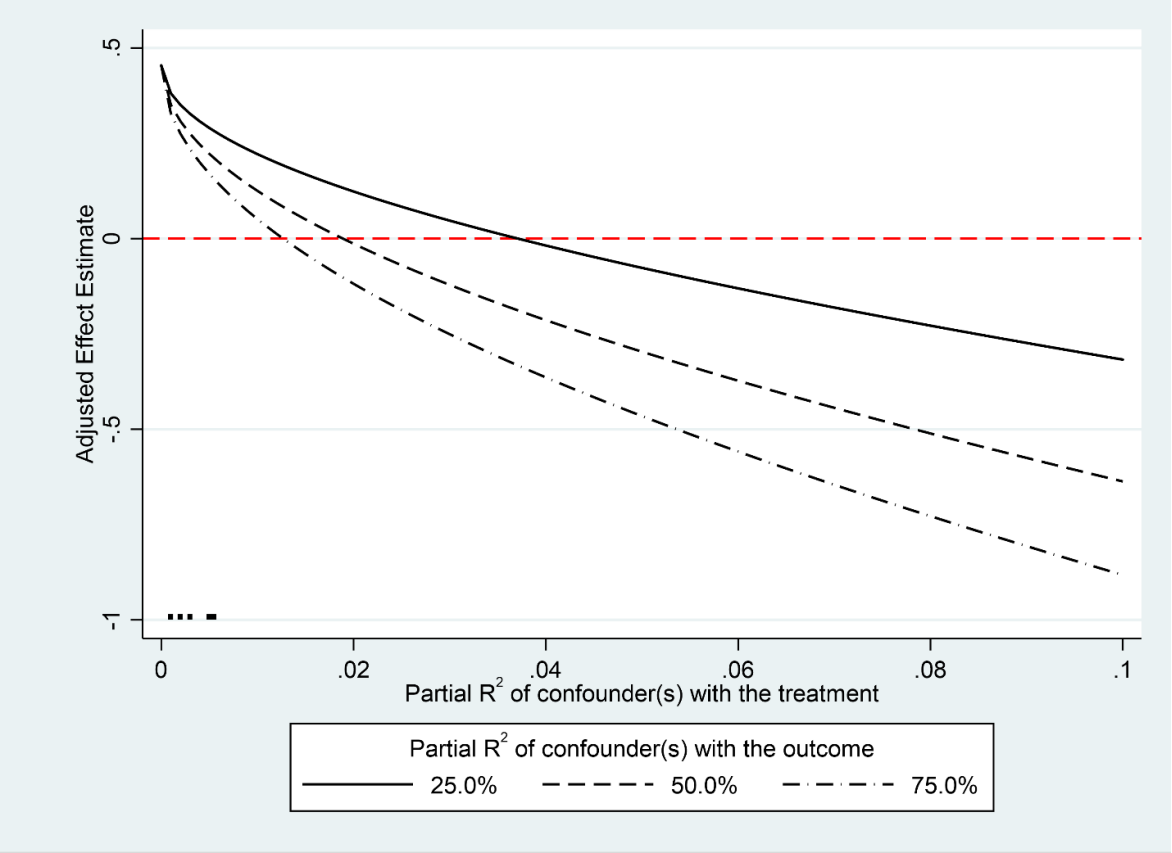


(a)



(b)

Appendix figure 1 - Sensitivity analysis using two benchmark covariates: (a) BMI and (b) age.



Appendix figure 2 - Sensitivity analysis using extreme scenarios of hypothesized unobserved confounders explaining 25%, 50% and 75% the residual variation in the outcome.

Chapter 3 – Distinct Domains of Childhood Disadvantage and Cognitive Performance Among Older Brazilians: Evidence from ELSI-Brazil

ABSTRACT

Objective: To investigate the relationship between of distinct domains of childhood disadvantage and cognitive performance among older adults within the context of a middle-income country.

Methods: This study used baseline data (2015/2016) from the Brazilian Longitudinal Study of Aging (ELSI), a nationally representative cohort of 9,412 adults aged 50 and over. Nine childhood exposure variables were grouped into three domains (family SES, childhood health, and cultural capital), for which scores were created. Survey-weighted Ordinary Least Squares (OLS) regressions estimated the association childhood disadvantage with cognitive performance as measured by immediate memory, late memory and semantic verbal fluency. Mediation analysis assessed whether adulthood socioeconomic status (SES) mediated this relationship of interest.

Results: Important disparities in cognitive performance were observed, particularly in terms of age, education, income, occupational status. Before controlling for adulthood SES in the multivariable analysis, all domains of childhood disadvantage were found to be associated with lower cognitive performance across all three measures. After inclusion of adulthood SES variables, the observed associations only remained for semantic verbal fluency. Formal mediation analysis indicated that adulthood SES mediates 55.4% (95% CI: 37.8% - 103.1%) of the association between later-life verbal fluency and poor childhood health, and 49.1% (95%CI: 43.1% - 57.1%) of the association between later-life verbal fluency and low childhood cultural capital.

Conclusions: We found that childhood disadvantage is associated with low performance in memory tests and semantic verbal fluency tests among older Brazilians. Adulthood SES fully mediated the association between all domains of childhood disadvantage and memory performance

and only partially mediated its association with verbal fluency. Our findings support policy efforts to enhance early childhood development and improve adulthood SES, and guide additional research to better the mechanisms driving these relationships.

Keywords: childhood disadvantage, childhood adversity, aging, cognition, memory, verbal fluency.

3.1. Introduction

The socioeconomic conditions in which individuals are born and raised have been shown to strongly influence health later in life (1–4). Previous research (5–7) has also shown that different childhood circumstances, such as poor parenting, inadequate nutrition, disadvantaged socioeconomic position may increase the risk of chronic conditions, such as cancer, in adult life. Stringhini et al (8) found that being in the lowest socioeconomic status (SES) groups during early stages of life was associated with increased risk of diabetes in later life. Similarly, childhood social disadvantage has been found to be associated with increased risk for cardiovascular diseases in adulthood (9,10). Evidence on the impact of early life stressors on a variety of health outcomes have been increasingly observed among older adults leading to a burgeoning literature, especially among higher-income countries (11–16).

The ways through which the socioeconomic environment "gets under our skin" (a process known as biological embedding (17,18)) seem to be numerous and are not thoroughly understood, despite the considerable growth of the literature around this topic. To date, several conceptual models have been proposed to explain the relationship between early life conditions and the health of older adults. These include the pathway model (which contends that childhood conditions put people on distinct life routes with important stressors for the health of individuals), the model of risk accumulation (which establishes that previous noxious exposures generate adverse effects that accumulate over time), and the social mobility model (which assumes that early life exposures may be modified by other socioeconomic environments throughout the life course) (19–22). Another explanation, known as the sensitive period model, suggests that experiences during sensitive periods of development (such as gestation, birth, childhood, and adolescence) produce far-reaching and long-lasting biological effects that may not be reversable and condition disease

risks in later life (11). Some researchers have additionally suggested that immune responses, stress-related endocrine pathways, neural processes and epigenetic transformations may be key biological drivers of this process (23,24).

While the models discussed above provide clues to understanding different pathways linking childhood experiences with later life health, there is currently insufficient empirical evidence about which childhood adverse events could be expected to affect which health outcomes in older adults. Results from aging cohort studies based in high-income countries have suggested that certain childhood disadvantage circumstances tend to be associated with lower cognitive performance and/or cognitive decline in later life (25–30) . But there have been fewer studies examining how these processes might unfold in low- and middle-income countries (LMICs) (31–33). The need for such evidence is particularly relevant in LMICs, given the rapid increase in the size of their older populations and their still developing economies and institutional capacities in terms of providing social protections for their aging citizens (34). For example, Ye et al found associations between low childhood socioeconomic status and poorer cognitive performance among older Chinese (35) while Lin et al (36) found that adverse childhood circumstances are also associated with faster cognitive decline among the same population. In India, deprivations in childhood were found to be associated with later-life cognitive impairment (37).

Understanding determinants of the aging process is particularly relevant in Brazil, which has the world's sixth largest population with 17.8 million adults (8.5%) aged 65 and over (38). In 2020, life expectancy was estimated at 76 years, placing it squarely within the median for the Latin America and the Caribbean region, but healthy life expectancy was only 65, suggesting considerable burden of morbidity within the population (39). Hallmark features of Brazil's social and economic context include its high level of income inequality (Gini Index of 48.9 in 2020),

making the country the 16th most unequal in the world in terms of income distribution (40) . Brazil is also known as a leader in innovative social policies, including a universal health system, a large conditional cash transfer program, and a national pension program, among others, although the impact of these programs on older adults as well as their long-term sustainability are largely unknown.

Given this context, the current study sought to address the following question: Is there an association between childhood disadvantage and cognitive performance in older adults in Brazil? More specifically, are there particular domains of childhood disadvantage that are more impactful on later-life cognition? Our hypothesis is that circumstances in early life related to disadvantaged socioeconomic status, poor quality parenting, lack of access to adequate nutrition and health care, late or inadequate schooling, among other variables, increase the risk of low cognitive performance later in life. Further, we aimed to address whether this relationship is potentially reversible by testing whether early adulthood experiences may mediate or moderate the relationship between early life disadvantage and cognitive performance in later life.

ANALYTICAL CONCEPTUAL FRAMEWORK

This study explores two main means by which childhood disadvantage may affect health in later life (see figure 1). The graphical portrayal of this conceptual framework is intended to make a theory-informed analysis of the association in question and to aid in choosing essential covariates. We note that the graphic is not a formal Directed Acyclic Graph (DAG), so the lack of arrows between some nodes should not be interpreted as evidence of no relationship. The most fundamental idea is that adversity events or disadvantageous circumstances that take place during

childhood can have a direct impact on the health of older people, which is represented by arrow ***a***. This sole arrow would be enough to represent the entire phenomenon by which childhood disadvantage affect later life health if intermediary stages of life had no relevance. A more reasonable approach, however, is to hypothesize that events in early and mid-adult life may actually alter the relationship of interest. And in this case, adult life variables can affect that relationship in two possible ways.

First, childhood disadvantage may lead to certain events or pathways in early adulthood that ultimately have direct impacts later in life. In other words, these intermediary stages of life may mediate the relationship of interest (represented by arrows ***b*** and ***c*** in figure 1). For instance, dropping out of school can have a direct impact on cognition in later life because there may be cognitive abilities that can only be developed during a critical period of childhood (arrow ***a***) as suggested by the pathway model or can impact cognition in advanced age because finishing school tends to provide better work and economic conditions throughout adult life and these better life conditions may lead to better cognitive performance in later life (arrows b and c) as suggested by the risk accumulation model. It is possible that some circumstances or domains of childhood disadvantage are fully mediated by adult life conditions, which means that such impacts could potentially be reversed with appropriate measures. If there is no evidence of mediation (either full or partial), that would be evidence that there may be domains of childhood disadvantage that have irreversible long-lasting effects as suggested by sensitive period hypothesis (41)

Second, the relationship between childhood disadvantage in later life health might be moderated by early and mid-adulthood circumstances (represented by arrow ***d***). It suggests that the causal mechanisms by which the explanatory variable affects the outcome does not include intermediary stages of life but can be modified by them.

Although we show these effects in different diagrams for illustrative purposes, both effects could happen at the same time. Nonetheless, disentangling these effects is vital for a deeper understanding of the drivers of healthy aging. In addition, many other variables may confound the relationship of interest and therefore these factors must be controlled for in statistical models.

3.2. Methods

Data

We used baseline data from the Brazilian Longitudinal Study of Aging (ELSI – *Estudo Longidutinal de Saúde do Idoso*). This ongoing study, part of the larger family of global Health and Retirement Surveys, aims to understand the social and biological aspects of aging in a middle-income country setting and to inform health and social policies in the country. Participants aged 50 and over were drawn from a multi-stage cluster sample, stratified by municipality, census tract and residence. The baseline assessment took place in 2015-2016 and included an extensive in-person interview and collection of biological materials and other measures. The baseline sample had a total of 9,412 people from 70 municipalities and is designed to be statistically representative of Brazil as a whole as well as all five of the country's major geographic region. A detailed methodological description of the study, its data collection procedures and strategy, and its preliminary results has been published elsewhere (38,42). Further information can also be found in the official ELSI website (43), where all baseline data are made publicly available. The ELSI-Brazil study was approved by the Research Ethics Committee of the Oswaldo Cruz Foundation, Minas Gerais (CAAE 34649814.3.0000.509).

Measures

Measures of childhood disadvantage. Nine variables representing possible harmful exposures in childhood were available in the survey data. Some of these were already categorized as binary variables due to the survey question wording itself, while others variables required decisions on how best to operationalize their categorization, as described below. Given the shared nature of these variables, and the fact that no single measure would encompass the multidimensional concept of childhood disadvantage, we combined them into three domains of childhood disadvantage (family SES, childhood health, and cultural capital). The binary variables for (i) poor family SES in childhood (self-declared as poor from birth to fifteen years of age), (ii) both parents are illiterate and (iii) overcrowded home (defined as having four or more people per bedroom when the survey participant was ten years old) were grouped into the family SES domain. The binary variables for (i) poor self-rated childhood health status (coded as "yes" for average, poor and very poor, and "no" for good or very good), (ii) lack of tap water (defined as having water supply with plumbing at age 10) and (iii) hunger experience (defined as having experienced lack of food at home and going to bed feeling hungry in the period from birth to fifteen years of age) were grouped into the childhood health domain. The binary variables for (i) out of school at age 10, (ii) no books at home and (iii) lived in rural setting until age 15 were grouped into the cultural capital domain. Examination of results from factor analysis (based on inspection of the resulting Eigenvalues and scree plots) confirmed that the variables composing each of the three scores were part of a single latent variable. In order to facilitate interpretation, we chose to operationalize each of these measures as a categorical variable with values representing 0, 1 or two or more 2 events within each domain.

Measures of cognitive abilities in later life. Two competencies were included in our study: memory and semantic verbal fluency. For assessing memory, survey respondents were asked to listen to a list of 10 random words and recall them immediately and then later in the interview. Thus, numerical variables (0-10) for immediate memory and late memory were generated. For semantical verbal fluency, each participant was asked to say as many animal names as possible in 1 minute, generating another numerical variable for cognition. These validated measures have been used widely in the aging and cognition literature (44–48).

Measures of early and mid-adulthood socioeconomic status. Three variables were operationalized for this purpose: 1) educational attainment (categories: no study, some or complete elementary school, some or complete middle school, some or complete high school, some college study or degree); 2) occupational status (categories: intense physical effort, some physical effort, standing or walking most of the time, seated most of the time); and 3) household income (expressed in terms of Brazilian monthly minimum wages). Due to their high correlation, we combined these three variables into a single score using polychoric factor analysis for the mediation analysis. Similar and/or identical measures have been widely used in studies relying on data from sister aging surveys, such as SHARE and ELSA (49–51)

For the construction of our multivariable models, we selected covariates based on insights from the existing literature and confirmed these choices using forward stepwise selection. These covariates include demographic characteristics and health behaviors/conditions that are known to be associated with cognitive performance and could therefore confound the relationship between early life circumstances and later life health outcomes. These covariates include: age group (50-59, 60-69, 70-79, and 80 and over as an overall measure of risk); birth sex – given evidence of gender differences in cognitive outcomes, self-reported skin color (white; black; brown or other as

a measure of exposure to racism and life chances); current residence in an urban area (yes or no as a measure of economic opportunity and access to services); living with a partner (yes or no as a measure of social support); poor current self-rated health (coded as "yes" for average, poor and very poor, and "no" for good or very good as a measure of overall health); three common health risk factors, daily smoking (yes or no) , alcohol consumption (never, occasionally, regularly) and body mass index (BMI) (normal weight, overweight, or obese; very few individuals were underweight and were grouped under normal weight); and the number of chronic conditions, operationalized as a simple sum of the binary variables for the following self-reported medical diagnoses: hypertension, diabetes, chronic-obstructive pulmonary disease (COPD), any heart disease, stroke, arthritis, osteoporosis, back pain, renal failure, depression, cancer, Alzheimer's disease, and Parkinson's disease.

Statistical Analysis

Univariate and bivariate analysis were used to describe the sample and descriptive statistics are presented as weighted proportions. The bivariate relationships between each exposure and each outcome variable were calculated and portrayed in a figure. Statistical significance for the bivariate analyses was obtained through the design-based F test (52). For multivariable analysis, ordinary least squares (OLS) regression models were applied and nested models (53,54) were used to study whether the addition of subsequent blocks of covariates improved model fit or provided evidence of possible mediation effects. Statistical significance of the OLS coefficients was obtained through the adjusted version of the Wald test (given the weighted, complex survey data) (52). To formally assess our hypotheses regarding mediation, a formal analysis based on the Baron and Kenny approach was conducted using a system of seemingly unrelated regressions (SUR) and 1000

bootstrap samples to calculate confidence intervals of indirect and direct effects (55). Missing data were generally low (about 4%) and were not concentrated in any specific variable type of individual. As a sensitivity test, we estimated our main regressions both with complete cases using listwise deletion and with imputed values using multiple imputation by chained equations (MICE) and found no clinically or statistically significant differences in results (data not shown). For simplicity, we report results of the complete case analysis.

All analyses were conducted in Stata 15 using the 'svy' command to account for the complex survey design and survey weights. Any not shown exploratory analysis is available under request.

3.3. Results

Table 1 presents descriptive statistics for individual characteristics stratified by the three measures of cognitive performance (classified into three levels). The mean immediate memory score was 4.4 (standard deviation: 0.05), mean late memory score was 2.9 (standard deviation: 0.06) and mean score in verbal fluency was 12.0 (standard deviation: 0.16). Statistically significant bivariate associations were found for all covariates, except sex in regard to memory. A clear gradient of cognitive performance was observed for age, educational attainment, occupational status and income. In terms of age, the older a person is, the lower is their performance in the memory test (both immediate and late memory). The percentage of individuals aged 50-59 achieving the highest level of memory performance is approximately 6 times larger than the one observed among those aged 80 and over. For verbal fluency, however, the age gradient is much less pronounced. For race/skin color, we observe that those who self-identify as white have better performance across all cognitive measures while the other groups perform similarly. Regarding

educational attainment, there is a sharp gradient indicating that the more educated a person is, the higher performance in cognitive tests. In the test of immediate memory, the percentage of people with less than five years of schooling in highest level of performance (8%) is around five times lower than among those with nine or more years of schooling (40%). For late memory, that gap goes to over 8 times. And for verbal fluency, the disparities are smaller, but still quite important. When it comes to occupational status, there is a gradient showing that the more physically intense is the work a person does/did, the lower their performance in these cognitive tests. For current household income, the pattern observed is that the higher the income the higher performance across all cognition measures. A statistically significant positive bivariate association was found for living with a partner in all three cognition tests, but its size is relatively small. Another relevant disparity in cognitive performance observed here was between rural and urban settings, as those living in rural settings perform substantially below those living in urban areas. In terms of macrogeographical regions in the country, those living in the South have the highest performances across all cognitive measures. Those living in the Northeast had consistently low performances. particularly in immediate and late memory tests, in which only 14% and 5% achieved the highest level of performance, representing about half of the performance observed in the South region. Another bivariate association was between the number of chronic conditions and the measures of cognitive performance. The higher the number of chronic conditions, the lower the cognitive performance. Lastly, those who in the poor current self-rated health category performed consistently lower in all three cognition tests.

Figure 2 depicts the bivariate relationships between the nine individual exposure variables in childhood and the three measures of cognitive performance. It also shows the percentage of individuals in the sample that experienced each exposure in childhood. The green bars show the

mean performance in the cognitive test among those who experience each one of the nine childhood exposures. The orange bars show the mean performance in the cognitive test among those who did not experience each one of the nine childhood exposures. The individual exposure variables are shown within their grouped domain (family SES, childhood health, or cultural capital. First, in regard to the domain 'family SES', we observed that being in poor financial status in childhood and have illiterate parents are associated with lower performance in all three tests, but no average association is observed for being raised in an overcrowded home. Second, among the exposure variables composing the domain 'childhood health', the only average association observed with lower cognitive performance was for those who grew up in homes with no access to tap water. Third, for the domain 'cultural capital', we found statistically significant associations between all their exposure variables and lower performance in all three tests. Being out of school of age 10, having no books at home and living in a rural setting until age 15 were also associated with lower performances in immediate memory, late memory and verbal fluency tests.

Table 2 shows the multivariable analysis based on OLS regression for all three outcome measures. Model 1 refers to regression including all explanatory variables (scores for each domain of childhood disadvantage) and the following relevant covariates: age, sex, race, living with a partner, current residence in urban area, geographic region, number of chronic conditions, current poor self-rated health status. Model 2 contains all these regressors as well as the adulthood SES variables (educational attainment, occupational status and household income) hypothesized as possible mediators and/or moderators. In other model specifications (data now shown), interaction terms were added (each childhood disadvantage score interacted with the adulthood SES variable), but they were not statistically significant neither they changed the size of coefficient of the explanatory variables. That ruled out the hypothesis of moderation effect by these adulthood SES

variables. When interpreting the coefficients described below, it is important to highlight the additional complexity created by our model specification that includes all exposure variables. For example, while exposure variable A may be a confounder for the relationship between exposure variable B and the outcome variable Y, by definition, exposure variable B is a mediator of the relationship between A and the outcome variable. These results should therefore be interpreted as the association of exposure A with outcome Y after controlling for appropriate covariates and independent of exposures B and C (56).

All domains of childhood disadvantage exhibited negative associations with memory measures (both immediate and late). On average, having 2 or more negative family SES exposures is associated with recalling 0.25 (95% CI: 0.37; 0.13) and 0.26 (95% CI: 0.11; 0.39) fewer words in the immediate and late memory tests, respectively, compared to not having any of these exposures in childhood. In comparison to not having any of the negative exposures of childhood health domain, having had one exposure is associated on average with 0.25 (95% CI: 0.15; 0.35) fewer words recalled in the immediate memory test and 0.23 (95% CI: 0.09; 0.37) fewer words in the late memory test. In terms of harmful exposures within the cultural capital domain, one score is associated on average with 0.15 (95% CI: 0.03; 0.27) and 0.27 (95% CI: 0.13; 0.41) fewer words recalled in the immediate and late memory tests, respectively, while having a score of 2+ is associated with 0.47 (95% CI: 0.33; 0.61) and 0.58 (95% CI: 0.16; 0;74) fewer words recalled in the immediate and late memory tests. Yet, these effects disappear when we control for variables of adulthood SES. The multivariable analysis for the memory outcomes further reinforced the positive impact of schooling and the higher income.

In regard to semantic verbal fluency, we found significant associations only for the childhood health and the cultural capital domains. Before controlling for the possible mediation

effect of adulthood SES variables, having at least one of three negative exposures of the childhood health domain is associated with 1.14 (95% CI: 0.85; 1.43) fewer animal names recalled in the verbal fluency test, which represents about 10% of the average performance in this population. This effect size is reduced to 0.77 (95% CI: 0.46; 1.08) after controlling for possible mediators. Without controlling for the possible mediation effect of adulthood SES variables, having one of three negative exposures of the cultural capital domain is associated on average with 1.33 (95% CI: 0.98; 1;.68) fewer animal names recalled in the verbal fluency test in comparison to not having any of these childhood exposures. Similarly, having two or more of these exposures is associated on average with 1.95 (95% CI: 1.60; 2.30) fewer animal names recalled in the verbal fluency test. After controlling for possible adulthood SES mediation, these last two coefficients decreased to 0.84 (95% CI: 0.53; 1.15) and 0.93 (95% CI: 0.56; 1.30), respectively.

The decrease in the OLS coefficients of the explanatory variables after the inclusion of adulthood SES variables suggest a mediation effect (as generally hypothesized in the analytical conceptual framework). To further investigate it, we conducted a formal mediation analysis using a single variable constructed through polychoric factor analysis using the three adulthood SES variables available: educational attainment, occupational status and income. It indicated that adulthood SES mediates 55.4% (95% CI: 37.8% - 103.1%) of the association between later-life verbal fluency and the harmful exposures of the childhood health domain, and 49.1% (95% CI: 43.1% - 57.1%) of the association between later-life verbal fluency and the harmful exposures of cultural capital domain in childhood.

3.4. Discussion

Our study sheds light on the relationship between childhood disadvantage and cognitive performance in later life within the context of a large middle-income country. We investigated the influence of nine potentially harmful exposure variables grouped within three domains of childhood disadvantage on three validated and widely used measures of cognition among older adults. Overall, our findings suggest that childhood disadvantage is associated with lower cognitive performance among older Brazilians. In the multivariable analysis, we found statistically significant associations between the scores for all domains of childhood disadvantage and all outcome measures of cognition. In particular, we observed that the associations between harmful exposures both of the 'family SES' domain and of the 'childhood health' domain with later-life memory performance may be fully mediated by adulthood SES. Yet, for verbal fluency, we observed no consistent association with the family SES domain, but important ones with the childhood health domain and the cultural capital domain. These last two associations were found to be partially mediated by adulthood SES. All that said, it is important to highlight that due to the fact that the final regression models contain multiple exposure variables, all these associations should be interpreted as "after controlling for appropriate covariates and independent of other exposures".

This work has several strengths. First, based on our scoping review of the literature, particularly those from existing aging cohorts, this study is unique in its investigation of the relationship between multiple measures of childhood disadvantage and later-life cognition in Latin America using nationally-representative data. Second, unlike other studies in the field that investigate the relationship between a single childhood exposure variable and/or a single health outcome in later life, we studied a variety of exposures, both individually and grouped within

domains of childhood disadvantage. The existence of these distinct domains was informed by theory and confirmed by factor analysis, allowing us not only to have a more nuanced view of the relationships between harmful childhood experiences and health outcomes across the life course, but also to obtain further insights on the possible underlying mechanisms. Third, by using a variety of model specifications in the multivariable analysis, we were able to disentangle different pathways that may exist (mediation) and those that seem to be weak or nonexistent (such as the lack of evidence for a moderation effect by latent variables representing mid-adulthood SES).

Although not the main focus of the present work, we found important socioeconomic disparities in cognitive performance. The gradients of cognitive performance in relation to education, income and occupational status are particularly salient. Macrogeographical disparities are also present, as has been previously documented by Castro-Costa et al (46).

Our findings suggest that the specific circumstances of childhood disadvantage may affect different aspects of cognition through different mechanisms. For example, while the results for memory point out directly to mechanisms related to the social mobility model, the findings around semantic verbal fluency suggest a mix of mechanisms related to social mobility but also to the sensitive period paradigm, given that there is a substantial portion of the observed that is direct.

While studies of this type are common in the high-income world, little evidence is available from LMICs. In a study of older rural South Africans (33), poor childhood health was found to be associated with lower cognitive scores while having had a father in a formal job was associated with better cognitive scores, but only the latter association was partially mediated by educational attainment. Another study using the same sample of older adults from South Africa found that most adverse childhood events (ACEs) were not associated with cognitive performance in older adults, except for having a parent who had a drug abuse problem (57). A study based on an aging cohort

study in India found that older adults who had poor health status and/or poor financial status in childhood were more likely to suffer from cognitive impairment in later life (37). Low childhood SES has been found to be associated with cognitive impairment in China (35,58) and this relationship was partially mediated by educational attainment. Cognitive decline has also been found to be associated with childhood disadvantage in China (36) and in this case education was also found to be an important mediator. Unlike what we saw in the Brazilian population of older adults, the study on Chinese older adults also found an important gender gap in cognitive performance. It is important to highlight the difficulty in directly comparing findings from these other studies because each has operationalized outcome measures in slightly different ways. Some studies, for example. combine memory tests with arithmetic tests into a cognitive score, some do not consider semantic verbal fluency, and others focus solely on the rate of cognitive decline. Nevertheless, taken together, these studies indicate the importance of early childhood on older adult health in LMICs.

Investigating the ways through which specific circumstances of childhood disadvantage affect health later in life is vital not only for expansion of scientific knowledge about the ways biological mechanisms underly these statistical associations, but also to aid in the development of tailored interventions to promote health among aging populations and tackle health disparities. Nonetheless, childhood disadvantage is a not phenomenon that manifests in single event or realm and may have an overall combined or cumulative impact via stress, biological underdevelopment, and more rapid decline of health functions.

Some limitations of this study must be taken into account when interpreting its findings. Because we relied on cross-sectional data, no longitudinal aspect involved in the phenomenon of interest could be investigated and therefore we are unable to determine for how long childhood

stressors affected these individuals neither could we assess whether their cognitive performances relate to a late decline in life or are linked to some unobserved factor. While the problem of reverse causality is less of a concern, the issue of omitted variable bias cannot be completely ruled out, although the careful work of theory-driven and statistically tested model specification provides some confidence in the results presented here. There is also a possible limitation related to a threat of recall bias, given that individuals were asked to recall conditions that occurred many decades in their past. Given that the cognitive performance (particularly memory) is the outcome, the exposure reporting is likely differential and may indeed have led to bias in our results. Another concern is that there might be sample selection (survival bias, which is typical of aging surveys), because only individuals who survived at least to age 50 when the survey baseline assessment occurred could be included in the study. This might be relevant for Brazil given that infant mortality was very high before the 1970s when survey participants were growing up (59). It is reasonable to hypothesize that survival bias could lead to an underestimate our coefficients, given the relationship between being older and cognitive decline. An additional limitation is that the health behaviors included as covariates could be also operating as mediators. It is unclear whether or not their inclusion is biasing the association estimate, even though they improve our statistical models' goodness of fit. A last possible concern is that of missing data, which was quite small at only 4%. Sensitivity tests that used multiple imputation by chained equations (MICE) provided virtually identical results to the ones obtained with listwise deletion suggesting that missing data did not overly affect our results.

3.5. Conclusion

Overall, our study found that multiple dimensions of childhood disadvantage are associated with lower performance in memory tests and semantic verbal fluency tests among older Brazilians. Breaking down childhood disadvantage into three different domains (family SES, childhood health, and cultural capital) helped us better understand the phenomenon and its possible mechanisms. In regard to memory tests, all domains of childhood disadvantage were found to be associated with lower performance in the multivariable analysis when excluding adulthood SES, indicating a total mediation pathway. For semantic verbal fluency, the childhood health domain and the cultural domain had more pronounced negative associations and were found to be mediated by adulthood SES (around half of the effect was indirect in both cases). These findings should inform efforts to develop interventions targeting early childhood development as well as fostering other key factors (such as education and poverty alleviation efforts sch a conditional cash transfers) to strengthen adulthood SES and thus lessen the impact of early life stressors on the health of older adults.

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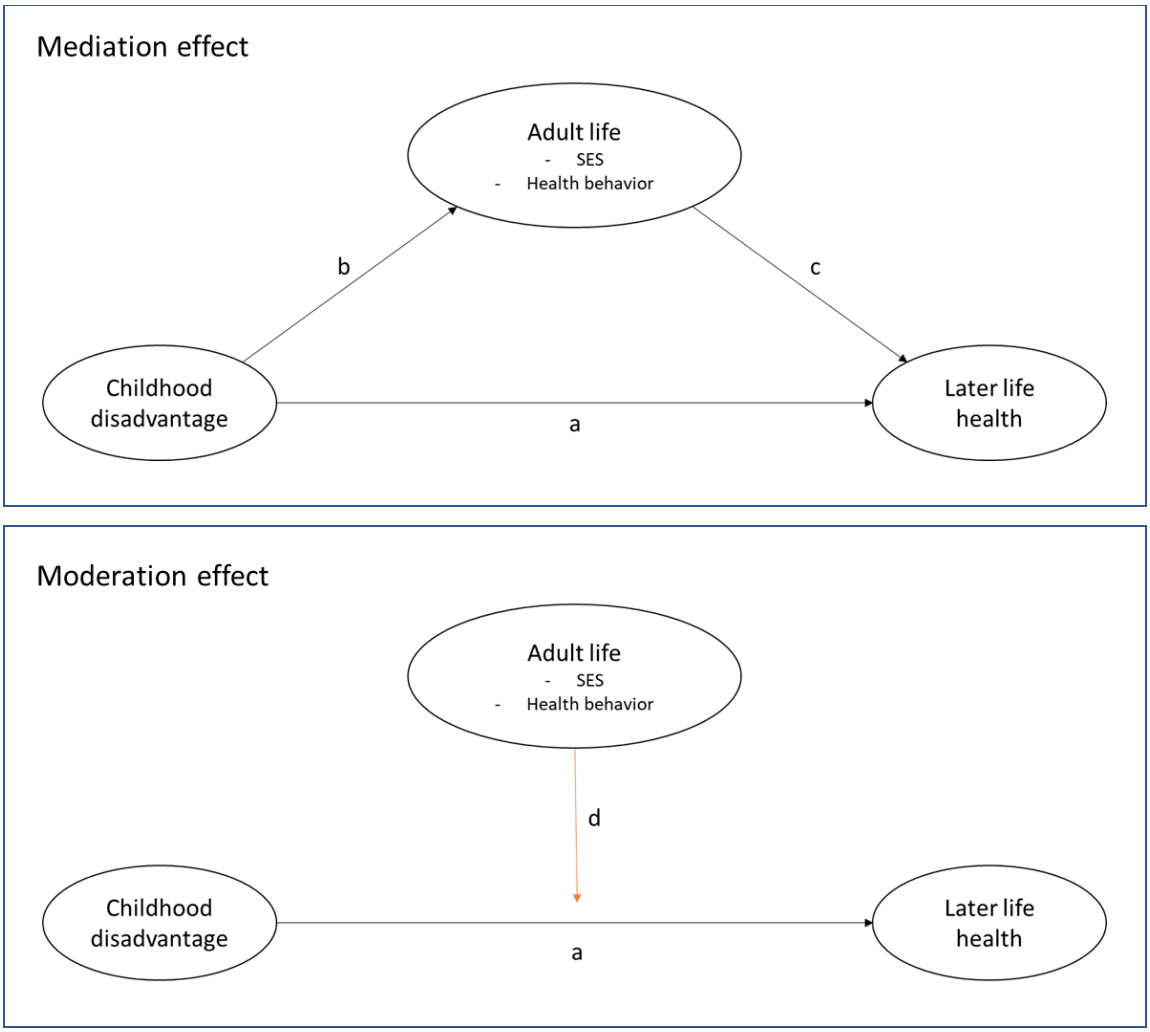

Figure 3-1 – Conceptual framework for different possible relationships between childhood disadvantage and later life health.

Table 3-1 – Sociodemographic and health characteristics by cognitive performance.

	Immediate memory *(Words recalled from a list of 10)*				***Late memory*** *(Words recalled from a list of 10)*				***Verbal fluency*** *(Animal names said in 1 minute)*			
	0-3 words	*4-5 words*	*6+ words*		*0-3 words*	*4-5 words*	*6+ words*		*<9 names*	*9-15 names*	*16+ names*	
	%	%	%		%	%	%		%	%	%	
Age groups												
50-59	18.49	51.44	30.07	***	53.14	35.54	11.32	***	16.39	57.90	25.71	***
60-69	28.59	48.17	23.23		62.84	30.08	7.08		19.51	60.71	19.78	
70-79	48.59	40.27	11.14		77.82	19.30	2.88		26.10	55.40	18.50	
80+	69.10	25.90	5.00		92.46	6.22	1.32		31.63	43.10	25.27	
Sex												
Female	29.13	46.47	24.39	.	61.13	30.21	8.66	.	22.12	57.07	20.81	***
Male	29.14	48.12	22.74		63.36	29.06	7.58		17.32	57.56	25.12	
Race												
White	23.50	48.82	27.68	***	56.61	32.59	10.79	***	15.25	57.66	27.09	***
Black	32.88	45.11	22.01		68.16	24.41	7.43		26.39	53.71	19.89	
Brown	31.83	47.10	21.07		64.86	28.77	6.37		21.23	58.40	20.37	
Others	34.31	44.82	20.87		65.69	27.85	6.46		25.78	51.78	22.44	
Education (Years of schooling)												
Less than 5	50.48	40.53	8.99	***	80.83	17.34	1.84	***	31.64	53.90	14.46	***
Between 5 and 8	26.54	53.37	20.09		65.39	29.09	5.53		20.50	62.09	17.41	
9 or more	12.68	47.71	39.61		42.98	41.00	16.03		8.56	56.42	35.03	
Occupational status												
Intense physical effort	39.70	46.01	14.29	***	72.26	23.54	4.20	***	24.12	57.21	18.67	***
Some physical effort	33.94	46.69	19.37		68.09	25.45	6.46		23.04	57.50	19.46	
Standing or walking most of the time	23.49	48.19	28.32		55.35	35.01	9.64		17.52	57.97	24.51	
Seated most of the time	18.51	47.86	33.63		52.00	34.46	13.54		13.20	55.80	31.00	
Household income												
Less than 2 Minimum Wages	37.27	46.88	15.85	***	70.89	24.37	4.74	***	28.10	55.58	16.31	***

2-5 Minimum Wages	29.25	47.83	22.92		62.90	29.41	7.69		18.77	58.78	22.46	
5-9 Minimum Wages	18.82	46.25	34.93		50.45	36.99	12.56		11.41	59.70	28.89	
9+ Minimum Wages	14.39	45.78	39.83		43.93	38.67	17.40		9.34	51.19	39.48	
Living with partner												
No partner	34.55	44.03	21.42	***	66.13	27.11	6.76	***	22.26	54.85	22.89	**
Living with partner	26.15	49.00	24.84		59.98	31.09	8.93		18.56	58.70	22.74	
Residence in urban area												
No	41.61	44.65	13.73	***	73.81	22.22	3.98	***	27.20	57.14	15.66	***
Yes	26.89	47.70	25.40		60.07	31.02	8.91		18.59	57.32	24.08	
Region												
North	33.37	45.11	21.52	***	63.58	29.56	6.85	***	20.62	60.62	18.76	***
Northeast	41.36	44.48	14.16		71.98	23.42	4.61		27.73	55.41	16.86	
Southeast	25.62	47.27	27.11		58.87	31.82	9.31		17.63	57.92	24.45	
South	22.70	48.99	28.30		59.13	30.93	9.94		16.41	57.49	26.10	
Midwest	22.90	54.27	22.83		56.90	33.79	9.31		15.88	56.42	27.71	
Chronic conditions												
None	24.28	47.74	27.99	***	58.40	31.10	10.50	***	17.91	55.46	26.64	**
One	29.18	47.75	23.06		62.45	30.04	7.51		19.71	59.20	21.09	
Two	31.38	46.65	21.98		63.26	29.91	6.83		21.37	56.06	22.57	
Three or more	33.10	46.37	20.53		65.55	26.88	7.58		21.25	58.00	20.75	
Poor self-rated health												
No	25.52	45.84	28.64	***	57.78	31.27	10.96	***	17.32	55.40	27.29	***
Yes	31.91	48.35	19.75		65.51	28.49	6.00		21.90	58.73	19.37	

Weighted and survey-adjusted proportions.
Design-corrected F-test *= p<0.05; **=p<0.01; ***p<0.001.
Data source: Brazilian Longitudinal Study of Aging (ELSI-Brazil), baseline assessment (2015-2016).

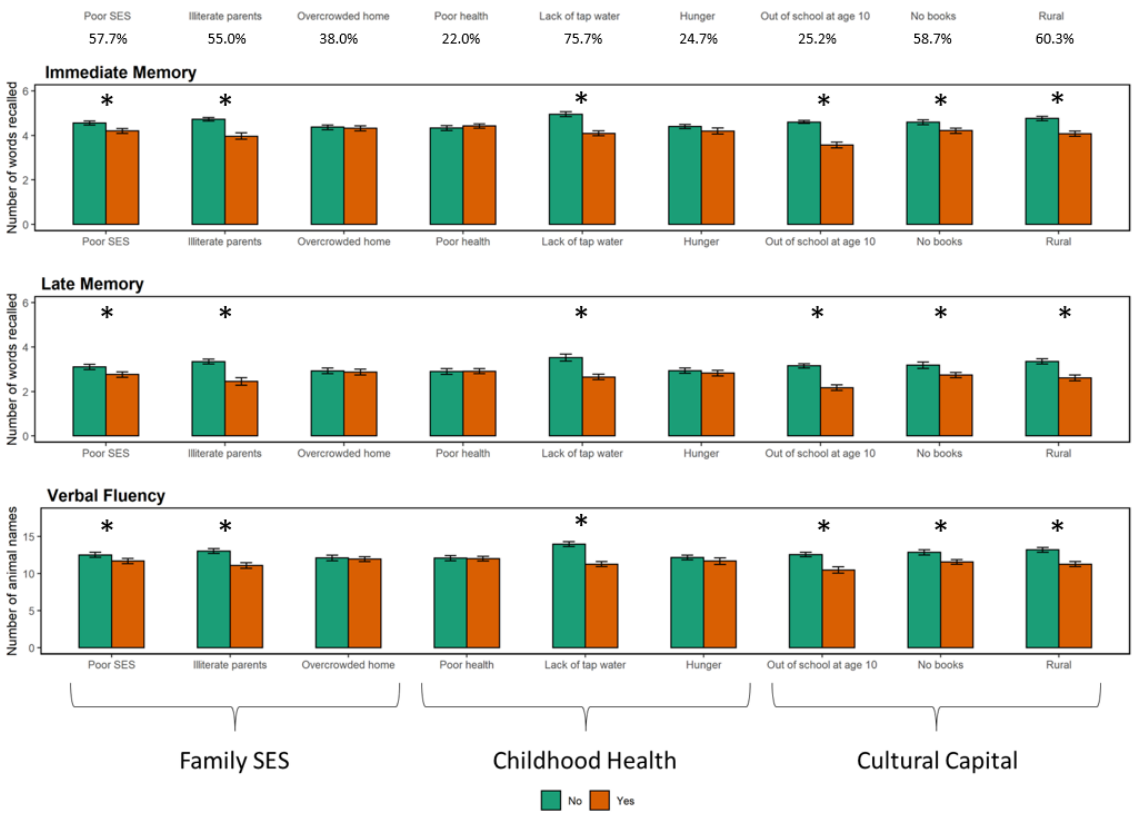

Figure 3-2 – Bivariate relationships between cognitive performance and measures of childhood disadvantage.

The numbers represent the percentage in the sample that experienced the exposure in question.
The * symbol represents that the difference is statistically significant at p-value <0.05.

Table 3-2 – OLS Estimates for Childhood Disadvantage Domains.

	Immediate Memory		Late Memory		Verbal Fluency	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Childhood Disadvantage Scores (0, 1 or 2+ events)						
Family SES Domain (ref: 0)						
1	-0.09	0.00	-0.06	0.04	-0.06	0.20
	(-0.06)	(-0.05)	(-0.06)	(-0.06)	(-0.20)	(-0.19)
2+	-0.25***	-0.05	-0.26***	-0.04	-0.17	0.34*
	(-0.06)	(-0.05)	(-0.07)	(-0.06)	(-0.19)	(-0.17)
Child Health Domain (ref: 0)						
1	-0.25***	-0.11*	-0.23***	-0.09	-1.14***	-0.77***
	(-0.05)	(-0.05)	(-0.07)	(-0.07)	(-0.15)	(-0.16)
2+	-0.22**	-0.06	-0.16*	0.01	-1.07***	-0.65***
	(-0.07)	(-0.07)	(-0.07)	(-0.07)	(-0.19)	(-0.20)
Cultural Capital Domain (ref: 0)						
1	-0.15**	0.02	-0.27***	-0.07	-1.33***	-0.84***
	(-0.06)	(-0.05)	(-0.07)	(-0.07)	(-0.18)	(-0.16)
2+	-0.47***	-0.04	-0.58***	-0.15	-1.95***	-0.93***
	(-0.07)	(-0.07)	(-0.08)	(-0.09)	(-0.18)	(-0.19)
Education (ref: less than 5 years of schooling)						
Between 5 and 8 years		0.54***		0.40***		0.75***
		(-0.05)		(-0.06)		(-0.18)
9 or more years		1.05***		1.07***		2.44***
		(-0.06)		(-0.07)		(-0.23)
Occupational status (ref: intense physical effort)						
Some physical effort		0.08		-0.04		-0.21
		(-0.06)		(-0.06)		(-0.19)
Standing or walking most of the time		0.21**		0.07		0.01
		(-0.07)		(-0.07)		(-0.17)
Seated most of the time		0.28***		0.11		0.33
		(-0.07)		(-0.09)		(-0.21)
Household income (ref: < 2 Minimum Wages)						
2-5 Minimum Wages		0.11*		0.10*		0.39**
		(-0.04)		(-0.05)		(-0.12)
5-9 Minimum Wages		0.27***		0.37***		0.87***
		(-0.06)		(-0.07)		(-0.20)
9+ Minimum Wages		0.33***		0.44***		1.24***
		(-0.09)		(-0.1)		(-0.26)
Observations	9,084		9,084		9,069	

Coefficients from survey-adjusted OLS regression. Standard errors in parentheses. *** p<0.001, ** p<0.01, * p<0.05. Other covariates include age, sex, race, macrogeographic region, urban residence, living with a partner, daily smoking, drinking.Data source: ELSI-Brazil, 2015-2016Differences in the number of observations across models refer to listwise deletion for missing data.

Chapter 4 – Assessing Robustness in Observational Studies: Applying a Formal Sensitivity Analysis to the Relationship between Childhood Disadvantage and Later-Life Health

ABSTRACT

Objective: There is strong theoretical justification and emerging empirical evidence for the role of early life conditions on the development of chronic conditions later in life. However, these associations may differ by place and by period and there are few longitudinal datasets that provide data over a long time span. Instead, many researchers have turned to cross-sectional datasets. This study assesses the relevance and applicability of a sensitivity analysis framework known as SenseMakr in public health research by assessing the robustness of associations between measures of childhood disadvantage and health outcomes in later life obtained from an observational study under imperfect identification.

Methods: This study uses baseline (2015/2016) data from the Brazilian Longitudinal Study of Aging (ELSI), a nationally representative cohort of 9,412 adults aged 50 and over. A series of ordinary least squares and binomial logistic regression models were used to assess the relationship between nine measures of childhood disadvantage (poor socioeconomic status, hunger, overcrowded housing, poor self-rated health, and rural residence) and a list of thirteen chronic conditions in a cross-sectional survey-based study. All analyses controlled for the complex survey design and incorporated survey weights. Given the potential for model misspecification due to omitted variables, the 65 hypothesized associations were evaluated using the SenseMakr framework.

Results: Out of the 65 possible associations, 24 were found to be statistically significant. Their robustness were assessed using the three main tools introduced by SenseMakr 1) the robustness value (defined as the proportion of residual variance in the treatment and outcome variables that a confounder would have to explain in order to eliminate the statistical significance observed); 2) the extreme scenario analysis (which considers scenarios in which a confounder explains high levels of the remaining variance in the outcome); and 3) the benchmark covariate approach (how strong the explanatory power of a possible unobserved confounder would have to be in comparison to the explanatory power of observed variables in order to eliminate the estimated treatment effect). Age and body mass index were chosen as benchmark covariates and showed that some associations were extremely robust while others are likely spurious.

Conclusions: Omitted variable bias remains an important threat in a cross-sectional design, even when such studies are based on strong theoretically-driven conceptual models, extensive exploratory statistical analysis and proper model specification. The SenseMakr framework does not provide thresholds to support any mechanistic conclusion as it is not possible to establish universal cutoff values for its robustness measures. Nevertheless, a holistic consideration of these measures provided strong empirical demonstration of the robustness of association estimates. This approach can be highly useful in other observational studies of aging and the life course.

Key-words: sensitivity analysis, confounder, omitted variable bias, life course perspective.

4.1. Introduction

There has been enormous growth in the life course literature over the past years with particular emphasis on associations between potentially harmful exposures in utero and during childhood and later-life health outcomes (1–7). The availability of nationally representative data on demographic factors, health characteristics and life trajectories from older adults in several countries has boosted such investigations. Cohort studies of older adults such as the HRS (Health and Retirement Study) in the US, ELSA (English Longitudinal Study of Ageing) and SHARE (Survey of Health, Ageing and Retirement in Europe, which collects data from 27 European countries and Israel) have been in place for many years, providing a rich data source for life course investigation. Sister studies have been replicated in many countries, such as China (8), Brazil (9), Mexico (10), Korea (11), and a few others. Also, harmonization initiatives have made comparative studies more practical and common (12).

Building on these already existing rich data sources, researchers have found a series of associations between certain self-reported exposure variables in childhood and health outcomes later in life using cross-sectional study designs. Examples abound in the literature showing statistically significant associations between childhood adversity experiences (and/or childhood socioeconomic disadvantage) and several later-life health outcomes, such as increased risk of cancer (5,13), diabetes (2,14,15), cardiovascular diseases (3,16–18), muscle strength (19,20) cognitive performance (21–24), and depression(25–28).

Considering the highly complex dynamics of life course phenomena and the multifactorial nature of disease onset, it is not unreasonable to hypothesize these associations and then test them in an observational study design. There is clearly enormous value in detecting harmful childhood exposures and their far-reaching and long-lasting effects on the health of adults in order to promote

public policies that protect children and foster healthier populations. Such studies are also important to shed light on possible mechanisms that connect harmful events with health circumstances decades later. Nonetheless, the existence of an increasing number of datasets in which researchers can easily pick exposure and outcome variables from existing publicly available data sources also poses an important problem: How robust are such associations? Are some of these associations spurious? Are these associations that reflect some true underlying causal pathway or simply due to chance or even due to researchers cherry-picking certain associations that happen to be statistically significant?

The nature of these research questions and the type of data available make it very difficult to put in place robust identification strategies, often leaving naïve regression models (or complex weighting schemes) as the only methodological option when there has not also been a natural experiment embedded within the research population's life course. In this paper, we investigate a series of hypothesized relationships between childhood exposure variables and later-life health outcomes and applied a formal framework of sensitivity analysis (SenseMakr) to investigate the robustness of any found statistically significant associations. We also discuss the pertinence and implications of multiple-testing adjustment of p-value thresholds in this context.

SenseMakr is a relatively novel framework of sensitivity analysis that allows researchers to examine how likely an unobserved confounder eliminates an estimated effect obtained through regression analysis (29). The framework uses the Frisch–Waugh–Lovell theorem to "partial out" the covariate effects in an ordinary least square regression in order to understand the impact of omitted variable bias on a phenomenon of interest. We assessed the robustness of several associations between measures of childhood disadvantage and health indicators in later life found

using a cross-sectional design based on data from the Brazilian Longitudinal Study of Aging (ELSI-Brazil).

4.2. Methods

Data

Baseline data from the Brazilian Longitudinal Study of Aging (ELSI – *Estudo Longidutinal de Saúde do Idoso*) was used in the present study. ELSI-Brazil aims to investigate social and biological aspects related to aging by following-up adults aged 50 and over that were drawn from a multi-stage cluster sample, stratified by municipality, census tract and residence. The baseline assessment took place in 2015-2016 and included an extensive in-person interview and collection of biological materials and other measures. The baseline sample had a total of 9,412 people from 70 municipalities and was designed to be statistically representative of Brazilians aged 50 and over. A detailed methodological description of the study, its data collection procedures and strategy, and its preliminary results has been published elsewhere (9,30). Further information can also be found in the official ELSI website (31), where all baseline data are made publicly available. The ELSI-Brazil study was approved by the Research Ethics Committee of the Oswaldo Cruz Foundation, Minas Gerais (CAAE 34649814.3.0000.509).

Measures

Measures of childhood disadvantage. Five binary exposure variables related to different aspects of childhood disadvantage were used: 1) poor financial status in childhood (self-declared as poor from birth to fifteen years of age); 2) poor self-rated health in childhood (coded as “yes” for average, poor and very poor, and “no” for good or very good); 3) raised in an overcrowded

home (defined here as having four or more people per bedroom when the survey participant was ten years old); 4) hunger in childhood (defined as having experienced lack of food at home and going to bed feeling hungry in the period from birth to fifteen years of age); 5) residence in a rural area until fifteen years old. These measures were included in the ELSI baseline interview and were adapted from a longer list of conditions use in both ELSA and SHARE.

Outcome measures in later life. Binary variables were created for self-reported presence of the following medical diagnosis: hypertension, diabetes, chronic-obstructive pulmonary disease (COPD), any heart disease, stroke, arthritis, osteoporosis, back pain, renal failure, depression, cancer, Alzheimer's disease, and Parkinson's disease.

Covariate adjustment. Covariate adjustment is essential here due to the heterogenous nature of the study population in terms of demographic, socioeconomic, health, and environmental characteristics. We included the following covariates in our models: age group (50-59, 60-69, 70-79, and 80 and over), birth sex, self-reported skin color (white; black; brown or other), educational attainment (less than five years of schooling; between five and eight years; nine or more), occupational status (categories that reflect the sociohistorical patterns of SES associated with function in the job market in a country marked by slavery and contempt for physical labor: intense physical effort; some physical effort; standing or walking most of the time; seated most of the time), household income (expressed in terms of Brazilian monthly minimum wages), residence in an urban area (yes or no), living with a partner (yes or no), poor current self-rated health (yes or no), daily smoking (yes or no), alcohol consumption (never; eventually; regularly) and body mass index (BMI) (normal weight, overweight, or obese; very few individuals were underweight and were grouped under normal weight).

Statistical Analysis

Univariate and bivariate analysis were used to describe the sample and descriptive statistics are presented as weighted proportions. Statistical significance for the bivariate analyses was obtained through the design-based F test (32). For the final multivariable analysis, we employed binomial logistic regression models and estimated odds ratios. Nested models (33,34) were used to study whether the addition of subsequent blocks of covariates improved model fit or provided evidence of possible mediation effects. Statistical significance of the regression coefficients was obtained through the adjusted version of the Wald test (given the weighted, complex survey data) (32). Missing data after listwise deletion in regression models were never above 4% and were not concentrated in any specific individual or type of variable.

All analyses were conducted in Stata 15 using the 'svy' command to account for the complex survey design and survey weights.

The Sensitivity Analysis Framework

SenseMakr is a novel framework for sensitivity analysis that uses the Frisch–Waugh–Lovell theorem to "partial out" the covariate effects in an Ordinary Least Square regression to understand the impact of omitted variable bias on the phenomenon of interest (29).

One of the measures provided by this framework is the Robustness Value, which can be either expressed as the proportion of residual variance in the treatment (or exposure) and outcome variables that a confounder would have to explain in order to bring the estimated effect down to zero (RV_q) or proportion of residual variance in the treatment and outcome variables that a confounder would have to explain in order to eliminate the statistical significance observed ($RV_{q,\alpha}$). Then, considering a well specified regression model, this measure helps us understanding

how likely is to imagine a confounder capable of explaining an amount of additional residual variance in both exposure and outcome variables that is above the robustness value. In other words, it indicates how likely is to have an important threat of omitted variable bias. Unfortunately, while useful, this econometric strategy does not allow us to set universal threshold values for these measures.

An alternative approach to the lack of a threshold for the robustness value is to rely on the idea of benchmark covariates. This approach could inform on how strong the explanatory power of a possible unobserved confounder would have to be in comparison to the explanatory power of observed variables in order to eliminate the estimated treatment effect. In other words, the benchmark covariates allow us to appraise the plausibility that a possible unobserved confounder would change or even invalidate our findings. We chose two variables as benchmark covariates: age and body mass index. These variables were chosen because older age is one of the most consistent and powerful determinants of poor health, especially chronic conditions. Body mass index has been identified has been identified as one of the most far-reaching determinants of metabolic imbalances, many of which are key to driving a wide range of common chronic conditions (35)

Given that observed associations range across covariate values, we can use a contour plot to visually represent the analysis with benchmark covariates. We plot the partial R^2 of the hypothesized confounder with the outcome on the y-axis and the partial R^2 of the "exposure" variable on the outcome on the x-axis, to assess by how much the potential confounder would have to explain the residual variance in exposure and outcome in order to change or invalidate our findings. In one version, the contours depict the adjusted estimate that would be obtained for a

possible confounder with the hypothesized values of the sensitivity parameters, which allows us to determine if any of that is sufficient to bring the effect point estimate down to zero.

Another Sensemakr tool is the "extreme scenario" analysis. We considered scenarios in which an unknown confounder explains 25%, 50% and 75% of the remaining variance in the outcome. For example, for a hypothetical confounder capable of explaining 75% of the residual variance in the outcome, we can determine how much of this same imagined unobserved confounder would still have to explain of the residual variance in the exposure variable.

Given that the SenseMakr framework is theoretically developed on OLS regression foundations, it was necessary to do some additional testing in order to apply it to logistic regression on our 13 binary outcomes. We compared estimates obtained from linear probability models to those obtained from the logit models. The average marginal effects obtained through the predicted probabilities from the logit model were very similar to the direct OLS estimates from the linear probability models (data not shown). This suggests that the use of Sensemakr to evaluate robustness here was appropriate.

4.3. Results

Table 1 presents descriptive statistics for the sociodemographic characteristics of our sample stratified by the number of chronic conditions. Less than 20% of older Brazilians reported having none of the diseases studied here and roughly 30% have three or more conditions. Age was significantly associated with the presence of chronic conditions and the number of diseases increases quite rapidly with age. Significant differences also exist in regard to birth sex. The percentage of women with three or more chronic conditions (38%) is nearly double that of men (20%). The number of chronic conditions did not vary significantly across different skin color/race

groups. Clear gradients are found for education and income, as the number of schooling years or income grows the number of chronic conditions decreases. Regional disparities in the number of chronic conditions were found to be statistically significant, being North and Northeast the sickest regions. Those who lived with a partner are found to be generally healthier. Drinking was also found to be significantly associated with the number of chronic diseases. Those who report drinking regularly have lower rates of chronic disease than those who drink occasionally, which in turn are healthier than those who never drink. In terms of body mass index, 70% of Brazilians aged 50 and over are either overweight or obese.

In terms of the exposure variables, table 2 shows their distribution in the population studied. 57.7% of participants reported living in a poor SES household during childhood, 56.3% had poor self-rated childhood health status, 24.7% experienced hunger at least once in childhood and 60.3% lived in rural area until the age of 15 years old. The differences between having and not having experienced these exposures in childhood were all statistically significant (p-value <0.01). However, only 38% of participants lived in overcrowded homes until the age of 10, but that number is not significantly different from not having experienced that exposure. In addition, exploratory analysis found age-related gradients for all exposure variables, except for poor childhood SES (data not shown).

Table 3 presents odds ratios for all the hypothesized associations. Out of 65 possible associations between the five exposure variables and the thirteen chronic conditions, 24 were found to be statistically significant. Poor socioeconomic status in childhood was found to be associated with higher likelihood of having back pain (OR = 1.185, 95% CI: 1.070 - 1.312), depression (OR = 1.190, 95% CI: 1.007 - 1.407) and diabetes (OR = 1.242, 95% CI: (1.040 - 1.483). Being raised in an overcrowded home was found to be significantly associated with

arthritis (OR = 1.214, 95% CI: 1.067 - 1.382) and osteoporosis (OR = 1.176, 95% CI: 1.025 - 1.349). Poor self-rated health in childhood was the exposure variable significantly associated with the highest number of chronic condition: arthritis (OR = 1.712, 95% CI: 1.463 - 2.003), back pain (OR = 1.593, 95% CI: 1.379 - 1.840), cancer (OR = 1.381, 95% CI: 1.129 - 1.689), COPD (OR = 1.976, 95% CI: 1.552 - 2.515), depression (OR = 1.757, 95% CI: 1.455 - 2.122), heart disease (OR = 1.822, 95% CI: 1.094 - 3.035) , osteoporosis (OR = 1.406, 95% CI: 1.178 - 1.679), renal failure (OR = 1.752, 95% CI: 1.371 - 2.240), and stroke (OR = 1.320, 95% CI: 1.037 - 1.680). Hunger in childhood had statistically significant associations with arthritis (OR = 1.276, 95 CI: 1.089 - 1.494), back pain (OR = 1.224, 95% CI: 1.109 - 1.350), COPD (OR = 1.506, 95% CI: 1.183 - 1.918), depression (OR = 1.527, 95% CI: 1.306 - 1.785), diabetes (OR = 1.199, 95% CI: 1.022 - 1.406), osteoporosis (OR = 1.377, 95% CI: 1.154 - 1.643), Parkinson's disease (OR = 2.094, 95% CI: 1.134 - 3.866), and renal failure (OR = 1.354, 95% CI: 1.062 - 1.726) . Lastly, being raised in a rural residence was found associated with arthritis (OR = 1.289, 95% CI: 1.105 - 1.504) and osteoporosis (OR =1.276, 95% CI: 1.077 - 1.511). Overall, no evident pattern was identified.

Figure 1 and 2 show examples of t-value contour plots for one of the statistically significant associations (the one between childhood poor SES and diabetes in later life) and the two benchmark covariates: age and BMI. Figure 1 indicates that a confounder with an impact on the residual variances of the exposure and outcome variables that is more than nine times the impact that the variable age has in the full model would make the association no longer statistically significant at $\alpha = 0.05$. Similarly, figure 2 indicates that only a confounder capable of explaining 20 times what BMI explains in the full model would also lower the exposure effect t-value below the 1.96 threshold.

The analysis with the two benchmark covariates was performed for all the 24 statistically significant associations vis-à-vis the two benchmark covariates: age and BMI. We summarize the findings in a table showing only the size of the explanatory powers of hypothetical confounders that would be necessary to bring down t-values below 1.96 (i.e., making exposure effect no longer statistically significant at the conventional threshold of $\alpha = 0.05$) expressed in terms of the observed explanatory power of the chosen benchmark covariates. Given that such analysis is done through trial and error to obtain the cutoff values numbers, we present only discrete numbers for thresholds to make sense of the robustness level of our estimates in relation to benchmark covariates in table 4.

In the first row of Table 4 are the results for the association between poor childhood SES and back pain, we can see the OLS coefficient, its standard error, the t-value for statistical significance of the OLS coefficient and the specific SenseMalr measures. First, we have the $R_{2Y\sim D|X}$, which constitutes the proportion of the residual variance of the exposure variable that a hypothetical confounder would have to explain if that same confounder also accounted for 100% of the remaining variance in the outcome. This is known as the "extreme scenario", in which all the residual variance in the outcome is assumed to be explained by a single confounder. In this case, the $R_{2Y\sim D|X}$ value suggests that if an unobserved confounder explains 100% of the remaining variation in outcome variable for diabetes, such a confounder would have to explain only 0.09% of the residual variation in the exposure variable (poor childhood SES) in order to eliminate the statistical significance at $\alpha = 0.05$. Next, we have the first Robustness Value RVq (0.0299), which tells us that a confounder capable of explaining at least 2.9% of the residual variance of diabetes and at the same time at least 2.9% of the residual variance in poor childhood SES would completely eliminate the estimated exposure effect. And it has a Robustness Value for statistical significance

($RV_{q,\ \alpha = 0.05}$ = 0.0091), which indicates that a hypothetical unobserved confounder capable of explaining at least 0.9% of the residual variance of both exposure and outcome variables is strong enough to make the observed association no longer statistically significant at α = 0.05. Lastly, we have the summarized information obtained from contour plots for the benchmark covariate analysis. This is how we read it: an unobserved confounder with an explanatory power with exposure (poor childhood SES) and the outcome (diabetes) that is larger than 11 times the explanatory power of age or 17 times the explanatory power of BMI in the full model would completely eliminate the statistical significance of the observed association.

As we can see in table 4, some of the associations show very little robustness, such as the association between poor childhood SES and depression (whose $RV_{q,\ \alpha = 0.05}$ = 0.0032 and whose benchmark covariate analysis shows that a cofounder with a little more than the explanatory power of age in the full model could eliminate its statistical significance) and the association between hunger in childhood and renal failure in later life (whose $RV_{q,\ \alpha = 0.05}$ = 0.0000 and for which even less than the explanatory power of age or BMI in the full model would be enough for an unobserved confounder to eliminate its statistical significance). On the contrary, other associations seem extremely robust and unlikely to be affect by any unobserved confounder, as for example the association between poor childhood health and back pain (whose $RV_{q,\ \alpha = 0.05}$ = 0.1628 and whose benchmark covariate analysis shows that only a cofounder with more than 250 times the explanatory power of age in the full model could eliminate its statistical significance) and the association between poor childhood health and later-life depression (whose $RV_{q,\ \alpha = 0.05}$ = 0.1429 and for which only a confounder capable of explaining more than 81 times what age explains in the full model could eliminate its statistical significance).

4.4. **Discussion**

The present work investigated the robustness of life course associations found in the context of observational studies of aging. By relying on data from one of the sister aging studies of nationally representative cohorts of older adults, the ELSI-Brazil, we evaluated 65 associations that are theoretically reasonable to be hypothesized between individual variables of childhood disadvantage and certain outcomes variables of health in later life. 24 of these associations were found to be statistically significant at $\alpha = 0.05$ in multivariable analysis that controls for several important covariates. Then, using the SenseMakr framework of sensitivity analysis, we evaluated the likelihood that the statistical significance of such associations could be being driven by an unobserved confounder.

The main idea here was to shed light on two important issues in the realm of observational studies in life course and aging. First, how can we obtain robust measures of variable relationships that cannot be studied employing more sophisticated identification strategies than naïve regression models in cross-sectional designs? Second, given the richness of publicly available data from aging surveys on self-reported factors throughout the life course and dozens of health outcomes, should we apply some further multiple-testing adjustment rationale on such investigations?

Regarding the first issue, i.e., the employment of strategies to check robustness of associations in observational studies, our work showed that SenseMakr offers a powerful systematic approach for the problem of unobserved confounding, combining mathematical empirical evaluation with theoretical understanding of the phenomenon of interest by using benchmark covariates. Despite the fact that the Robustness Values (RVs) cannot be compared against a universal threshold for omitted variable bias, those numbers still offer an additional piece of information for researchers to reflect on the relevance of its statistical findings beyond

conventional statistical significance levels and discussions of model specifications. Most importantly, the benchmark covariate analysis was shown to be a useful tool that clearly expresses the likelihood of omitted variable bias in terms of well-known covariates. It still requires critical thinking from researchers and readers as it does not provide a mechanistic solution for the internal threat of unobserved confounding, but offers insights based on strong empirical evidence. For example, when we compare the odds ratio for the association between hunger in childhood and renal failure in later life (OR = 1.354, 95% CI: 1.062 - 1.726) to the odds ratio for the association between poor childhood SES and diabetes (OR = 1.242, 95% CI: 1.040 - 1.483), we see that the latter association has lower effect size and a confidence interval whose lower bound is closer to 1. Nonetheless, the benchmark covariate analysis shows that the latter association is substantially more robust than the former. While a hypothetical unobserved confounder that explains less than what age or BMI explains in the full regression model would be enough to completely eliminate the statistical significance of the association between hunger in childhood and later-life renal failure, only an unobserved confounder with the explanatory power greater than 9 times of age or 21 times of BMI would eliminate the statistical significance of the association between poor childhood SES and diabetes. Given our methodological focus here, a detailed discussion of each association robustness is beyond the scope of this work. But by discussing some examples we demonstrated that the SenseMakr framework can be extremely useful to evaluate robustness in observational studies in aging and life course, particularly under imperfect identification strategies.

In respect to the multiple testing done here, we also shed light on an important topic. It is not unreasonable to imagine that each of the 65 hypothesized associations here could constitute matter for 65 standalone papers, as we often seen in the aging and life course literature when the association between a single exposure variable and a single outcome variable is tested (2,3,13–

26,28). In a study with multiple testing, it is clear that there is increased probability of finding statistically associations at random. But in individual papers where these general hypotheses are based vaguely on the complex life course literature, it is not always clear whether the randomness could be driving the associations among variables that are at hand in publicly available datasets. That is why there is a great need for more refined theoretical reasoning of the possible causal mechanisms underlying the hypothesized relationship between two variables as well as a careful work of sensitivity analysis, particularly when a cross-sectional design is the only option and better identification strategies are not available.

Had we applied, for instance, the Bonferroni adjustment (by large the most commonly done p-value adjustment in the health sciences (36)), the threshold for statistical significance would have been α/n, i.e., $0.05/65 = 0.00076$. That would make all the associations here not significant. More contemporary authors that criticized that approach because a) p-value adjustments are based on the number of tests considered, which is an arbitrary number, and because b) p-value adjustments decrease the chance of type I errors but increase the chance of type II errors (or drastically reduce the analysis power) (37). Other less conservative alternatives for multiple-testing adjustments of p-values have been contended and developed, such as the false discovery rate control (36) and stepwise and weighted versions of the classical Bonferroni and Simes test (38). No particular approach has gained the gold standard status in multiple-testing adjustment. Overall, it is important that a proper balance of theoretical reasoning for picking exposure and outcome variables from these aging surveys and a global assessment of the multiple methodological factors that contribute to a statistically significant association, such as p-value threshold, effect size, model specification and robustness checks.

Our work has several strengths. First, to our knowledge this is the first study to investigate the relevance and application of the SenseMakr framework in the realm of observational studies in public health. We demonstrated its enormous usefulness in evaluating the robustness of regression estimates, particularly under imperfect identification approach. Second, we carefully investigated a multiplicity of theoretically reasonable associations between childhood exposures and later-life health outcomes, providing an overview of a wide array of life course phenomena and how some of these associations, often studied individually, could be happening at random. Third, the study relied on data from of the many sister studies on aging that follow nationally representative samples of older adults and therefore could be easily expanded to a multi-national approach, with even more exposure and outcome variables.

In terms of limitations, a few deserve mentioning. First, despite the insightful help from the SsenseMakr framework of sensitivity analysis, it does not provide a unique mechanistic solution to definitely determine whether or not a regression estimate is free from the threat of omitted variable bias, and it sill requires some further thinking that combines theoretical understanding of the phenomena with the numerical representations of robustness it provides. Second, this tool is based on OLS while all the outcome variables here are by definition categorical binary variables. As per recommendation of the SenseMakr`s creator (personal conversation), we can perform this methodological extrapolation by checking whether linear probability models are appropriate by comparing the average marginal effects from the linear probability models (OLS regression) to non-exponentiated coefficients obtained from the logit models. And in this regard, we found virtually identical numbers (data not shown).

4.5. Conclusion

Understanding how individuals and populations become (un)healthy over time has increasingly become a central topic for the public health community, especially given the rapid aging of populations worldwide and its implications for national health and welfare systems. The efforts in collection of rich and high-quality data on cohorts of older adults have grown and become coordinated, making it easier to conduct research that connects childhood and early adulthood experiences with later-life health. Given the nature of such data, collected simultaneously on a wide variety of variables that can be later picked by researchers, the randomness of such choices remains an important issue. In addition, the use of cross-sectional designs as the often only methodological choice creates further concern on the robustness of found associations.

Our work demonstrated that it is necessary to have strong theoretically-driven conceptual models, extensive exploratory statistical analysis, proper model specification and global assessment of robustness in order to minimize the risk of omitted variable bias. The SenseMakr framework was proven to be a very useful approach to robustness assessment in this context and contribute to the aging and life literature with insights that go beyond the mere statistical significance convention approach.

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Table 4-1 - Descriptive statistics, by number of chronic conditions.

			Chronic conditions				
	Sample Size	*Total*	*None*	*One*	*Two*	*Three or more*	
Covariates	(n = 9,412)	*%*	% 19.21	27.82	23.61	29.37	
Age groups							
50-59	3,980	47.62	24.97	29.91	22.05	23.07	***
60-69	2,875	29.66	15.04	27.16	25.48	32.33	
70-79	1,781	15.65	12.55	25.04	23.42	38.99	
80+	776	7.08	12.62	22.72	26.64	38.02	
Sex							
Female	5,314	53.95	13.91	24.44	23.92	37.73	***
Male	4,098	46.05	25.41	31.79	23.23	19.57	
Race/Skin color							
White	3,590	42.71	19.30	26.93	23.10	30.67	.
Black	887	9.69	16.09	28.51	25.24	30.16	
Brown	4,283	44.67	20.26	28.48	23.31	27.95	
Others	310	2.93	15.16	24.98	27.49	32.37	
Education (Years of schooling)							
Less than 5	3,463	32.85	16.07	27.43	23.83	32.67	***
Between 5 and 8	2,845	31.44	18.84	26.62	24.49	30.06	
9 or more	3,042	35.71	22.57	29.23	22.60	25.60	
Household income							
Less than 2 Minimum Wages	3,153	30.47	18.58	28.27	21.13	32.02	***
2-5 Minimum Wages	4,294	48.38	17.87	27.30	25.25	29.57	
5-9 Minimum Wages	1,148	14.16	22.65	27.85	23.96	25.54	
9+ Minimum Wages	546	6.99	23.78	31.26	21.56	23.40	
Occupational status							
Intense physical effort	1,841	19.31	17.00	26.47	24.96	31.57	.
Some physical effort	2,977	32.20	19.67	27.76	23.11	29.46	

Standing or walking most of the time	2,955	32.63	20.00	27.98	23.37	28.64	
Seated most of the time	1,414	15.86	19.45	29.62	23.16	27.77	
Region							
North	743	5.56	23.65	26.95	22.64	26.76	**
Northeast	2,549	24.10	21.61	31.03	22.74	24.62	
Southeast	3,922	47.19	17.93	27.94	23.98	30.15	
South	1,278	16.55	17.74	23.97	23.80	34.50	
Midwest	920	6.60	19.54	25.62	24.41	30.43	
Residence in urban area							
No	1,477	15.31	21.46	29.08	22.10	27.36	.
Yes	7,935	84.69	18.80	27.59	23.88	29.73	
Living with partner							
No partner	3,970	36.53	18.13	25.96	23.37	32.54	***
Living with partner	5,442	63.47	19.83	28.89	23.74	27.54	
Poor self-rated health							
No	3,970	43.71	29.43	32.54	20.82	17.20	***
Yes	5,420	56.29	11.26	24.12	25.79	38.83	
Daily smoking							
No	4,775	50.97	18.21	28.29	23.96	29.54	.
Yes	4,634	49.03	20.26	27.30	23.24	29.20	
Drink							
Never	6,909	70.89	16.63	26.51	23.74	33.12	***
Eventually	544	6.01	22.32	27.95	23.16	26.58	
Regularly	1,952	23.10	26.36	31.89	23.18	18.57	
Body Mass Index							
Normal	2,803	29.18	24.84	29.24	22.60	23.32	***
Overweight	3,561	37.71	19.77	28.08	24.79	27.36	
Obese	3,048	33.12	13.60	26.27	23.14	36.98	

Weighted and survey-adjusted proportions.
Design-corrected F-test *= p<0.05; **=p<0.01; ***p<0.001.
Data source: Brazilian Longitudinal Study of Aging (ELSI-Brazil), baseline assessment (2015-2016)

Table 4-2 - Distribution of exposure variables in the sample.

Exposure variables	*Sample size* (n = 9,412)	*Total* %	
Poor childhood SES			
No	3,817	42.31	***
Yes	5,555	57.69	
Overcrowded home in childhood			
No	5,693	61.99	
Yes	3,719	38.01	
Poor self-rated health			
No	3,970	43.71	***
Yes	5,420	56.29	
Hunger in childhood			
No	6,847	75.31	***
Yes	2,476	24.69	
Lived in rural area until 15 y/o			
No	3,511	39.68	**
Yes	5,888	60.32	

Weighted and survey-adjusted proportions.
Design-corrected F-test *= $p<0.05$; **=$p<0.01$; ***$p<0.001$.
Data source: Brazilian Longitudinal Study of Aging (ELSI-Brazil), baseline assessment (2015-2016)

Table 4-3 – Associations between childhood exposure variables and later-life occurrence of chronic conditions expressed as odds ratios.

	Odds Ratio (95% Confidence Intervals)				
Variables	Poor SES	Overcrowded home	Poor childhood health	Hunger in childhood	Rural residence
Alzheimer's	0.998	0.864	1.235	1.354	0.934
	(0.565 - 1.763)	(0.469 - 1.591)	(0.577 - 2.644)	(0.728 - 2.517)	(0.529 - 1.649)
Arthritis	1.110	1.214**	1.712***	1.276**	1.289**
	(0.959 - 1.286)	(1.067 - 1.382)	(1.463 - 2.003)	(1.089 - 1.494)	(1.105 - 1.504)
Back pain	1.185**	1.057	1.593***	1.224***	1.154
	(1.070 - 1.312)	(0.947 - 1.180)	(1.379 - 1.840)	(1.109 - 1.350)	(0.998 - 1.334)
Cancer	1.030	0.980	1.381**	1.123	1.008
	(0.827 - 1.282)	(0.744 - 1.290)	(1.129 - 1.689)	(0.839 - 1.502)	(0.777 - 1.308)
COPD	1.005	1.054	1.976***	1.506***	0.907
	(0.819 - 1.233)	(0.838 - 1.325)	(1.552 - 2.515)	(1.183 - 1.918)	(0.728 - 1.131)
Depression	1.190*	1.144	1.757***	1.527***	0.918
	(1.007 - 1.407)	(0.968 - 1.353)	(1.455 - 2.122)	(1.306 - 1.785)	(0.775 - 1.086)
Diabetes	1.242*	1.094	0.971	1.199*	0.889
	(1.040 - 1.483)	(0.944 - 1.268)	(0.814 - 1.158)	(1.022 - 1.406)	(0.756 - 1.046)
Heart disease	0.965	0.983	1.822*	1.539	0.892
	(0.610 - 1.527)	(0.580 - 1.664)	(1.094 - 3.035)	(0.840 - 2.819)	(0.449 - 1.774)
Hypertension	1.092	0.988	1.088	1.121	1.110
	(0.966 - 1.236)	(0.887 - 1.101)	(0.971 - 1.220)	(0.983 - 1.279)	(0.983 - 1.254)
Osteoporosis	1.200	1.176*	1.406***	1.377***	1.276**
	(0.977 - 1.473)	(1.025 - 1.349)	(1.178 - 1.679)	(1.154 - 1.643)	(1.077 - 1.511)

Parkinson's	0.680	1.012	1.169	2.094*	0.550
	(0.394 - 1.174)	(0.559 - 1.833)	(0.534 - 2.560)	(1.134 - 3.866)	(0.214 - 1.414)
Renal failure	0.994	1.001	1.752***	1.354*	1.022
	(0.769 - 1.284)	(0.799 - 1.253)	(1.371 - 2.240)	(1.062 - 1.726)	(0.749 - 1.395)
Stroke	1.111	1.076	1.320*	1.064	0.992
	(0.830 - 1.488)	(0.827 - 1.401)	(1.037 - 1.680)	(0.793 - 1.428)	(0.766 - 1.285)

*** p<0.001, ** p<0.01, * p<0.05. Adjusted odds ratios were obtained from logistic regressions controlling for age, sex, race, macrogeographic region, urban residence, educational attainment, household income, occupational status, living with a partner, daily smoking, drinking and body mass index. Data source: ELSI-Brazil, 2015-2016.

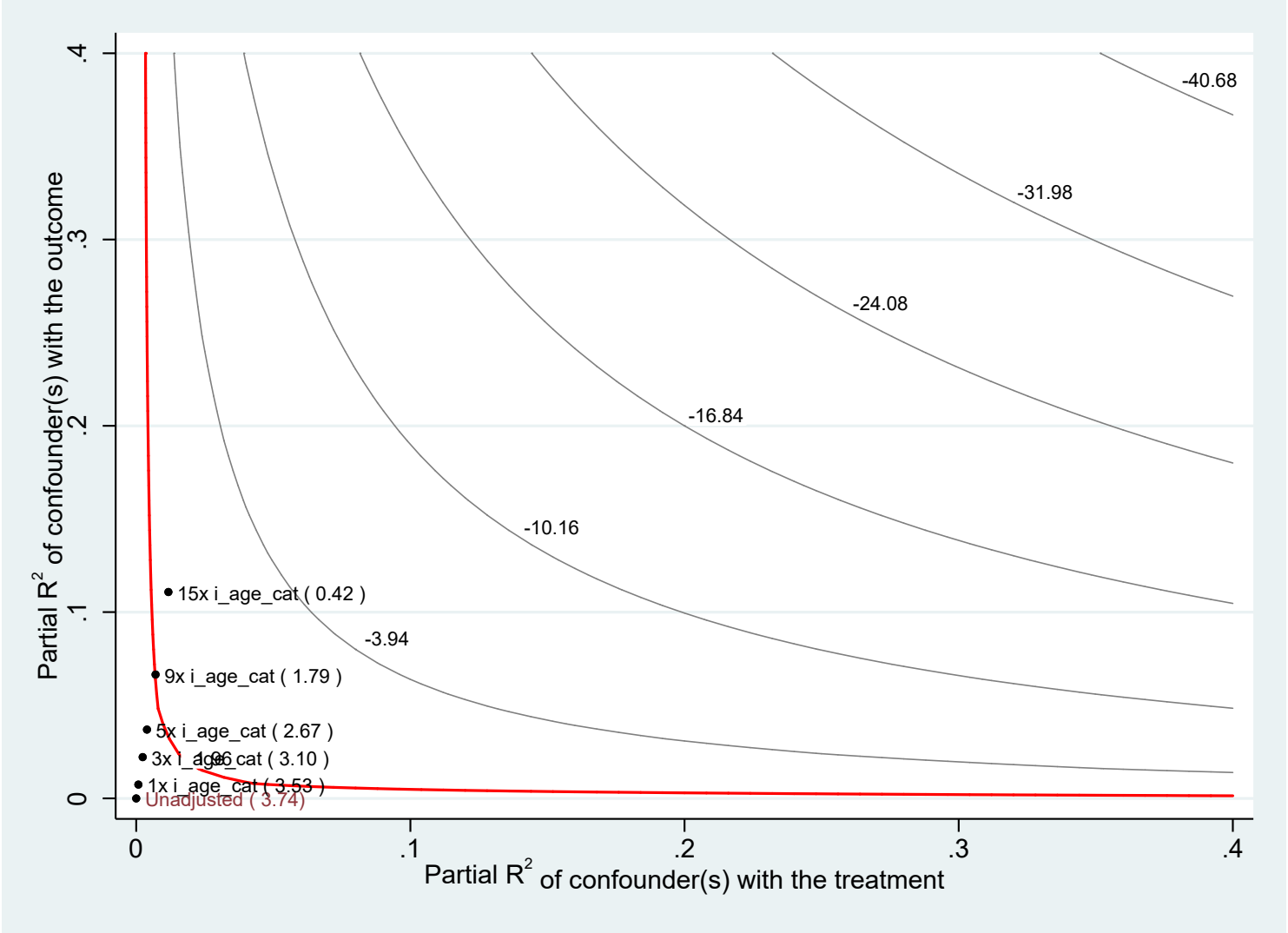

Figure 4-1 – Contour t-value plot for the outcome diabetes and age as a benchmark covariate..

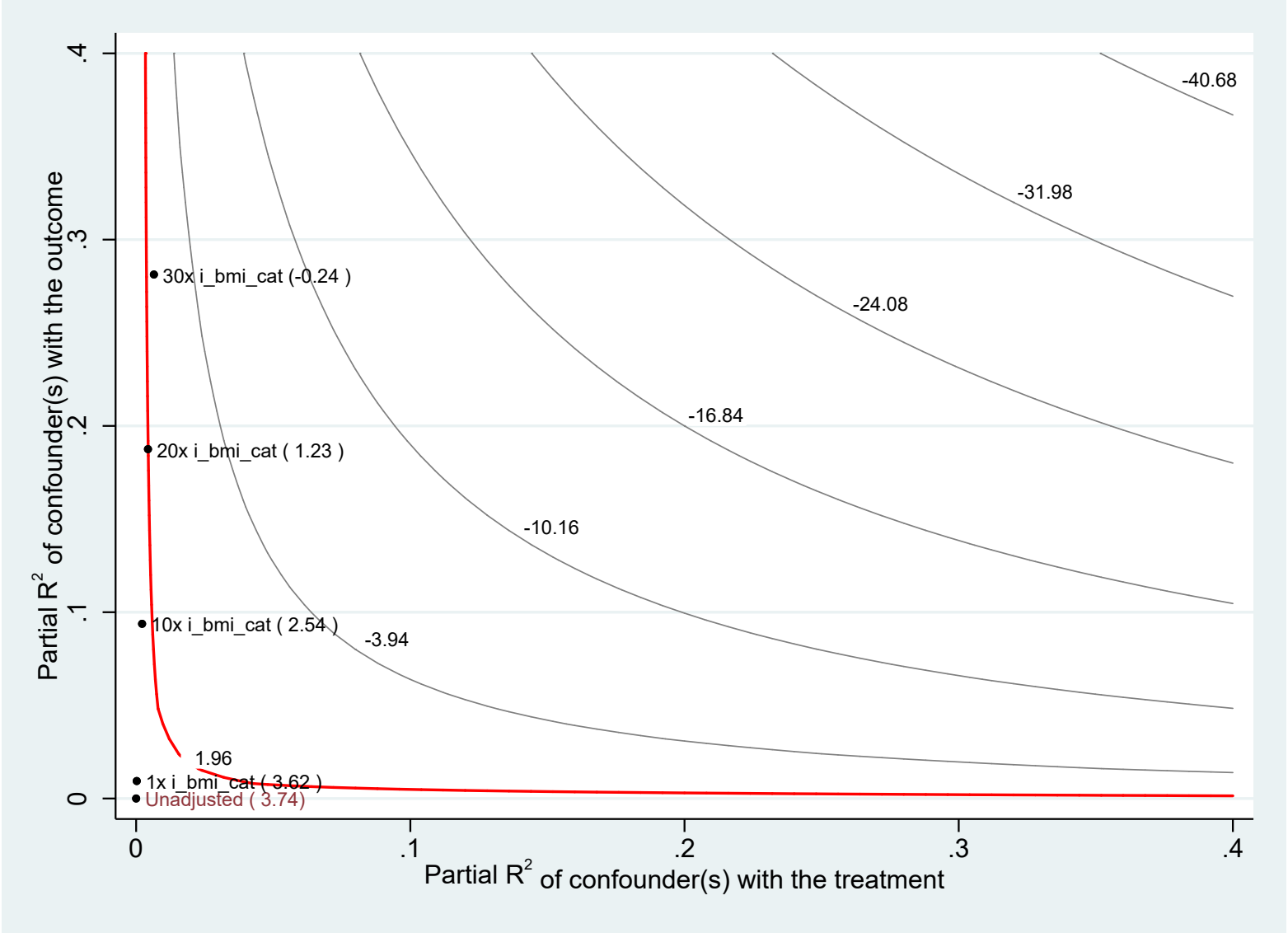

Figure 4-2 – Contour t-value plot for the outcome diabetes and BMI as a benchmark covariate.

Table 4-4 – Sensitivity analysis measures for all the statistically significant associations.

	Exposure variable: Poor SES							
Outcomes	Exposure variable OLS coefficient	Standard Error	t-value (H0)	R2y ~ d | x	Robustness Value (RVq)	Robustness Value α =0.05	Benchmark covariate Age	Benchmark covariate BMI
Back pain	0.0312	0.0111	2.7981	0.0009	0.0299	0.0091	> 11	> 17
Depression	0.0193	0.0085	2.2552	0.0006	0.0242	0.0032	> 1	> 7
Diabetes	0.0310	0.0083	3.7359	0.0016	0.0398	0.0191	> 9	> 21

	Exposure variable: Overcrowded home							
Outcomes	Exposure variable OLS coefficient	Standard Error	t-value (H0)	R2y ~ d | x	Robustness Value (RVq)	Robustness Value α =0.05	Benchmark covariate Age	Benchmark covariate BMI
Arthritis	0.0227	0.0091	2.5051	0.0007	0.0268	0.0059	> 1	> 7
Osteoporosis	0.0174	0.0081	2.1529	0.0005	0.0231	0.0021	< 1	> 4

	Exposure variable: Poor childhood health							
Outcomes	Exposure variable OLS coefficient	Standard Error	t-value (H0)	R2y ~ d | x	Robustness Value (RVq)	Robustness Value α =0.05	Benchmark covariate Age	Benchmark covariate BMI
Arthritis	0.1401	0.0090	15.5278	0.0277	0.1551	0.1370	> 74	> 48
Back pain	0.1997	0.0109	18.3592	0.0382	0.1804	0.1628	> 250	> 105
Cancer	0.0323	0.0051	6.3052	0.0047	0.0661	0.0460	> 29	> 58
COPD	0.0476	0.0053	9.0387	0.0095	0.0933	0.0739	> 119	> 52
Depression	0.1196	0.0084	14.2281	0.0233	0.1429	0.1245	> 81	> 106
Heart	0.0102	0.0022	4.5797	0.0025	0.0484	0.0280	> 32	> 31
Osteoporosis	0.0980	0.0081	12.1541	0.0172	0.1237	0.1049	> 42	> 75
Renal failure	0.0422	0.0048	8.8393	0.0091	0.0914	0.0719	> 121	> 84
Stroke	0.0316	0.0052	6.0912	0.0043	0.0639	0.0438	> 21	> 16

	Exposure variable: Hunger in childhood							
Outcomes	Exposure variable OLS coefficient	Standard Error	t-value (H0)	R2y ~ d | x	Robustness Value (RVq)	Robustness Value α =0.05	Benchmark covariate Age	Benchmark covariate BMI
Arthritis	0.0294	0.0102	2.8849	0.0010	0.0310	0.0100	< 1	> 28
Back pain	0.0522	0.0124	4.2191	0.0021	0.0449	0.0243	> 6	> 170
COPD	0.0247	0.0059	4.1772	0.0021	0.0444	0.0238	> 6	> 190
Depression	0.0588	0.0095	6.2085	0.0045	0.0653	0.0452	> 2	> 500
Diabetes	0.0154	0.0092	1.6680	0.0003	0.0180	0.0000	< 1	< 1
Osteoporosis	0.0433	0.0091	4.7814	0.0027	0.0508	0.0303	> 2	> 300
Parkinson	0.0048	0.0020	2.3705	0.0007	0.0255	0.0045	> 1	> 75
Renal failure	0.0061	0.0053	1.1484	0.0002	0.0124	0.0000	< 1	< 1

	Exposure variable: Rural residence							
Outcomes	Exposure variable OLS coefficient	Standard Error	t-value (H0)	R2y ~ d | x	Robustness Value (RVq)	Robustness Value α =0.05	Benchmark covariate Age	Benchmark covariate BMI
Arthritis	0.0364	0.0102	3.5523	0.0015	0.0379	0.0171	> 4	> 6
Osteoporosis	0.0299	0.0091	3.2878	0.0013	0.0351	0.0143	> 2	> 10

Data source: ELSI-Brazil, 2015-2016.

The $R_{2Y\sim D|X}$, constitutes the proportion of the residual variance of the exposure variable that a hypothetical confounder would have to explain if that same confounder also accounted for 100% of the remaining variance in the outcome