Research paper

How sex differences in schooling and income contribute to sex differences in depression, anxiety and common mental disorders: The mental health sex-gap in a birth cohort from Brazil

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ABSTRACT

Background: Reasons for the higher rates of depression, anxiety and common mental disorders among women are unclear. We investigated the mediating effect of schooling and personal income and the effect modification of maternal schooling and family income at baseline.

Methods: In 1982, the maternity hospitals of Pelotas (Southern Brazil) were daily visits and those livebirths whose family lived in the urban area of the city were examined and their mothers interviewed. At 30 years, the presence of major depression (MD) and generalized anxiety disorder (GAD) was assessed using the Mini-International Psychiatric Interview, and common mental disorders (CMD) with the self-rated questionnaire. We used Mantel-Haenszel test to assess effect modification and a counterfactual framework using inverse probability weights (IPW) and G-computation to analyze mediation.

Results: Income at 30 years captured part of the association of sex with MD (16.5%), GAD (14.2%), and CMD (18.0%). Schooling at 30 years was higher in women (p<0.001), and therefore inversely mediated the association with MD (-5.4%), GAD (-4.8%), and CMD (-6.7%). If we fixed the mediator to earning more than 3 minimum salaries, the effect of sex, was reduced in 64.9%, 56.7% and 31.4%, for MD, GAD and CMD, respectively, and 62.4%, 13.6% and 23.8%, if fixed to 12 or more years of schooling.

Limitations: We were not able to evaluate mental health and socioeconomic changes, or assess a bidirectional effect

Conclusion: Personal income and schooling at 30 years, are important mediators and effect modifiers of the association between sex and MD, GAD, and CMD.

1. Introduction

Prevalence of depression and anxiety is 2 to 3 times higher among women (Arias-de la Torre et al., 2018; Bromet et al., 2011; Ferrari et al., 2013; Ferrari et al., 2013; Kessler and Bromet, 2013; Piccinelli and Wilkinson, 2000). Biological characteristics could explain part of this sex-gap (Bhui, 2018; Kuehner, 2017; Piccinelli and Wilkinson, 2000), but there is not enough empirical evidence to fully support this as the main explanation (Kuehner, 2017). Women are more prone to disparities in employment, education and salary rates which are probably the most important predictors of depression and anxiety (Almeida-Filho et al., 2004; Bhui, 2018; Alize J. Ferrari et al., 2013; Howard et al., 2017; Kuehner, 2017; Schuch et al., 2014). Gender roles and empowerment effects over mental health in society have not been given the importance they deserve and require further empirical population-based studies. (Bhui, 2018; Howard et al., 2017;

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Kuehner, 2017)

Some studies have already shown that the association between biological sex and depression differs among countries, and seems to be modified by socioeconomic characteristics (Almeida-Filho et al., 2004; Alvarado et al., 2007; Arias-de la Torre et al., 2018; Kosidou et al., 2011; Leupp, 2017; Lucht et al., 2003; Nicholson et al., 2008; Ross and Mirowsky, 2006; Van de Velde et al., 2010). However, this evidence comes mostly from cross sectional studies, and from stratifying the effect of social and sex characteristics for each other. Socioeconomic position could be an inherent condition of the family in which an individual is born, independently of its sex, but in adulthood it could be a consequence, especially in an unequal context were women are offered less developmental opportunities and earn less. In a causal pathway, socioeconomic position could be a mediator in the association between sex and mental health, stratifying the effect (conditioning) could imply over adjustment, and result in biased estimates. (Schisterman et al., 2009)

In that sense, we aimed to assess and disentangle the pathway leading women to a higher prevalence of depression, anxiety and common mental disorders. We evaluated the association between sex and mental health outcomes and explored how family income and/or maternal schooling at the time of birth and adulthood modified this association. In addition, we evaluated the mediating effect of personal income and/or schooling in adulthood using a counterfactual framework.

2. Materials and Methods

This is a cohort study using data from the baseline and 30 years follow-up of the 1982 Pelotas Birth Cohort. In 1982, all maternity hospitals in Pelotas (Southern Brazil) were visited daily, and those livebirths whose family lived in the urban area of the city (n = 5914) were examined and their mothers interviewed on sociodemographic and health related variables, which included, family income, collected in categories of minimum salaries: ≤ 1, 1,1-3, 3,1-6, 6,1-10, > 10; maternal schooling (numbers of completed years of formal education). These individuals have been followed on several occasions and further details on the study methodology have been published elsewhere. (Barros et al., 2008)

From June 2012 to February 2013, at a mean age of 30.2 years, we tried to follow the whole cohort (Horta et al., 2015). In this visit, a psychological interview was carried out using the Mini-International Psychiatric Interview (MINI) V5.0 (Amorim, 2000), which allowed us to evaluate several psychiatric disorders. For this study, we used the MINI diagnosis of generalized anxiety disorder (GAD), during the last 6 months, and considered cases of major depression (MD) those individuals who were positive for an episode of major depression during the past 2 weeks and negative for a lifetime episode of hypomania or mania. In addition, we used the self-reported questionnaire (SRQ-20), validated for Brazil, to assess the presence of common mental disorders (CMD), males with a score of six or higher and women with eight or higher were considered as positive for CMD. The SRQ-20 has shown a sensitivity of 83%, specificity 80%, and the correlation between the questionnaire total scores and independent clinical judgment was moderate (r = +0.70) (Mari and Williams, 1986)

At 30 years, we also evaluated personal income, measured as the total number of Brazilian Reais (US$1 was worth 0.49 real in 2012) the individual earned during the last month, and total number of formal years of schooling.

Personal income was transformed in number of minimum wages, using as reference the mean minimum wage for the Brazilian population in 2012 (DEC 7.655/2011 12/26/2011), and then categorized in:

no income, 1 or less, > 1-2, > 2-3, and more than 3. Schooling at 30 years and maternal schooling were categorized in 0-4, 5-8, 9-11, and 12 or more years of formal education.

Family income and maternal schooling were collected at baseline and should be interpreted as the income and schooling at the time the individuals were born.

Based on results from effect modification analysis, explained in Supplementary file 1, we dichotomized the variables personal income (≤ 3 or > 3 minimum salaries) and schooling (< 12 or ≥ 12 years) at 30 years.

For all our analysis we used STATA v.13.1. We used Chi-square test to compare proportions, and the Mantel-Hanszel (M-H) test to evaluate the effect modification of family income and maternal schooling at baseline, and personal income and schooling at 30 years, over the association between sex and mental health outcomes.

Since personal income and schooling at 30 years could be a consequence of sex, and therefore mediators of the association with mental health, only stratifying the effect of sex by these two socioeconomic variables could result in an over adjustment of our estimates (adjustment for mediator) (Schisterman et al., 2009). We adopted a counterfactual-based approach to mediation analysis (VanderWeele, 2016). We used inverse probability weighting (IPW), as proposed by VanderWeele (VanderWeele et al., 2013), to correctly decompose the total effects of the exposure (sex) on the outcome (MD, GAD or CMD) into direct and indirect effects in the presence of two consecutive mediators (schooling and income) (Figure 1). We estimated the natural direct effect (NDE) and natural indirect effect (NIE), of sex on MD, GAD and CMD, using each mediator separately and both together.

The methodology proposed by VanderWeele, does not give us a straightforward way of calculating the controlled direct effect (CDE), therefore, we additionally used G-computation, using the *gformula* command (Daniel et al., 2011) to assess the CDE of the association of sex and mental health outcomes, where income and schooling at 30 years were maintained constant. We used independent models for each mediator in the g-computation analysis only.

The NDE represents the effect of the exposure (being a woman) on the outcomes (MD, GAD and CMD) that is not captured by the mediator (income and/or schooling), while the NIE estimates the effect that is captured. The sum of the NDE and NIE would represent the total causal effect, and the quotient of dividing the NIE by the total effect would represent the percentage of the effect that is captured by a mediator. The CDE would represent the effect of the exposure on the outcome if we were able to control the mediator (maintain constant or fixed at one level). In our mediation analysis, family income and maternal schooling at baseline were considered as confounders of the association. Standard errors for mediation analyses were calculated using boot strapping with 10000 simulations.

2.1. Ethics and consent statement

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. We obtained ethical approval for the study from the ethics committee of the 'Universidade Federal de Pelotas'. Written informed consent was obtained from all subjects.

3. Results

In the 2012-13 visit, 3701 subjects were evaluated and data on mental health was available for 1770 men and 1899 women (n = 3669).
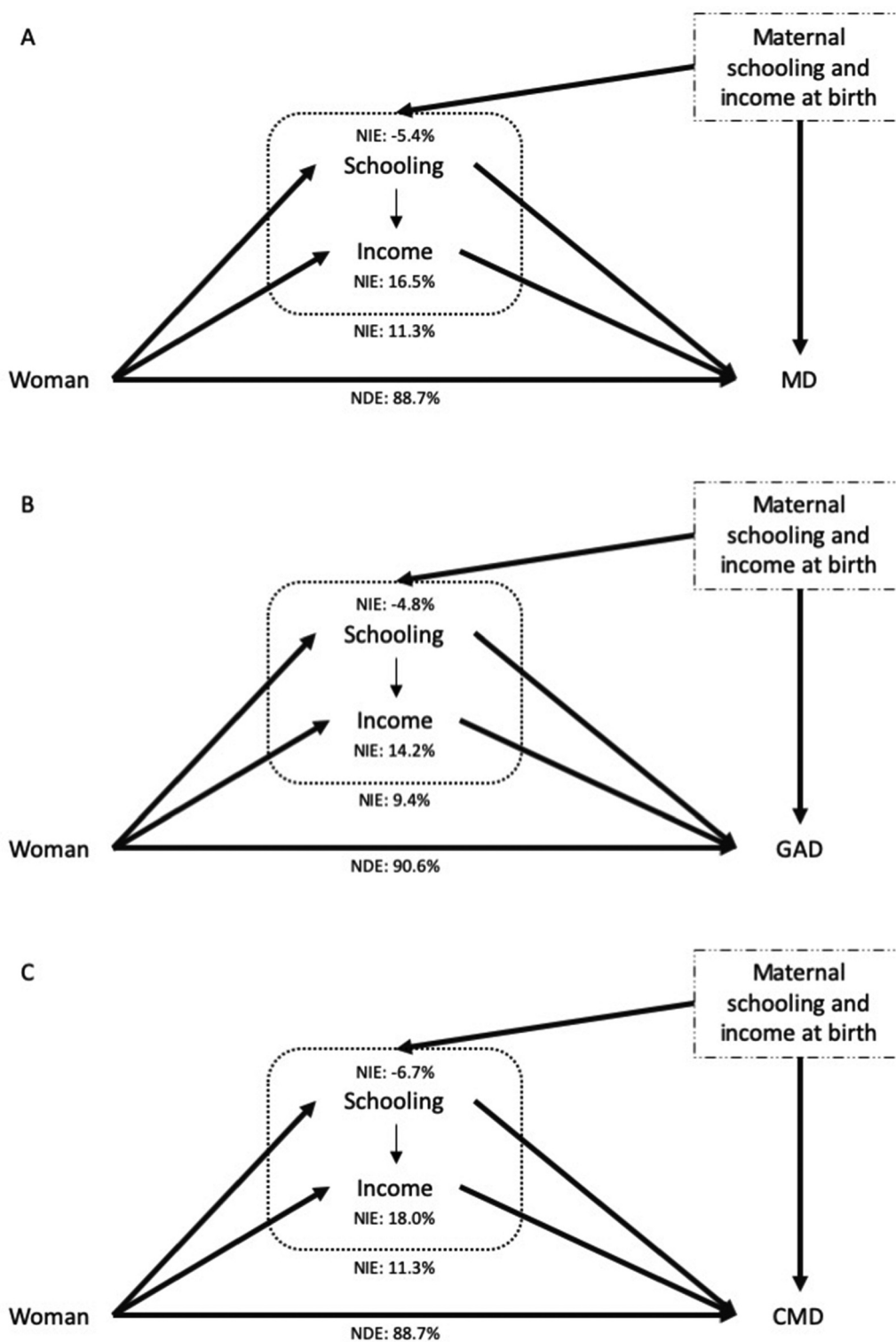
Figure 1. Decomposition of the mediating effect of individual income and schooling at 30 years in the pathway between female and mental health outcomes. A. MD as outcome. B. GAD as outcome. C. CMD as outcome. CMD = Common mental disorder. GAD = Generalized anxiety disorder. MD = Major depression. NDE = Natural direct effect. NIE = Natural indirect effect.

Women showed a higher prevalence of MD (11.4% vs 4.2%), GAD (17.8% vs 7.1%) and CMD (27.1% vs 21.3%).

Attrition rate was 62%, and it was higher in women (p < 0.001), those whose family earned less than 3 minimum salaries (p < 0.001), or with a mother who at baseline had less than 12 years of education (p < 0.001) (supplementary table 3) .

Table 1
Socioeconomic and mental health variables of men and women of the 1982 Pelotas birth cohort at baseline and at 30 years.

	Men (n = 1770)	Women (n = 1899)	P-value
Variables at baseline (birth)	N (%)	N (%)	
Family income in minimum wage (MW)			0.91
1 or less	349 (20.0)	366 (19.5)	
1.1-3	853 (48.9)	933 (49.8)	
3.1-6	349 (20.0)	362 (19.3)	
>6	193 (11.1)	123 (11.4)	
Maternal schooling (years)			0.75
0-4	559 (32.0)	607 (32.2)	
5-8	767 (43.9)	799 (42.5)	
9-11	190 (10.9)	206 (11.0)	
12 or more	232 (13.3)	270 (14.3)	
Variables at 30 years			
Individual income in minimum wage (MW)			<0.001
No income	178 (10.1)	508 (26.8)	
1 or less	127 (7.2)	330 (17.4)	
>1-2	505 (28.5)	560 (29.5)	
>2-3	356 (20.1)	186 (9.8)	
>3	604 (34.1)	315 (16.6)	
Schooling (years)			<0.001
0-4	110 (6.3)	113 (6.0)	
5-8	399 (22.8)	325 (17.3)	
9-11	561 (32.0)	531 (28.2)	
12 or more	681 (38.9)	915 (48.6)	
MD	72 (4.2)	212 (11.4)	<0.001
GAD	122 (7.1)	330 (17.8)	<0.001
CMD	374 (21.3)	511 (27.1)	<0.001

CMD = Common mental disorder. GAD = Generalized anxiety disorder. MD = Major depression

At baseline, family income and maternal schooling were similar for both men and women. At 30 years the distribution of personal income and schooling differed among them, 54.2% of men earned more than 2 minimum salaries (34.1% more than 3), while only 26.4% of women earned the same, and 26.8% had no personal income at all. In terms of schooling, 48.6% of women studied 12 years or more, compared to 38.9% of men. (Table 1)

Table 2 shows that there was no evidence of effect modification of family income or maternal schooling on the association between sex and any of the outcomes. However, in adulthood, among those who earned ≤3 minimum salaries, women's prevalence of MD was 2.95 [95%CI (2.18-3.99)] times higher, and for CMD it was 1.26 [95%CI (1.11-1.43)]. Among those earning >3 minimum salaries, PRs for MD and CMD were reduced or inverted, and confidence intervals included the reference. Similarly, among those with <12 years of schooling, the prevalence of MD and CMD was 3.52 [95%CI (2.55-4.86)] and 1.55 [95%CI (1.35-1.78)] times higher for women compared to men, respectively, and among those with 12 or more years of schooling, the PR for MD was 1.84 [95%CI (1.19-2.85)] and for CMD 0.99 [95%CI (0.80-1.23)]. When we analyzed personal income and schooling together, the effect modification persisted, for both MD (M-H p = 0.018) and CMD (M-H p < 0.001). There was no evidence for an effect modification for GAD. (Table 2)

Supplementary Table 2 and Figure 1, show the results of our mediation analysis. We found that together schooling and personal income at 30 years captured 11.3% of the effect of sex over MD and CMD, and 9.4% of the effect over GAD. However, these two variables mediated the effect in opposite directions. Through schooling's independent pathway the total effect of being a woman was reduced in 5.4%, 4.8% and 6.7%, for MD, GAD and CMD, respectively. The pathway of personal income at 30 years, on the other hand, captured 16.5%, 14.2% and 18.0% of the total effect of being a woman over MD, GAD, and CMD, respectively, in the direction of higher chance.

In our g-computation analysis (Supplementary Table 2) when we fixed the mediator personal income to earning more than 3 minimum salaries, we evidenced that the CDE represented 35.1% of the total effect of sex over MD, 43.3% of the effect over GAD and 68.6% over CMD. These indicates that the effect of sex, if all individuals earned that amount, would be reduced in 64.9%, 56.7% and 31.4%, respectively. When we fixed the mediator schooling to 12 or more years, we evidenced that the CDE represented 37.6% of the total effect of sex over MD, 86.4% of the effect over GAD and 76.2% over CMD. Therefore, if all individuals had 12 years or more of schooling, the effect of sex on mental outcomes would be reduced in 62.4%, 13.6% and 23.8%, respectively.

Table 2
Prevalence and prevalence ratios of mental health disorders at 30 years, according to sex and dichotomized socioeconomic variables at baseline and 30 years.

	MD			GAD			CMD		
	N (%)*M	N (%)*W	PR (95%CI)**	N (%)*M	N (%)*W	PR (95%CI)**	N (%)*M	N (%)*W	PR (95%CI)**
Family income at baseline in MW			p = 0.815			p = 0.631			p = 0.088
0-3	54 (4.6)	160 (12.6)	2.75 (2.04-3.70)	95 (8.0)	248 (19.5)	2.43 (1.94-3.03)	277 (22.9)	401 (30.9)	1.35 (1.18-1.53)
>3	18 (3.4)	50 (8.7)	2.56 (1.51-4.32)	27 (5.1)	80 (13.9)	2.73 (1.79-4.15)	95 (17.5)	106 (18.4)	1.05 (0.82-1.35)
Maternal Schooling at baseline (years)			p = 0.499			p = 0.06			p = 0.37
0-11	66 (4.4)	197 (12.4)	2.79 (2.13-3.65)	108 (7.3)	306 (19.3)	2.65 (2.16-3.27)	341 (22.4)	473 (29.3)	1.31 (1.16-1.48)
12 or more	6 (2.6)	14 (5.3)	1.99 (0.78-5.10)	14 (6.2)	23 (8.6)	1.40 (0.74-2.66)	30 (12.9)	37 (13.7)	1.06 (0.68-1.66)
Individual income at 30 years in MW			p = 0.007			p = 0.054			p = 0.039
0-3	49 (4.4)	199 (12.9)	2.95 (2.18-3.99)	90 (8.0)	306 (19.8)	2.47 (1.98-3.09)	276 (23.9)	474 (30.2)	1.26 (1.11-1.43)
>3	23 (3.9)	13 (4.2)	1.08 (0.55-2.1)	32 (5.4)	24 (7.7)	1.43 (0.86-2.38)	98 (16.2)	37 (11.8)	0.73 (0.51-1.03)
Schooling at 30 years (years)			p = 0.019			p = 0.265			p = 0.001
0-11	45 (4.3)	144 (15.2)	3.52 (2.55-4.86)	85 (8.2)	217 (23.0)	2.82 (2.23-3.56)	251 (23.6)	354 (36.5)	1.55 (1.35-1.78)
12 or more	27 (4.0)	67 (7.4)	1.84 (1.19-2.85)	37 (5.5)	110 (12.2)	2.21 (1.54-3.16)	118 (17.3)	157 (17.2)	0.99 (0.8-1.23)
Individual income (MW) + schooling (years)			p = 0.018			p = 0.196			p = <0.001
0-3 MW + 0-11 years	33 (4.0)	141 (15.4)	3.81 (2.64-5.5)	67 (8.2)	214 (23.4)	2.86 (2.21-3.7)	203 (24.3)	349 (37.2)	1.53 (1.33-1.77)
0-3 MW + 12 or more years	16 (5.4)	57 (9.2)	1.72 (1.01-2.94)	23 (7.7)	89 (14.4)	1.87 (1.21-2.89)	68 (22.3)	125 (19.8)	0.89 (0.68-1.16)
>3 MW + 0-11 years	12 (5.3)	3 (9.7)	1.81 (0.54-6.07)	18 (8.0)	3 (9.7)	1.21 (0.38-3.87)	48 (21.1)	5 (16.1)	0.77 (0.33-1.78)
>3 MW + 12 or more years	11 (3.0)	10 (3.6)	1.2 (0.52-2.78)	14 (3.8)	21 (7.5)	1.98 (1.02-3.81)	50 (13.3)	32 (11.3)	0.85 (0.56-1.29)

CMD = Common mental disorder. GAD = Generalized anxiety disorder. MD = Major depression. MW = Minimum wage * N and percentage of men (M) and women (W) with each mental health outcome. ** Prevalence ratios represent the risk in women of having each mental disorder compared to men, for each category of individual income and schooling. P-values for Chi2 squared test of homogeneity of prevalence ratios using Mantel-Haenszel

4. Discussion

4.1. Main findings

We found that women have a higher prevalence of MD, GAD and CMD, compared to men, and that schooling and personal income at 30 years are mediators of these associations. In this southern Brazilian birth cohort, the pathway involving a higher schooling reduced the effect (total effect) of being a woman over the outcomes. This is to be expected since in the 1982 Pelotas birth cohort women have actually more years of schooling than men. Therefore, what naturally happens is that being a woman would increase the chances of having a higher level of schooling and therefore less chances of MD, GAD or CMD. If this was not to be the case and women had less education, the total effect of being a woman over mental health outcomes would had been even higher. On the contrary for income, even when women are more educated, they had a lower chance of earning more than 3 minimum salaries, and consequently a higher prevalence of MD, GAD and CMD. Around 1/6 of the total effect of being a woman over mental health was captured by the pathway of personal income at 30 years.

In addition, personal income and schooling, at 30 years, but not family income nor maternal schooling, were effect modifiers of the studied associations. Among individuals who earn > 3 minimum salaries and have 12 or more years of schooling women do not have a higher prevalence of MD or CMD. Therefore, it is not the socioeconomic position in which women are born but their schooling and personal income as adults what would determine their higher prevalence of depression.

In the presence of an interaction between exposure and mediator, we would expect a different effect of the exposure on the outcome at each level of the mediator. Therefore, the effect of an intervention might not be the same as what the natural pathway describes, since the NDE would be different than the CDE. When the mediators schooling and personal income were not allowed to vary according to the exposure (being a man or woman), but we fix them to having 12 or more years of schooling or earning more than 3 minimum salaries, we found that CDE, was considerably lower than the total effect. This suggests that if we were able to give this level of education or income to all individuals the higher prevalence, in women, of MD, GAD and CMD would be reduced significantly. Especially in the case of MD and GAD were the effect was reduced in less than half.

4.2. Comparison with the Literature

Studies had already reported that socioeconomic position could modify the association between sex and mental health outcomes. Most used traditional approaches and observed similar results to ours (Almeida-Filho et al., 2004; Alvarado et al., 2007; Kosidou et al., 2011; Leupp, 2017; Lucht et al., 2003; Nicholson et al., 2008; Ross and Mirowsky, 2006; Van de Velde et al., 2010). In a German sample, women reduced the likelihood of unipolar depression, compared to men, when they had 12 or more years of schooling (Lucht et al., 2003) and in US adults the gender gap in depression essentially disappears among individuals with a college degree or higher (Ross and Mirowsky, 2006). A population-based study in Stockholm found that a higher household income was protective of depression in women (Kosidou et al., 2011) and in the National Longitudinal Survey of Youth, 1979 Cohort, researchers found that paid working mothers were less likely of presenting depressive symptoms (Leupp, 2017). In a study from Russia, Poland and the Czech republic, researchers found that depression was largely influenced by current financial difficulties or less household belongings, rather than by early life disadvantages or education (Nicholson et al., 2008).

In Europe an analysis of 23 countries, prevalence of depression was higher among women, but there was significant cross-national variation in this gap. Gender differences in depression were larger in some of the Eastern and Southern European countries and smallest in Ireland, Slovakia and some Nordic countries. But in general, education and household income moderated the association between sex and depression (Van de Velde et al., 2010). In a population based Spanish study, however, researchers found that prevalence of depression in women, even when it was twice as high as in men, it was not moderate by education, employment of social class (Arias-de la Torre et al., 2018). Suggesting that in some contexts, social mediators and moderators could be different.

In Latin America, a collaborative study with samples from Argentina, Brazil, Chile, Cuba, Mexico and Uruguay, pointed out that the gender gap in depression observed among elders reflects gender-related disadvantages regarding their current perception and source of income, as well as the cumulative life course exposure to social and material disadvantage, like education and occupation (Alvarado et al., 2007). Another study from Brazil, in a highly unequal context, found that actually it is poor women, or in the working-class group, which are at a higher risk of having depression, and that women are protected by placement into the local dominant classes (Almeida-Filho et al., 2004).

As we see, most of the evidence seems to go in the same direction, suggesting and effect modification of socioeconomic variables over the association of sex with mental health outcomes, like depression and anxiety. However, measures of socioeconomic position differ between studies. Not all measure schooling and personal income, some evaluate working or occupation, household items, or even household income. Therefore, we should be cautious when comparing our results. In our study we preferred using personal income since it would be a better measure of not only socioeconomic position, but also the capacity of acquiring things through a compensation received from their own work, and not from others, like household income. It could even be a measure of empowerment, while schooling would be a measure of individual human capital. These variables are more likely to be a consequence of an individuals' sex, especially in a gender unequal context. Other variables like household income or belongings, could better reflect other aspects of the socioeconomic environment in which a person lives, and might not be a consequence of being a woman or man. Therefore, it is more plausible to use them as effect modifiers, rather than mediators.

Work or occupation could be a mediator of the association between schooling and personal income, and therefore part of its effect could be explained by the effect of personal income. However, empirical studies should formally evaluate its mediating effect since the confounding structure surrounding work or occupation could be different. Current evidence on the effect of work in the association between sex and mental health comes from studies in which they stratify the analysis by this possible mediator, therefore appropriate statistical tools for mediation need to be used in future studies.

In addition, some studies do not take into account socioeconomic position in childhood, which could be an important confounder in the association of current socioeconomic variables with mental health. Low socioeconomic position in childhood is associated to a higher risk of major depression in adults, and there is modest support for the hypothesis that it contributes to adult sex differences in depression (Elovainio et al., 2012; Gilman et al., 2002; Wirback et al., 2014). Some studies in adolescence and childhood, show that at that particular moment in life depressive symptomatology is associated with socioeconomic variables, and that these variables might explain the gap between boys and girls (Wirback et al., 2014). However, it seems that

the effect of childhood socioeconomic variables start to lose its effect through life (Elovainio et al., 2012), suggesting that the association might be between current socioeconomic variables and mental health. More distal socioeconomic factors could have an effect through stressful life events over mental health outcomes, but might not be enough to explain the gap between adult men and women (Alvarado et al., 2007).

We should acknowledge that our results suggest that a considerable part of the etiological effect of sex over mental health outcomes was not mediated by our socioeconomic variables. Gender roles, violence, stressful life events, and other social gender-related disparities seem to be plausible explanations for the sex-gap in mental health, not explained by the socioeconomic characteristics explored in this study. (Alvarado et al., 2007; Bhui, 2018; Howard et al., 2017; Kessler and Bromet, 2013; Kuehner, 2017; Piccinelli and Wilkinson, 2000)

On the other hand, some have proposed biological pathways as an explanation for the mental health sex-gap (Bhui, 2018; Kuehner, 2017; Piccinelli and Wilkinson, 2000). However, most of this evidence needs to be tested in further empirical studies.

The structure of depression symptomatology might also be different between men and women, and the latter might report more diagnostics symptoms, gender-related subtypes of depression are suggested to exist, and some have proposed that this could account for the different rates in men and women (Kuehner, 2017). However, this theory could be refuted by results of some empirical studies. In a population-based study of adults living in East Baltimore, researchers found that during the 13 years follow-up, men and women reported similar patterns of depressive symptoms (Bogner and Gallo, 2004). Others have found some differences in the patterns, but even when this might have some clinical implications, it does not seem to explain the gap in the diagnosis between men and women (Schuch et al., 2014).

There are also some studies and reports suggesting that there is a gender bias in the diagnoses or even treatment of depression and anxiety in clinical settings. However, all studies included in this section use standardized methods to measure these mental health variables, in both men and women, reducing the chances of this kind of bias.

4.3. Strengthens and limitations

We did not evaluate the effect of other socioeconomic variables in adulthood, like assets index, household income, or even working class. Even when these are variables which could modify the explored associations, we consider that contextual variables are not a consequence of being a man or a woman. Therefore, a mediation analysis would not have been adequate. In the case of working class, we could have included it in the explored pathways. However, this would imply a more complex model, with three mediators, in which a counterfactual approach is not suitable. Other statistical approaches, like structural equation modelling, are capable of handling several mediators. However, they do not take into account and explore the interaction between exposure and mediators, something that showed to be of great importance in our study. In addition, working class would be itself a mediator between schooling and income, in that sense we do not consider that not including it would have biased our results, since we took into account this pathway in our overall analysis.

Other possible confounders, like maternal depression or anxiety, associated with the mediators (personal income and schooling at 30 years) and mental health outcomes, were not available in our sample. However, it has been shown that socioeconomic characteristics are important predictors of depression and anxiety. Therefore, when adjusting by maternal income and schooling we are already taking into account some of the confounding effect of maternal mental health.

Other social variables like violence or discrimination could be risk

factors of our outcomes. However, in order to be considered confounders, they need to be risk factors also of our exposure or mediators. Since violence and discrimination could actually be a consequence of sex, schooling or income, we did not include them in our modeling since they would be mediators of their own pathways and not confounders of ours. This does not mean they are not important in the causal model explaining the mental health sex-gap and should be further explored in other studies.

We were not able to disentangle a probable bidirectional effect, because we did not have data from multiple time points to evaluate mental health. However, for this to discredit our results we would need to assume that the mental health sex-gap in youth had an effect on the socioeconomic characteristics of our sample in adulthood. Therefore, women should have a lower rate of schooling, but this is not the case. Women have a higher education, and if we assume that income is at least in part a consequence of schooling it is more plausible to think that current mental health outcomes are determined by socioeconomic position and not the other way around. Why women even with a higher education earn less is a question that should be answered in a separate analysis, but most likely we assume is not because of their mental health status but other determinants like gender role, violence and discrimination. We based our model on what most of the literature proposes as plausible, and our sample characteristics, that is that socioeconomic characteristics determine part of your chances of presenting depression, anxiety and common mental disorders.

We should also acknowledge our limitations in terms of measurement error. Mental health outcomes even when they were evaluated using the MINI we cannot assume that they are a diagnosis, and the SRQ-20 which explores common mental disorders is an screening tool. Similarly, measuring socioeconomic variables is always complicated, specially income, many people could be less prone to declare the real amount of money they earn. However, it is likely that these measurement errors were at random (not associated with our variables) or at least non-differential. If we assume the later, our total association measures could in fact be higher.

The attrition rate at the 30 years follow up was around 62%. Even when most cohorts in the world has normally lower attrition rates than ours after so many years, we should acknowledge that this could still affect our results because of a probable attrition bias. At the 30 years follow-up, attrition rates were better for women, and those with a family income at baseline of less than 3 minimum salaries or with a mother with less than 12 years of schooling (supplementary table 3). Given the fact that it is likely that at 30 years losses to follow-up were higher among those with a mental health condition, and in those earning more and with a better education, our estimates could be biased up to some degree. However, this is something that could always happen in any cohort, and what it is important is the degree at which this bias has affected our measures of association. Since our results are very similar to those reported in the literature around the world, we are confident that this probable bias effect did not make our results unreliable.

In terms of the specificity of our results, we should mention that in the whole sample, among those with MD, 52.8% had also GAD, and among those with GAD, the prevalence of MD was 33.0%. This shows that the comorbidity between these two conditions is fairly high. Therefore, even when we have reported specific measures for each pathway, separately, for each of these mental disorders, some overlapping might be occurring due to comorbidity. We could have further divided our sample in more specific groups (only MD, only GAD, MD +GAD), but this would have diminished our statistical power since groups would have been considerably smaller. Even when this limits our capacity of expressing specificity, it does not undermine the fact

that the reported associations exist and that each pathway captures part of the higher chance of presenting each of these mental disorders.

On the other hand, this study has many strengthens that should be acknowledge. None had ever studied how socioeconomic variables affect the association between sex and depression or anxiety using a counterfactual approach to explore their mediating effect. We have used a birth cohort study from a middle-income country. This cohort has an attrition rate at 30 years of almost 70%, something few have accomplished, which most likely reduced our chances of selection bias. In this follow-up we used a structured interview to assess MD and GAD in more than 3500 individuals using trained psychologist, reducing chances of measurement bias.

Using this mediation analysis approach, we are able to see how each pathway naturally contributes to the higher prevalence of depression and anxiety in women, therefore being able to describe etiological pathways and at the same time we took into account the fact that there is an interaction between sex and socioeconomic variables. We opted for a counterfactual approach for one main reason, the interaction between exposure and mediator. This is something a path analysis or a structural equation modeling approach cannot handle. They would give you the direct and indirect effect, which would be the equivalent of what we refer in the paper to NDE and NIE, but the CDE is something that only a counterfactual modeling can give you, and since in this case the interaction between sex and any of our mediators was so important we decided to use this approach.

Results from the traditional effect modification approach using M-H, were different to those from the g-computation, especially for GAD. Using the latter, we were able to see that personal income and schooling modify the effect of sex over GAD. Modelling using a counterfactual approach have many benefits, including the possibility of specifying a mediation model including interactions terms. In the traditional M-H approach the stratification is straightforward but would imply conditioning on the mediator using a model that would not decompose

appropriately the effect. This could have biased our results in the M-H analysis for GAD and that would explain the different results.

Another important strength of this study is that we evaluated socioeconomic characteristics at two important time points in life. Even when in our sample maternal schooling and income did not modify the effect of sex over mental health outcomes, we still include them as confounders in our analysis, since they could still confound the association between current socioeconomic characteristics and mental health. Therefore, we are confident that the mediating effects found here are not confounded by childhood socioeconomic characteristics, and less prone to be biased.

4.4. Conclusion and implications

Our results suggest that the mental health sex-gap was not attributable to early socioeconomic conditions but to current ones. In individuals with 12 or more years of schooling, the gap was smaller, suggesting that assuring a higher education to all might reduce the higher rates of MD, GAD and CMD in women, compared to men. On the other hand, earning more is a protective factor for the explored mental health outcomes, but since women earn less, even when they have a higher schooling, their chances of a poorer mental health were higher.

These all suggest that the social determinants of mental health are probably important contributors to the mental health sex-gap, and that assuring sex related social equity could reduce the mental health sex-gap. We have explored a small part of the complex social structure in which people live. However, it seems plausible to think that this structure contributes considerably to this gap. Future research should focus on exploring other social pathways leading women to a poorer mental health and clinicians should consider these determinants when dealing with women with one of these mental health conditions.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Where it can be found in our manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Final words of the Title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	First paragraphs of the Introduction section
Objectives	3	State specific objectives, including any prespecified hypotheses	Final paragraph of the Introduction section
Methods			
Study design	4	Present key elements of study design early in the paper	First sentence of the Materials and Methods section
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	First two paragraphs of the Materials and Methods section
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	From the 2nd to the 4th paragraphs of the Materials and Methods section
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	From the 2nd to the 4th paragraphs of the Materials and Methods section
Bias	9	Describe any efforts to address potential sources of bias	Throughout the Materials and Methods section
Study size	10	Explain how the study size was arrived at	First two paragraphs of the Materials and Methods section
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Final paragraphs of the Materials and Methods section
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Final paragraphs of the Materials and Methods section
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	

Results		Where it can be found in our	
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	First paragraph of the results section
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	No flow diagram was presented
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	First paragraph of the results section
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	2nd-4th paragraphs of the results section
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	First paragraph of the discussion section
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Subsection in the discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Main finding and conclusion section
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussed throughout the discussion section.
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Source was given at the submission

Authors' contributions

CLM, MXC, and BH, wrote the first version of the article. CLM and MXC conducted the analysis, BH and CLM supervised the writing and the analysis. HG, LQ, RP, JM collaborated on the interpretation and writing of the findings. All authors contributed and have approved the final manuscript.

Data availability

Data is not openly available but could be upon reasonable request to a data management committee.

Declaration of conflict of interest

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.05.033.

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