



Gender inequality and depression among medical students: A global meta-regression analysis



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ABSTRACT

Depression is a serious mental health problem with a high prevalence among medical students. It is unclear whether a gender disparity of depression exists in this population, and whether gender inequality influences depression estimates by gender. We conducted a systematic search for published systematic reviews or meta-analyses in six databases and primary studies were obtained from those records. Studies were included if they contained original data on the prevalence of depression among male and female medical students. The Gender Inequality Index (GII) and the Human Development Index (HDI) were obtained from the United Nations Development Programme website. A random effects meta-analysis of the odds ratio for depression between females and males was conducted. Meta-regression analyses were conducted to assess the association of GII and prevalence of depression. The HDI was later incorporated in a multivariable model. We included a total of 106 studies and 84,119 students from 32 different countries. Female medical students are at higher odds of depression (OR = 1.30, 95% CI 1.17–1.44, $p < 0.01$). A significant correlation was found between GII and prevalence of depression for female ($\beta = 0.24$, $p = 0.02$) medical students, but not for male medical students. This association remained significant after adjusting for HDI. The female gender was associated with higher prevalence of depression in this population. The gender disparity in depression may be explained by the effect of gender inequality.

1. Introduction

Depression is a common mental disorder (World Health Organization, 2017) characterized by the core symptoms of low mood and loss of interest or pleasure in one's daily activities (American Psychiatric Association, 2013). The course of illness is associated with higher rates of comorbid disorders, decreased functionality, recurrence of symptoms and suicide attempts (Global Burden of Disease Study, 2013 Collaborators, 2015; Hasin et al., 2018; Kessler et al., 2003).

Medical students exhibit higher prevalence of depression when compared to the general population (Dyrbye et al., 2014). Several individual studies indicate a markedly higher prevalence of depression among female medical students (Pacheco et al., 2017), suggesting this is a high-risk subgroup.

For most individuals, the period of studies in higher education is marked by the challenges and lifestyle changes involved in the transition to adulthood. Medical students face several additional stressors, such as lack of financial resources, moral abuse by classmates and

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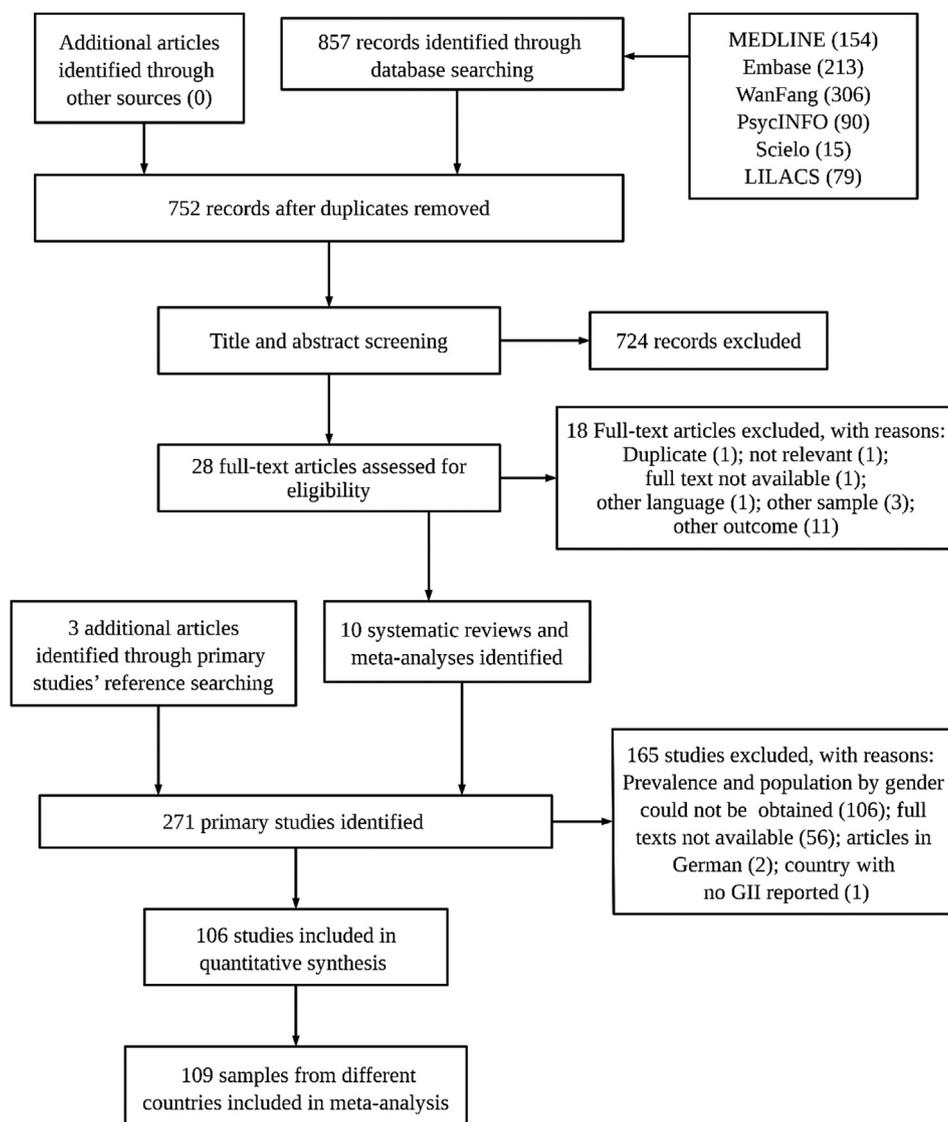


Fig. 1. Flow diagram of the process of study identification, screening and selection. After the identification of 10 systematic reviews and meta-analyses, primary studies were obtained from them and assessed for eligibility.

teachers, lack of time, high social pressure, fears, demands and insecurities regarding the medical profession (Tempski et al., 2012). This period of enormous pressure potentially leads to higher vulnerability to hazardous contexts of discrimination and socio-economic hardship experienced by the female gender, which is a potential explanation for the higher prevalence of depression among female medical students.

Gender, as socially constructed norms, behaviours and roles of women and men, are a basis for discrimination in many societies (World Health Organization, 2002). Patterns of social division based on gender ranges from cruel forms, in which the female gender is exposed to rape, domestic violence and genital mutilation to other less overt forms of discrimination, such as differences in earnings, access to health resources, education and political power (Doyal, 2000; World Health Organization, 2010). The negative consequences of discrimination by gender can be measured and compared between countries. Tools such as the Gender Inequality Index (GII) are able to translate issues regarding inequities in empowerment, economic status and reproductive health. However, little is known about the effect of gender inequality on the mental health of women. Additionally, a direct influence of GII on the prevalence of depression among women is still inconsistent. In a global study, Yu (2018) observed that in regions of the world with higher GII, female to male ratios of depression tend to increase.

However, depression estimates by gender subgroups did not reach statistical significance.

As previously mentioned, the stress and time pressure experienced during medical training might act as a catalyst of the additional burdens women are confronted with, potentially leading to poorer mental health. The literature suggests female physicians face significantly higher career obstacles when compared to their male counterparts (Arrizabalaga et al., 2015; Bates et al., 2016). There appears to exist a pattern of unprivileged positions for women doctors in research (Eloy et al., 2013; Fridner et al., 2015), surgical specialties (Bucknor et al., 2018), leadership roles (Kværner et al., 1999) and primary care (Delgado et al., 2011). This trend, combined with other stressors (Babaria et al., 2009) such as harassment, coercive sexual advances, moral abuse, cynicism and sexist comments, are potential drivers of depression vulnerability for females in medical schools. However, an investigation of the relationship between gender inequality at a societal level (as opposed to the individual level) and depression still lacks in the literature for this high-risk population. This study focuses on capturing the impact of harmful social patterns of discrimination on the mental health of future doctors, thus providing a basis for intervention and monitoring in public policy. Understanding the pathways involved in this relationship may lead to greater quality of life for female medical

students and doctors.

Contrasting the findings of studies conducted in the general population (Andrade et al., 2012; Hasin et al., 2018), recent meta-analyses have found a non-significant difference in the prevalence of depression between genders among medical students (Pacheco et al., 2017; Puthran et al., 2016; Rotenstein et al., 2016). We further investigate these findings in the present study, as confusion on whether a gender difference exists may delay interventions aimed at this issue.

The present study aims at (a) determining whether there is a difference in depression estimates between male and female medical students and (b) investigating the role of gender inequality in the prevalence of depression among male and female medical students worldwide. We hypothesized female medical students would be at higher odds of depression, and that higher gender inequality at the country-level would be associated with greater prevalence of depression among female medical students. To test a potential confounding between issues of gender with general socio-economic hardships, we also assessed the influence of another a widely used estimate, the Human Development Index.

2. Material and methods

We used the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement (Stroup et al., 2000) to guide the reporting of the present study.

2.1. Searches and study selection

In recent years, a significant number of systematic reviews and meta-analyses were published on the topic of depression among medical students. Hence, the authors expected to obtain a comprehensive set of primary studies by searching review-type studies. In this sense, the selection of studies involved two steps: (a) literature search for systematic reviews and meta-analyses on the topic and (b) identification of primary studies included in the studies from the first step. The process of selection of studies is shown in Fig. 1.

A similar search strategy (described in the Supplementary Data 1) was developed for MEDLINE, EMBASE, PsycINFO, WanFang, Scielo and LILACS. This search strategy was also used for the development of an overview of systematic reviews on depression among medical students (Tam et al., 2018). The databases were searched from inception with no language restrictions.

On 13 March 2018, WT searched MEDLINE, EMBASE and PsycINFO, and duplicates were removed via the Ovid platform. In the same week, KL searched the Chinese database WanFang. WT and KL independently screened titles and abstracts for the studies obtained from these data sets. On 13 March 2018, JP searched Scielo and LILACS for studies from Latin America and Africa. Results from Scielo and LILACS were then screened. Full texts of studies were then evaluated by any two of the three (WT, KL or JP). In this first step, studies were included if (a) they were systematic reviews of meta-analyses that (b) reported the prevalence of depression among medical students. Studies were excluded when the language of publication was other than English, Spanish, Portuguese or Chinese.

The systematic reviews and meta-analyses that were identified were then explored for primary studies. The references of the included primary studies were also assessed for further material. These records were assessed for eligibility according to the criteria described in the next section.

2.2. Inclusion and exclusion criteria

We included studies if they (a) evaluated medical students; (b) were primary and observational; (c) reported the prevalence and the population by gender (male and female).

We excluded studies if (a) the authors were not able to translate the

full text; (b) the country where the study was conducted had no GII report available; (c) full text was not available after internet search; (d) population and prevalence for males or females could not be obtained after e-mail request. We requested essential missing data (such as total number and depression cases in male and female subgroups) via-email from the corresponding author of each study. A minimum period of 4 weeks was given for an initial response.

2.3. Data extraction and collection of additional data

Two authors (JBS and RF) independently extracted the following data from each included study: (a) year of publication; (b) overall sample size; (c) overall prevalence; (d) country where study was conducted; (e) male sample size; (f) female sample size; (g) male number of depression cases; (h) female number of depression cases; (i) mean age; (j) study design. Number of cases were inferred from the prevalence when they were not clearly reported.

To assess gender inequality, the GII was obtained from the Human Development Reports' website (<http://hdr.undp.org/en/data>) for the countries where the included studies were conducted. The GII is a country-level variable that is intended to be a measure of the loss in potential human development because of the discrepancy in empowerment and economic status between males and females and the countries' situation regarding women's reproductive health (United Nations Development Programme, 2016a). The index ranges from 0 to 1, with higher values representing higher inequalities. The details on calculating GII are explained in the 2016 HDR's technical notes (United Nations Development Programme, 2016b).

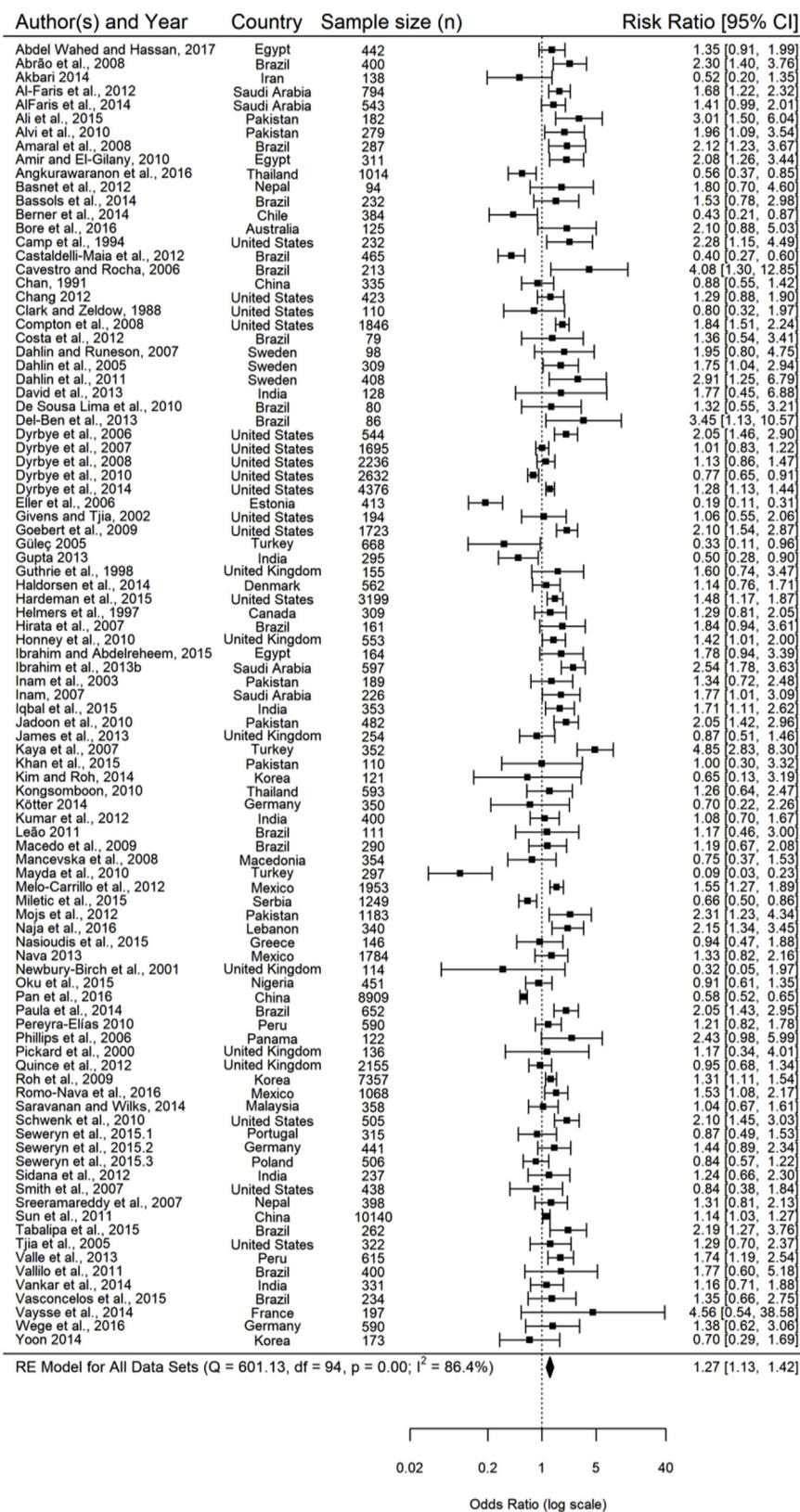
Although issued in 2010, the GII was available for the following years: 1995, 2000, 2005, 2010, 2011, 2012, 2013, 2014 and 2015. This is possible because the index relies on international, publicly available databases. Thus, the year of publication of each primary study was considered for the extraction of GII. When GII was not reported for a specific year, the closest date was chosen. Only one study was excluded because its respective country (Nigeria) had no GII data available. When multiple countries were assessed in a single study, GII was recorded for each individual country and study subset. We also obtained the Human Development Index (HDI) for each country from the HDR's website. This index also ranges from 0 to 1, with higher values representing higher human development. As the HDI is available for every year since 1990, the exact year of publication for each study was considered for collection.

2.4. Risk of bias assessment

Two authors (JBS and RF) independently assessed each included study using the risk of bias assessment tool developed by Hoy et al. (2012). The chance-adjusted agreement between two raters (kappa statistic) for this assessment was 0.94. This tool consists of 10 items comprising the assessment of internal and external validity. The largest proportion of disagreements were about studies' external validity. Specifically, on whether the sampling frame was a true representation of the target population (second item of the tool) and whether some form of random selection was used (third item). We used this tool because of its ease of use and high inter-rater agreement (Hoy et al., 2012; Munn et al., 2014). The two authors resolved disagreements with the first author (JP) and the ratings were used to generate a risk-of-bias index that later integrated the meta-regression analysis.

2.5. Statistical analysis

We pooled the prevalence overall and by subgroups of gender using a random-effects model. To test whether the estimates by gender were different, we conducted a meta-regression including all studies using gender as dichotomous moderator. We reported the results by describing the aggregate prevalence, corresponding p-value and the 95%



Legend: Each square represents the odds ratio for each contributing data set (n = 92). Horizontal lines indicate 95% confidence intervals (95% CI).

Fig. 2. Forest plot of the meta-analysis of the female-male odds ratio of the prevalence of depression among medical students. Legend: Each square represents the odds ratio for each contributing data set (n = 92). Horizontal lines indicate 95% confidence intervals (95% CI).

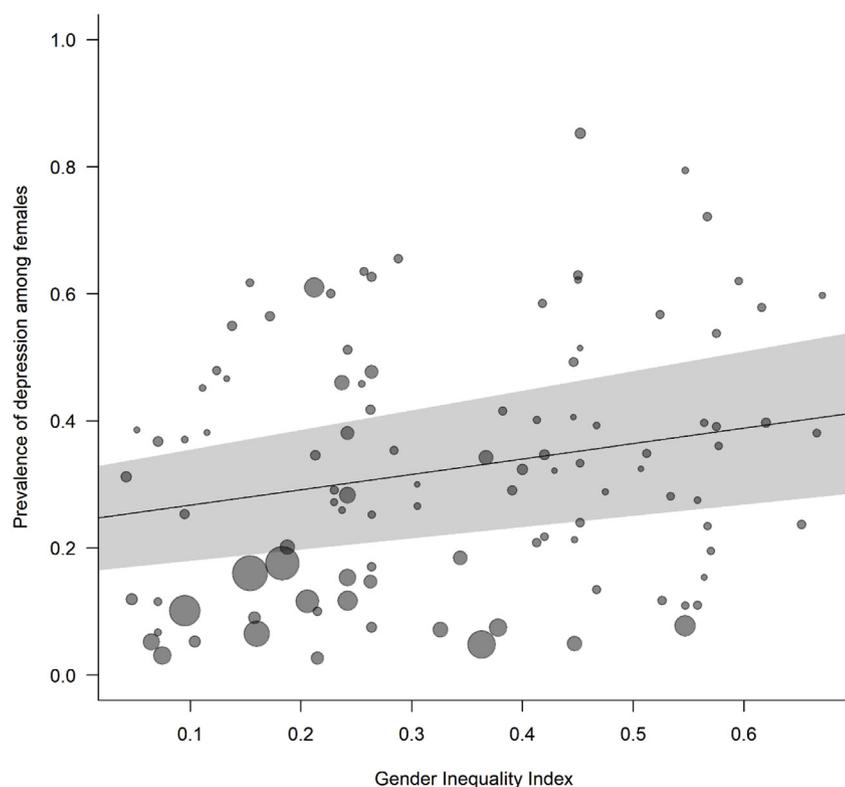


Fig. 3. Meta-regression of the prevalence of depression among female medical students and Gender Inequality Index for the year and country where studies were conducted. Scatter plot, regression line and confidence intervals are depicted. Each circle indicates a data set (103 data sets), with larger circles representing larger sample sizes.

Legend: $R^2 = 3.97\%$, $\beta = 0.24$, $z = 2.22$, $p = 0.02$.

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confidence interval. We assessed heterogeneity using I^2 statistic. When above 75%, heterogeneity was considered high (Higgins et al., 2003). The I^2 statistic represents the proportion of variability in the results due to heterogeneity rather than sampling error (Higgins and Thompson, 2002).

We also assessed the association of gender and depression by calculating the odds ratio of depression when prevalence for both subgroups was reported in the included studies. We conducted a random-effects meta-analysis, and reported the results by describing the pooled odds ratio (female vs. male), confidence intervals, corresponding p-value and I^2 value. Evidence of publication bias was assessed using the Egger's test.

To assess an expected correlation between gender inequality and human development, we examined the association between countries' GII and HDI for the included studies using Pearson's correlation coefficient (r).

We conducted meta-regression analyses using the prevalence of depression as dependent variable. This was done for medical students overall and for males and females separately. We reported the results using the coefficient of determination (R^2), the standardized coefficient (β), p-value and the z-statistic. For the simple meta-regression of country-level indices, we assessed GII and HDI. These independent variables were then included in the multiple meta-regression model. To assess whether the risk of bias of the studies would potentially interfere with the results, we conducted simple meta-regression by a risk-of-bias index ranging from 0 to 1 derived from the previously mentioned risk-of-bias assessment tool.

Sensitivity analysis is the process of testing if the statistical model is sensitive to different ways of estimating the same outcome (The Cochrane Collaboration, 2011). We understood it would be desirable to test whether the results were influenced by studies in which a single subgroup of gender was assessed (males or females). Hence, we conducted a sensitivity analysis of the multivariable model by excluding

studies in which a single subgroup of gender was reported. We assessed publication bias using Egger's test and visual inspection of funnel plots for all prevalence estimates and the odds ratio meta-analysis. All the statistical analyses were conducted in R software version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) using the 'metafor' package. We considered a significance threshold of $p < 0.05$ for all statistical tests.

3. Results

The database search yielded 10 systematic reviews or meta-analyses (Bacchi and Licinio, 2015; Coentre and Figueira, 2015; Cuttilan et al., 2016; Dyrbye et al., 2006; Gong et al., 2016; Hope and Henderson, 2014; Lei et al., 2016; Pacheco et al., 2017; Puthran et al., 2016; Rotenstein et al., 2016), from which 268 records were assessed against the inclusion and exclusion criteria (see Fig. 1). We included 106 studies in the quantitative synthesis, involving a total of 84,119 medical students. From those, two studies (see Supplementary Table 1) were further stratified into two and three different sets of students, because different countries were assessed within them. Selected characteristics of the included studies are provided in Supplementary Table 1. Regarding gender subgroups, 95 studies (98 sets, $n = 39,702$) have reported information on male students and 101 (103 sets, $n = 44,417$) on females.

Our study incorporates data from 32 different countries. Considering the included studies and respective years, GII ranges from 0.042 (Denmark, 2014) to 0.671 (Saudi Arabia, 2007), with an average value of 0.344 ($n = 109$ sets, $SD = 0.176$). The value of HDI ranges from 0.473 (Pakistan, 2003) to 0.938 (Australia, 2016), with an average value of 0.779 ($n = 109$ sets, $SD = 0.124$). The GII and HDI show a strong and significant negative correlation ($r = -0.767$, $p < 0.01$). Subgroup analyses show no difference (meta-regression $p = 0.05$) in the prevalence of depression between males (27.21%, 95% CI

23.50–30.92, $p < 0.01$, $I^2 = 99.14\%$) and females (32.46%, 95% CI 28.67–36.24, $p < 0.01$, $I^2 = 99.17\%$). However, the meta-analysis of the odds ratio ($n = 92$ sets) yields significant results (Fig. 2), with a pooled odds ratio of 1.30 (95% CI 1.17–1.44, $p < 0.01$, $I^2 = 83.31\%$).

3.1. Meta-regression analyses

For the univariate meta-regression analyses, GII is a significant moderator for depression among female medical students ($R^2 = 3.97\%$, $\beta = 0.24$, $z = 2.22$, $p = 0.02$). The scatter plot depicting this relationship is shown in Fig. 3. However, GII is not a significant moderator for depression neither overall ($p = 0.10$) nor for the male gender ($p = 0.07$).

Alone, HDI is not a significant moderator of depression among medical students neither among gender subgroups (male $p = 0.17$, female $p = 0.23$) nor overall ($p = 0.31$).

For the meta-regression analyses with GII and HDI as moderators, GII is still significant for depression among females ($R^2 = 3.89\%$, $\beta = 0.37$, $z = 2.07$, $p = 0.03$). Neither GII nor HDI are significant moderators for depression overall or among male medical students.

3.2. Sensitivity analysis

For the sensitivity analysis, we excluded studies which reported the prevalence for males ($n = 5$) or females ($n = 10$) only, thus keeping 92 sets of data in the final list. In this model, GII shows a significant correlation with the prevalence of depression overall ($R^2 = 4.29\%$, $\beta = 0.24$, $z = 2.22$, $p = 0.02$) and in the female subgroup ($R^2 = 6.17\%$, $\beta = 0.30$, $z = 2.59$, $p < 0.01$), but not in the male subgroup ($p = 0.05$).

The results of the multiple meta-regression model with GII and HDI yields significant results only for GII as a moderator of depression among females ($R^2 = 5.83\%$, $\beta = 0.42$, $z = 2.16$, $p = 0.03$), but not for males or medical students overall.

3.3. Assessment of studies' risk of bias and publication bias

The risk-of-bias scores range from 6 to 10, with a mode of 8. Meta-regression analyses using a risk-of-bias index of the studies as a moderator does not yield significant results, neither for depression overall ($p = 0.09$) nor for male ($p = 0.19$) or female ($p = 0.12$) students.

There is evidence of publication bias for studies reporting on depression overall, and among female and male medical students ($p < 0.01$). Visual inspection of the respective funnel plots reveals significant asymmetry, indicating that smaller studies tend to report larger depression estimates, and that results from smaller studies present more variability. There is no evidence of publication bias ($p = 0.81$) for the female-male odds ratio meta-analysis and its respective funnel plot reveals no significant asymmetry. All funnel plots are depicted in Supplementary Figs. 1–4.

4. Discussion

The results from the present study suggest country-level gender inequality negatively affects the mental health of female medical students. The meta-regression analysis shows that, as gender inequality increases, higher prevalence of depression is found among female medical students. The GII derives from aspects of society where women are negatively affected in terms of health, labour and political influence. The HDI was initially included in the model to control for the potential effect of general socio-economic factors (such as life expectancy, education and income), leaving aside gender issues. When HDI is added to the statistical model, the effect of GII increases, as shown by the change in the standardized coefficient (β) from 0.24 to 0.37. As HDI shows a high correlation with GII, the results highlight that inequality between genders alone is a potential macro-determinant

of depression among medical students.

To our knowledge, this is the first study to assess the effect of national-level gender inequality on depression among university students, thus supporting the evidence of a correlation between social factors and depression at a macro-social level. Potential explanations for this interplay might be found among factors associated with depression that also show gender-specific aspects. These might include, as a short illustration, early adverse experiences, endocrine stress reactivity, genetic effects, economic status and working hour differences (Kuehner, 2003; Wada et al., 2013; Wittenborn et al., 2016) between men and women.

Our study indicates a differential influence of GII for the genders. In contrast, when subgroups of gender were analysed elsewhere (Yu, 2018), no direct associations were found between gender inequality and depression rates. In this sense, the interaction of issues particular to university students could potentially explain an increased vulnerability to gender-specific stressors and associated mental disorders in this population.

The subgroup analyses by gender are in line with the findings from previous studies (Pacheco et al., 2017; Puthran et al., 2016; Rotenstein et al., 2016), with no difference in the prevalence of depression between male and female medical students. However, our additional analysis shows female medical students to be at higher odds of depression (OR = 1.30, 95% CI 1.17–1.44, $p < 0.01$). Subgroup analyses assume the pooled estimates are from different studies, even when studies report results for both males and females. In the scenario of high heterogeneity between studies, this might have led to a masking of the difference between genders in the current and in previous subgroup analyses (Puthran et al., 2016; Rotenstein et al., 2016). Although prevalence is similar in both male and female students, different mechanisms might be driving vulnerability to depression. Further studies should evaluate macro-social aspects implicated in the mental health of male students, as the present analysis did not capture this subgroup.

In the present study, the GII was able to translate gender differences (biological, social, economic, genetic) into a sensitive measure of the gender gap of depression. Although currently no country has achieved perfect equality between genders (United Nations Development Programme, 2016a), our results suggest the cause of the gender gap of depression might rely on gender differences itself rather than more complex mechanisms.

4.1. Strengths and limitations

The strengths of this study lies mainly on the inclusion of an extensive number of studies on the topic and the appraisal of internationally comparable indices. We believe the inclusion of 106 studies comprising students from countries with different levels of gender inequality and human development greatly improved the significance of our findings.

This study has important limitations. The main caution that should be taken is that as GII and HDI are calculated as country-level variables, the correlations with depression should not be sought at an individual level. This is typically described as ecological bias (Greenland and Morgenstern, 1989). Considering the variables that compose the indices constitute mainly of social factors, decision-makers might be inclined to deduce the correlations with depression are due to social factors alone, however other biological and psychological factors should be investigated before moving closer to this type of inference.

Regarding the prevalence of depression among medical students, significant evidence of publication bias was detected, which might have influenced the results of the meta-regression analysis. Current approaches, such as the trim and fill method, perform poorly in adjusting for publication bias when high heterogeneity exists (Peters et al., 2007). Additionally, this method does not allow for the inclusion of moderators, such as the GII and HDI. A lack of measurement equivalence of depression between genders might have affected the results of the

present meta-analyses. This issue is common among self-report measures (Rose et al., 2015), in which the present meta-analysis mainly relied on. To overcome these issues, a large, multinational study using a single measure of depression should be considered for future investigations.

High and unexplained heterogeneity existed among studies. Possible causes of this phenomenon are the use of different study designs, environments, measuring tools, cut-off values, as well as individual differences. In a previous meta-analysis, we found risk of bias was a potential reason for inter-study differences (Pacheco et al., 2017). However, in the present analysis, our risk-of-bias index was not a significant moderator.

4.2. Implications

The present study found a significant association between country-level GII and prevalence of depression among female medical students, which remained significant after adjusting for HDI. Our study highlights the need for efforts to reduce gender inequality globally. Further studies should investigate the impact of policies on the prevalence of depression and on other mental health estimates. In the specific case of medical schools, interventions to minimize the effect of gender inequality are required to mitigate against the mental health vulnerability of students, especially in countries where gender inequality is higher.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jpsychires.2019.01.013>.

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