Manuscript word count = 3,750

Abstract (248/250)

Tables 2

Figures 2

Depression and severe pain:

Primary data and meta-analysis among 237,952 people across 47 low- and middle-income countries

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Funding – This paper received no specific grant of direct funding.

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Background

Depression and pain are leading causes of global disability. Despite this, there is a paucity of multinational population data assessing the association between depression and pain, particularly among low- and middle-income countries (LMICs). Therefore, we investigated this association across 47 LMICs.

Methods

Community-based data on 273,952 individuals from 47 LMICs recruited via the World Health Survey were analyzed. Multivariable logistic and linear regression analysis were performed to assess the association between past-12 month ICD-10 depression/depression subtypes and pain in the previous 30 days. Country wide meta-analysis adjusting for age and ex was also conducted.

Results

The prevalence of severe pain was 8.0%, 28.2%, 20.2%, and 34.0% for no depression, subsyndromal depression, brief depressive episode and depressive episode respectively. Logistic regression adjusted for socio-demographic variables, anxiety and chronic conditions demonstrated that compare to no depression, those with subsyndromal depression, brief depressive episode, and depressive episode were associated with a 2.16 (95%CI=1.83-2.55), 1.45 (95%CI=1.22-1.73), and 2.11 (95%CI=1.87-2.39) increase in odds of severe pain respectively. Similar results were obtained when a continuous pain scale was used as the outcome. Depression was significantly associated with severe pain in 44/47 countries with a pooled OR of 3.93 (95%CI=3.54-4.37).

Conclusion

Depression and severe pain are highly comorbid across LMICs, independent of anxiety and chronic conditions. Individuals with pain or depression should be systematically considered at risk for depression-pain comorbidity. Whether depression treatment or pain management in patients with comorbid pain and depression leads to better clinical outcome is an area for future research.

Key words: Depression, pain, depressive symptoms, comorbidity,

Introduction

Depression is estimated to affect 350 million people worldwide and is a leading cause of global disability (Ferrari *et al*., 2013). A confirmed diagnosis of major depressive disorder (MDD) accounts for 8.2% of the total worldwide years lived with disability (YLDs) (Ferrari *et al*., 2013). There is increasing recognition that depression lies on a continuum, with subsyndromal depression and brief depressive episodes also being relatively common and associated with poor health (Ayuso-Mateos *et al*., 2010). Within the past decade, there has been an increasing emphasis on the physical health challenges of people with depression (Henningsen *et al*., 2003).

Pain is also highly prevalent (Breivik *et al*., 2006) and a leading cause of global burden and YLD (Murray *et al*., 2012). The management of pain is associated with considerable financial burden (Breivik *et al*., 2013). A previous systematic review over a decade ago demonstrated that pain and depression are highly comorbid and associated with worse outcomes compared to when each condition exists on its own (Bair *et al*., 2003). Moreover, comorbid pain and depression are related to increased costs and burden on healthcare services (Rayner *et al*., 2016). Therefore, understanding the pain and depression relationship has important health and economic consequences.

To date, most of the research investigating the pain and depression relationship has focused on the Western world. For instance, in a large representative study conducted in the United Kingdom, Nicholl et al (Nicholl *et al*., 2014) found that depression was associated with increased odds of pain. Pain is also common in low- and middle-income countries (LMICs) and is in particular related to trauma, cancer, birth complications, congenital defects, and surgical complications, all potentially leading to chronic pain if not treated or if treated inadequately(Jackson *et al*., 2015, Jackson *et al*.,

2016). There is a however a distinct paucity of representative population cohort studies investigating associations between depression and pain in LMICs. Such data would be valuable as depression is highly pervasive among people in LMICs (Andreasen *et al*., 2014, Guerra *et al*., 2016, Prina *et al*., 2011). To date, three large-scale studies have investigated pain and depression comorbidity across multiple countries including a small number of LMICs (Demyttenaere *et al*., 2007, Gureje *et al*., 2008, Tsang *et al*., 2008). These studies found that across 18 countries (8 in LMICs), people with multisite pain (Gureje *et al*., 2008) and chronic pain (Tsang *et al*., 2008) are at increased risk of mood disorders. Moreover, chronic neck and back pain is associated with an increased odds of mood disorder (Demyttenaere *et al*., 2007). Whilst helpful and clearly advancing the field, the lack of focus specifically on LMICs does not make the results generalizable to this region (only 8 countries were considered), nor give sufficient coverage and attention to this neglected phenomenon. A number of pertinent questions also remain unanswered. First, it remains unclear if the relationship between pain and depression is influenced across the spectrum from brief depressive episode, subsyndromal depression and depression. Second, the relationship between the most severe pain and the depression spectrum is unclear. Finally, many LMICs do not have data on the pain and depression comorbidity.

Thus, the aims of the current study were to:1) explore the relationship between severe pain and subsyndromal depression, brief depressive episode and a depressive episode across 47 LMICs; 2) Investigate the factors that might influence the pain and depression relationship; and 3) conduct a country wide meta-analysis to explore if pain and depression comorbidity is significantly increased across all 47 countries.

Methods

The survey

The current paper utilized data from the World Health Survey (WHS), a cross-sectional study undertaken in 2002-2004 in 70 countries worldwide. Data were collected using single-stage random sampling and stratified multi-stage random cluster sampling across 10 and 60 countries respectively. Full details of the WHS are freely available elsewhere (http://www.who.int/healthinfo/survey/en/). Briefly, persons aged ≥18 years with a valid home address were eligible to participate. Each member of the household had equal probability of being selected by utilizing Kish tables. A standardized questionnaire, translated accordingly was used across all countries. Linguists were utilized to ensure that the translation was conducted to a high standard.

The individual response rate (i.e. ratio of completed interviews among selected respondents after excluding ineligible respondents from the denominator) ranged from 63% (Israel) to 99% (Philippines) (Moussavi *et al*., 2007). In order to conduct the study, ethical approval was obtained from the ethical boards at each study site. Sampling weights were generated to adjust for non-response and the population distribution reported by the United Nations Statistical Division. Informed consent was obtained from all participants.

Of the 70 countries, 69 had data which is publicly available. Of these, 10 countries (Austria, Belgium, Denmark, Germany, Greece, Guatemala, Italy, Netherlands, Slovenia, and UK) were excluded due to lack of data on sampling information. Furthermore, 10 high-income countries (Finland, France, Ireland, Israel, Luxembourg, Norway, Portugal, Spain, Sweden, United Arab Emirates) were excluded in order to

focus on LMICs. Moreover, Turkey and Morocco were also excluded due to missing information on some of the variables of interest. Thus, the final sample consisted of 47 countries which corresponded to 21 low-income and 26 middle-income countries according to the World Bank classification (http://chartsbin.com/view/2438) at the time of the survey (2003). The data were nationally representative in all countries with the exception of China, Comoros, the Republic of Congo, Ivory Coast, India, and Russia.

Variables

Pain (outcome variable)

Pain was assessed in two ways. Participants were asked "Overall in the last 30 days, how much bodily aches or pains did you have?" with answer options none, mild, moderate, severe, and extreme. In line with a previous publication using the same dataset (Koyanagi and Stickley, 2015), those who answered severe or extreme were considered to have severe pain. Second, another pain measure was constructed with the use of the above-mentioned question "In the last 30 days, how much bodily discomfort did you have?" which also had the same response options. A factor analysis with polychoric correlations was used in order to obtain a factor score which was converted into a scale ranging from 0 to 100 with higher scores corresponding to higher levels of pain/discomfort. This pain score has been used in previous WHS publications (Koyanagi *et al*., 2016, Nuevo *et al*., 2013).

Depression (exposure variable)

Depressive symptoms were classified based on individual questions from the WHS version of the World Health Organization World Mental Health Composite International Diagnostic Interviewwhich captures the duration and persistence of

depressive symptoms in the preceding 12 months (Kessler and Ustun, 2004). A similar algorithm was utilized based on previously published papers from the WHS (Ayuso-Mateos *et al*., 2010),which includes four mutually exclusive groups based on the ICD-10 Diagnostic Criteria for Research (ICD-10-DCR) (World Health Organization, 1993)where criterion B referred to symptoms of depressed mood, loss of interest, and fatigability. The algorithms used to define the four groups were the following: (a) Depressive episode group: At least two criterion B symptoms with a total of at least four depressive symptoms lasting two weeks most of the day or all of the day. (b) Brief depressive episode group: Same criteria as depressive episode but did not meet the two-week duration criterion. (c) Subsyndromal depression: At least one criterion B symptom with the total number of symptoms being three or less, lasting two weeks most of the day or all of the day The criteria of duration of at least two weeks and presence of symptoms during most of the day had to be met. (d) No depressive disorder group: None of the above. Within the results, any depression refers to depressive episode, brief depressive episode or subsyndromal depression.

Other variables

A range of other sociodemographic information was captured including sex, age, education, and wealth. For the current paper, education was categorized as: no formal education, primary education, secondary or high school completed, or tertiary education completed. Principal component analysis based on 15-20 assets was conducted to establish country-wise wealth quintiles. Anxiety was assessed by the question "Overall in the past 30 days, how much of a problem did you have with worry or anxiety?". Those who answered severe or extreme were considered to have anxiety, in accordance with previous publications(Koyanagi *et al*., 2016, Wong *et al*., 2013). We also

considered other physical health diagnoses known to be associated with pain and depression including arthritis, asthma, and diabetes, all of which were based on self-reported lifetime diagnosis. For angina, in addition to a self-reported diagnosis, a symptom-based diagnosis based on the Rose questionnaire was also used (Rose, 1962).

Statistical analysis

The statistical analysis was performed with Stata 14.1 (Stata Corp LP, College station, Texas). The difference in sample characteristics between those with and without severe pain was tested by Chi-squared tests. We assessed the association between depression and pain in two ways. First, we conducted multivariable binary logistic regression analysis which used the dichotomous severe pain variable as the outcome. Second, multivariable linear regression analysis with the continuous pain score as the outcome was also performed. The former analysis was intended to assess specific associations with extreme levels of pain for its clinical relevance, whereas the latter was intended to capture increasing levels of pain associated with depression while using a combined measure of pain and discomfort. We conducted hierarchical analysis based on wider literature to assess how the inclusion of different control variables affected the coefficient of depression. Three models were constructed: Model 1 - adjusted for socio-demographics (sex, age, education, wealth) and country; Model 2 - adjusted for socio-demographics, anxiety, and country; and Model 3 - adjusted for socio-demographics, anxiety, chronic physical conditions (arthritis, diabetes, angina, asthma), and country. Specifically each of the variables were chosen based on past literature due to their relationship with pain and/ or depression (Bair *et al*., 2003, Rayner *et al*., 2016).To adjust for country, dummy variables for each country were included in the models, following the methods used in previous WHS publications (Koyanagi *et al*., 2016,

Nuevo *et al*., 2012). We also conducted country-wide logistic regression analysis to assess the association between depression and severe pain while adjusting for sex and age. A pooled estimate was obtained by combining the estimates for each country into a random-effect meta-analysis. This was done to evaluate the generalizability of our findings across countries. The sample weighting and the complex study design were taken into account in all analyses. Results from the logistic and linear regression models are presented as odds ratios (ORs) and regression coefficients (Bs) respectively, with 95% confidence intervals (CIs). The level of statistical significance was set at $p<0.05$.

Results

Prevalence of depression and pain

The final sample size was 237,952 with a mean age of 38.4 years of whom 49.2% were male. The prevalence of subsyndromal depression, brief depressive episode, and depressive episode were 2.5%, 2.7%, and 6.5% respectively. The prevalence of severe pain across the entire sample was 10.7%. The mean (SD) pain scores were 23.3 (26.0), 43.0 (26.2), 41.7 (26.8), and 49.9 (26.2) for no depression, subsyndromal depression, brief depressive episode, and depressive episode respectively, while the prevalence of severe pain for these four conditions were 8.0%, 28.2%, 20.2%, and 34.0% respectively.

Regression analyses

A linear increase in the prevalence of all types of depression was observed with increasing pain scores, with the increment of depressive episode being most pronounced (**Figure 1**). The sample characteristics are illustrated in **Table 1**.

Table 1 here

Figure 1 here

Female sex, older age, lower levels of education and wealth, anxiety, arthritis, diabetes, angina, and asthma were significantly associated with higher prevalence of severe pain. The association between different types of depression and pain are illustrated in **Table 2** and **Table 3**. In the logistic regression model, compared to those with no depression, depression was associated with 2.80 (subsyndromal depression) to 4.01 (depressive episode) times higher odds for severe pain after adjustment for socio-demographics (Table 2, Model 1). When anxiety was included in the model, a moderate attenuation in the ORs were observed (Table 2, Model 2) while further adjustment for chronic conditions lead to a further albeit less pronounced attenuation in the ORs with the ORs

(95%CIs) for subsyndromal depression, brief depressive episode, and depressive episode being 2.16 (1.83-2.55), 1.45 (1.22-1.73), and 2.11 (1.87-2.39) respectively in the fully adjusted model (Table 2, Model 3). Similar declines in the coefficients of depression were observed in the linear regression model across Model 1 and 3 (Table 3). Compared to those with no depression, the b-coefficient (95%CI) for subsyndromal depression, brief depressive episode, and depressive episode were 11.15 (9.62-12.68), 9.52 (8.17-10.87), and 12.52 (11.24-13.80) respectively in the fully adjusted model (Table 3, Model 3). These coefficients can be interpreted as the mean increase in the pain score (range 0-100) for that depression category when compared to those with no depression.

Table 2 here

Table 3 here

Country wide meta-analysis of depression and pain association

Finally, the results of the country-wise association between any depression and severe pain estimated by logistic regression are illustrated in **Figure 2**. The pooled OR across 47 countries adjusted for age and sex demonstrated that depression was associated with a nearly 4 fourfold increase in odds (OR 3.93 (3.54-4.37) of severe pain. Across the 47 countries, 44 demonstrated statistically significant increased odds of depression and pain. Particularly high odds ratios were observed in China (OR 13.94), Malaysia (OR 10.33), Mauritania (OR 7.12), Maturitas (OR 6.82), Philippines (OR 6.73) and Laos (OR 6.34).

Figure 2 here

Discussion

General findings

The current study found that pain and depression are strongly associated across 44/47 LMICs. Our results provide the first evidence that depression is more strongly associated with pain, than among people with subsyndromal and brief episode of depression in LMICs. Anxiety and chronic conditions were influential factors in the association between pain and depression but did not fully explain or ameliorate the association. Our country wide meta-analysis demonstrates that pain is associated with an increased odds of depression across most LMICs.

Despite wide variation in socio-economic, demographical and cultural characteristics across the participating countries, and in the magnitude of country-specific associations between depression and pain, several findings were consistent across the large number of countries. Our data suggests that women exhibited a higher overall prevalence of physical pain than men in line with prior research(Mogil, 2012). Several mechanisms are related to these gender differences including the influence of physiological factors such as sex hormones and psychological factors such as more anxiety or catastrophizing responses in women (Melchior *et al*., 2016). Another cross-national consistent finding that confirms published epidemiological surveys is an increased vulnerability to physical pain with increasing age(Tsang *et al*., 2008). The present study suggests that the same clinical sensitivity to comorbid mental disorders and physical pain, in particular arthritis, diabetes, angina, and asthma is essential in the elderly population.Of interest, higher education status and higher income were associated with less pain. The reason for this relationship might be an increased awareness of health risks that might cause pain and less trauma and accidents in higher educated people while those with a

better socio-economic status have a better health coverage than those who can't afford it, in particular in LMICs(Asante *et al*., 2016).

There are several hypotheses which might explain why people with depression report higher levels of severe pain. First, and as indicated in the current study, is that the heightened prevalence of somatic co-morbidity among people with depression might play a role, which has been reported in previous research (De Hert *et al*., 2011c). Pain is a primary symptom of many physical health conditions and the increased pain - depression relationship could be a underlying symptom of poorer physical health. Alternatively, suboptimal treatment for physical health condition due to inequality in access to health care, stigma and discrimination and less attention by care givers to comorbidities in people with mental illness may be other explanations(De Hert *et al*., 2011b).It is established that among people with mental illness there are health inequalities and people are less likely to receive physical healthcare (De Hert *et al*., 2011a). Thus, the heightened relationship we observed may be related to under addressed physical comorbidity. Clearly this is an issue in LMICs where resources are sparser than in established Western society. Third, inflammatory processes have been implicated in the pathogenesis of pain in depression(Bai *et al*., 2014). Recent evidence has demonstrated that depression is also associated with considerable inflammation (Strawbridge *et al*., 2015). Moreover, there is an increasing evidence base to suggest that anti-inflammatory treatments such as statins offer favourable improvements in depressive symptomology in people with depression (Salagre *et al*., 2016). Such findings seem to support the notion that depression and pain may also be linked through inflammatory pathways. Related to the inflammatory hypothesis, sedentary behaviour is also associated with inflammation (Hamer *et al*., 2012a, Hamer *et al*., 2012b) and

both pain (Stubbs *et al*., 2014) and depression are associated with sedentary behaviour (Vancampfort *et al*., 2015). Given that physical activity can improve inflammatory markers (Hamer *et al*., 2014), interventions increasing activity levels may improve pain symptoms (Uthman *et al*., 2013) and depression (Schuch *et al*., 2016a, Schuch *et al*., 2016b) and at a population level may be a particularly viable option in LMICs. Another potential option is that areas of the brain linked to mood dysregulation (e.g. amygdala, insular) also project to structures involved in pain modulation (e.g. periaqueductal gray). Therefore, the neurobiological changes among people with depression could increase the risk of pain. However, clearly, future research is required to explore all of the aforementioned hypotheses.

Clinical implications

Our data demonstrates that physical pain is an important problem across the depression spectrum in LMICs. Strategies to deal with this are urgently needed. For example, pain assessment, prevention and management should be integrated in the clinical practice guidelines for subsyndromal depression, brief depressive episode, and depressive episode. Existing health care models should adapt to the high pain rates. This is especially relevant in LMICs, where all levels of care must be carefully planned in the context of economic restraints. Health care systems in LMICS including policy makers should embrace physical health needs in the management of depression at all levels of care including primary health care. An important environmental barrier in the care of people with depression in LMICs is the lack of integrated mental and medical services and the poorly developed community-based psychiatric services (Mugisha *et al*., 2016). In addition, LMICs have limited access to most expensive novel antidepressants, as the Norepinephrine Serotonin Reuptake Inhibitor (NSRI) drugs for example, a scenario

which further increase the burden associated to depression-pain interface (Pan *et al*., 2015). This is compelling considering that a considerable number of individuals living in LMICs may "manifest" depression complaining for (medically-unexplained) somatic pain (Fornaro *et al*., 2011) rather than verbal communication of their own emotions due to stigma issues(Fornaro *et al*., 2009). Also, pain is a risk factor for pain-killer self-medication and eventually abuse, with connected physical consequences, and dependence syndrome development should the pain killers be opioid medications (Webster *et al*., 2016). Closer integration of primary care and mental health in these countries is needed, but without obscuring the responsibility for pain assessment, prevention and management. We suggest that pain assessment, prevention and management has an important role in health services, particularly when one considers the heightened risk of suicidal behaviours in those with painful comorbidities (Stubbs, 2016). However, it should be acknowledged that many mental health providers do not ask about physical pain in their patients because of lack of consideration of this health care aspect, lack of time or lack of resources directly available to them(De Hert *et al*., 2011b). Therefore, first of all, there is a clear need to increase awareness of the importance physical health needs of patients with depression among mental health providers in LMICs. Continued medical education (CMEs which is a common practice in LMICs(Mugisha *et al*., 2016)) should be used to inform health providers on the importance of assessing physical pain in people with subsyndromal depression, brief depressive episode, and depressive episode. Health providers in LMICs need to be informed that their roles extend beyond taking care of the mental or physical health of their patients and assume responsibility for both the mental and physical health of their patients. There is also the need for mental health training institutions that train medical personnel to include physical pain assessment as part of their curriculum and training

programs. Policy makers should be made aware that investment in CME and in screening for physical pain could optimize mental and physical health improvements. However, effective pain screening/monitoring is not sufficient on its own, as appropriate treatment is also mandatory. Patients should be provided self-care management strategies including advise on a healthy and active lifestyle and prioritizing the prevention of chronic pain and avoiding fragmented care (De Hert *et al*., 2011b).Concomitant pain and mental health disorders often complicate pharmacological management, but several drug classes, including serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and anticonvulsants, have efficacy for both conditions and should be considered first-line treatment agents (Hooten, 2016).

Limitations

Current findings should be interpreted in the light of some limitations. First, the pain assessment was based on two main dimensions of pain and specific details regarding the duration, type and site of pain were not characterized. Since the WHS was conducted in many different cultural settings and was primarily aimed to assess mental health issues, it was not feasible to include a more comprehensive pain assessment. Previous research also demonstrated that self-report measures may be more amenable to under representation compared to behavioural pain measures among people with mental health diagnoses (Stubbs *et al*., 2015, Stubbs *et al*., 2016). Therefore, our results may actually be an under representation of the pain and depression comorbidity. Second, the diagnosis of subsyndromal depression, brief depressive episode, and depressive episode was not assessed by a clinical interview. Finally, the data are cross sectional. Therefore, the directionality of the relationships cannot be deduced from our data. Nonetheless, the strengths of the study include the large sample size and the multi-national scope,

including most regions of the world, but in particular LMICs in Africa, Latin-America, Asia and Eastern Europe.

In conclusion, our data demonstrates that depression (particularly those with a full depressive episode) is associated with increased severe pain. The results were consistent across almost all of the 47 LMICs even after adjusting for multiple confounders. Clearly efforts are needed to tackle pain and depression comorbidity in LMICs. Future research is also needed to attempt to elucidate the underlying mechanisms explaining this association, which might also offer a window of opportunity for viable treatment options in this region with sparse resources.

Conflict of interest

BS, AK, DV, MF, MS, NV, TT have no conflict of interest to declare.

Acknowledgements

BS receives funding from the National Institute for Health Research Collaboration for Leadership in Applied Health Research & Care Funding scheme. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Ai Koyanagi's work was supported by the Miguel Servet contract financed by the CP13/00150 and PI15/00862 projects, integrated into the National R + D + I and funded by the ISCIII - General Branch Evaluation and Promotion of Health Research - and the European Regional Development Fund (ERDF-FEDER).

Table 1 Characteristics of the study sample (overall and by severe pain)

Characteristic	Category	Overall	Severe pain	
			No	Yes
Sex	Male	49.2	51.0	34.7
	Female	50.8	49.0	65.3
Age (years)	18-34	47.9	50.2	28.4
	35-59	39.1	38.7	42.4
	≥60	13.0	11.0	29.2
Education	No formal	26.0	24.6	37.6
	≤Primary	31.0	30.5	35.1
	Secondary completed	33.7	35.2	21.7
	Tertiary	9.2	9.7	5.6
Wealth	Poorest	20.1	19.5	25.6
	Poorer	20.0	19.7	22.3
	Middle	19.9	19.9	19.7
	Richer	20.0	20.2	18.0
	Richest	20.0	20.7	14.4
Anxiety	No	88.5	91.6	62.7
	Yes	11.5	8.4	37.3
Arthritis	No	87.0	89.3	67.3
	Yes	13.0	10.7	32.7
Diabetes	No	97.0	97.5	92.9
	Yes	3.0	2.5	7.1
Angina	No	85.5	87.9	64.9
	Yes	14.5	12.1	35.1
Asthma	No	94.8	95.5	89.6
	Yes	5.2	4.5	10.4

Estimates are based on weighted sample.
Difference in sample characteristics between those with and without severe pain is statistically significant (Chi-squared text $p<0.0001$).

Table 2 Association between types of depression and severe pain estimated by multivariable logistic regression

	Model 1		**Model 2**		**Model 3**	
Characteristic	OR	95%CI	OR	95%CI	OR	95%CI
Depression type						
No depression	1.00		1.00		1.00	
Subsyndromal depression	2.80***	[2.40,3.26]	2.41***	[2.05,2.82]	2.16***	[1.83,2.55]
Brief depressive episode	2.21***	[1.90,2.57]	1.66***	[1.41,1.95]	1.45***	[1.22,1.73]
Depressive episode	4.01***	[3.62,4.45]	2.57***	[2.30,2.88]	2.11***	[1.87,2.39]
Sex						
Male	1.00		1.00		1.00	
Female	1.75***	[1.63,1.88]	1.65***	[1.54,1.78]	1.57***	[1.45,1.71]
Age (years)						
18-34	1.00		1.00		1.00	
35-59	1.74***	[1.59,1.92]	1.63***	[1.48,1.80]	1.40***	[1.26,1.56]
≥60	3.77***	[3.42,4.17]	3.49***	[3.16,3.87]	2.43***	[2.18,2.72]
Education						
No formal	1.00		1.00		1.00	
≤Primary	1.01	[0.93,1.11]	1.01	[0.92,1.11]	0.98	[0.89,1.08]
Secondary completed	0.65***	[0.57,0.74]	0.66***	[0.58,0.76]	0.66***	[0.57,0.76]
Tertiary	0.50***	[0.42,0.61]	0.50***	[0.42,0.61]	0.53***	[0.43,0.64]
Wealth						
Poorest	1.00		1.00		1.00	
Poorer	0.91	[0.83,1.00]	0.93	[0.84,1.03]	0.93	[0.83,1.03]
Middle	0.85***	[0.77,0.93]	0.89*	[0.80,0.98]	0.92	[0.83,1.02]
Richer	0.85**	[0.76,0.94]	0.89*	[0.80,1.00]	0.93	[0.83,1.04]
Richest	0.76***	[0.67,0.87]	0.81**	[0.71,0.93]	0.84*	[0.72,0.98]
Anxiety			4.49***	[4.10,4.91]	4.17***	[3.79,4.59]
Arthritis					2.16***	[1.96,2.38]
Diabetes					1.38***	[1.17,1.62]
Angina					1.94***	[1.77,2.12]
Asthma					1.33***	[1.13,1.57]

Abbreviation: OR odds ratio; CI confidence interval
Models are adjusted for all variables in the respective column and country.
* p<0.05, ** p<0.01, *** p<0.001

Table 3 Association between types of depression and pain score estimated by multivariable linear regression

	Model 1		**Model 2**		**Model 3**	
Characteristic	B	95%CI	B	95%CI	B	95%CI
Depression type						
No depression	Ref.		Ref.		Ref.	
Subsyndromal depression	14.92***	[13.33,16.52]	13.05***	[11.52,14.59]	11.15***	[9.62,12.68]
Brief depressive episode	14.37***	[13.08,15.66]	11.45***	[10.18,12.72]	9.52***	[8.17,10.87]
Depressive episode	20.86***	[19.52,22.20]	15.60***	[14.32,16.88]	12.52***	[11.24,13.80]
Sex						
Male	Ref.		Ref.		Ref.	
Female	6.56***	[6.06,7.05]	6.06***	[5.58,6.53]	5.21***	[4.72,5.70]
Age (years)						
18-34	Ref.		Ref.		Ref.	
35-59	7.63***	[7.09,8.18]	7.18***	[6.64,7.71]	5.45***	[4.91,5.99]
≥60	19.81***	[18.96,20.66]	18.84***	[18.01,19.68]	13.75***	[12.90,14.60]
Education						
No formal	Ref.		Ref.		Ref.	
≤Primary	-0.91*	[-1.65,-0.17]	-0.86*	[-1.57,-0.15]	-0.91*	[-1.61,-0.22]
Secondary completed	-4.08***	[-4.98,-3.17]	-3.81***	[-4.70,-2.92]	-3.47***	[-4.34,-2.60]
Tertiary	-5.64***	[-6.92,-4.36]	-5.41***	[-6.61,-4.21]	-4.60***	[-5.75,-3.44]
Wealth						
Poorest	Ref.		Ref.		Ref.	
Poorer	-0.98**	[-1.69,-0.27]	-0.81*	[-1.51,-0.11]	-0.85*	[-1.53,-0.17]
Middle	-2.30***	[-3.01,-1.58]	-1.94***	[-2.64,-1.24]	-1.57***	[-2.26,-0.88]
Richer	-1.94***	[-2.75,-1.13]	-1.62***	[-2.39,-0.84]	-1.16**	[-1.92,-0.40]
Richest	-3.56***	[-4.40,-2.72]	-3.16***	[-3.98,-2.34]	-2.76***	[-3.57,-1.96]
Anxiety			17.72***	[16.81,18.62]	15.79***	[14.91,16.68]
Arthritis					11.59***	[10.81,12.37]
Diabetes					4.59***	[3.25,5.93]
Angina					10.08***	[9.37,10.79]
Asthma					5.18***	[3.87,6.49]

Abbreviation: Ref. Reference category; CI confidence interval

Models are adjusted for all variables in the respective column and country. The score ranges from 0 to 100 with higher scores corresponding to higher levels of pain.

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

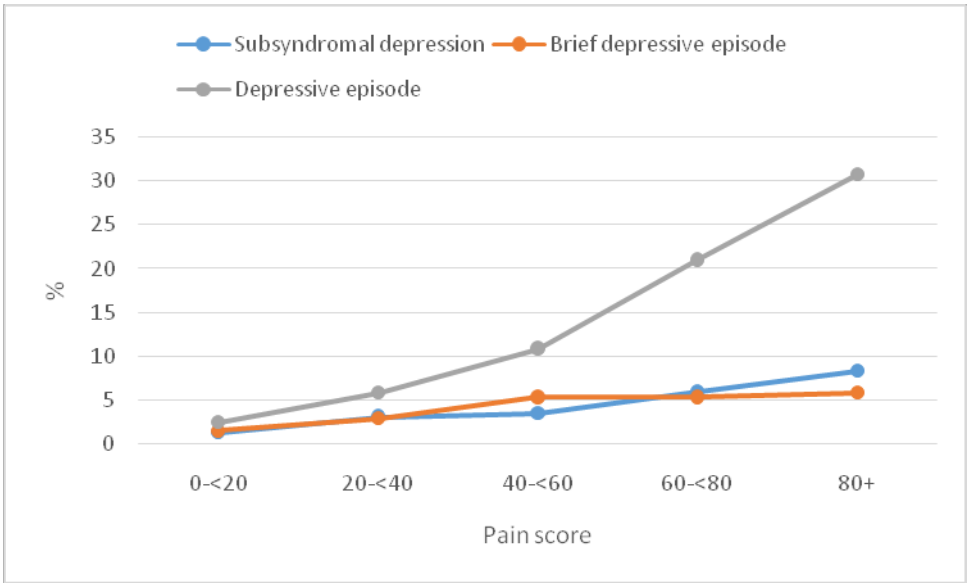

Figure 1 Prevalence of different types of depression by pain score
Estimates are based on weighted sample. The pain score ranges from 0 to 100 with higher scores corresponding to higher levels of pain.

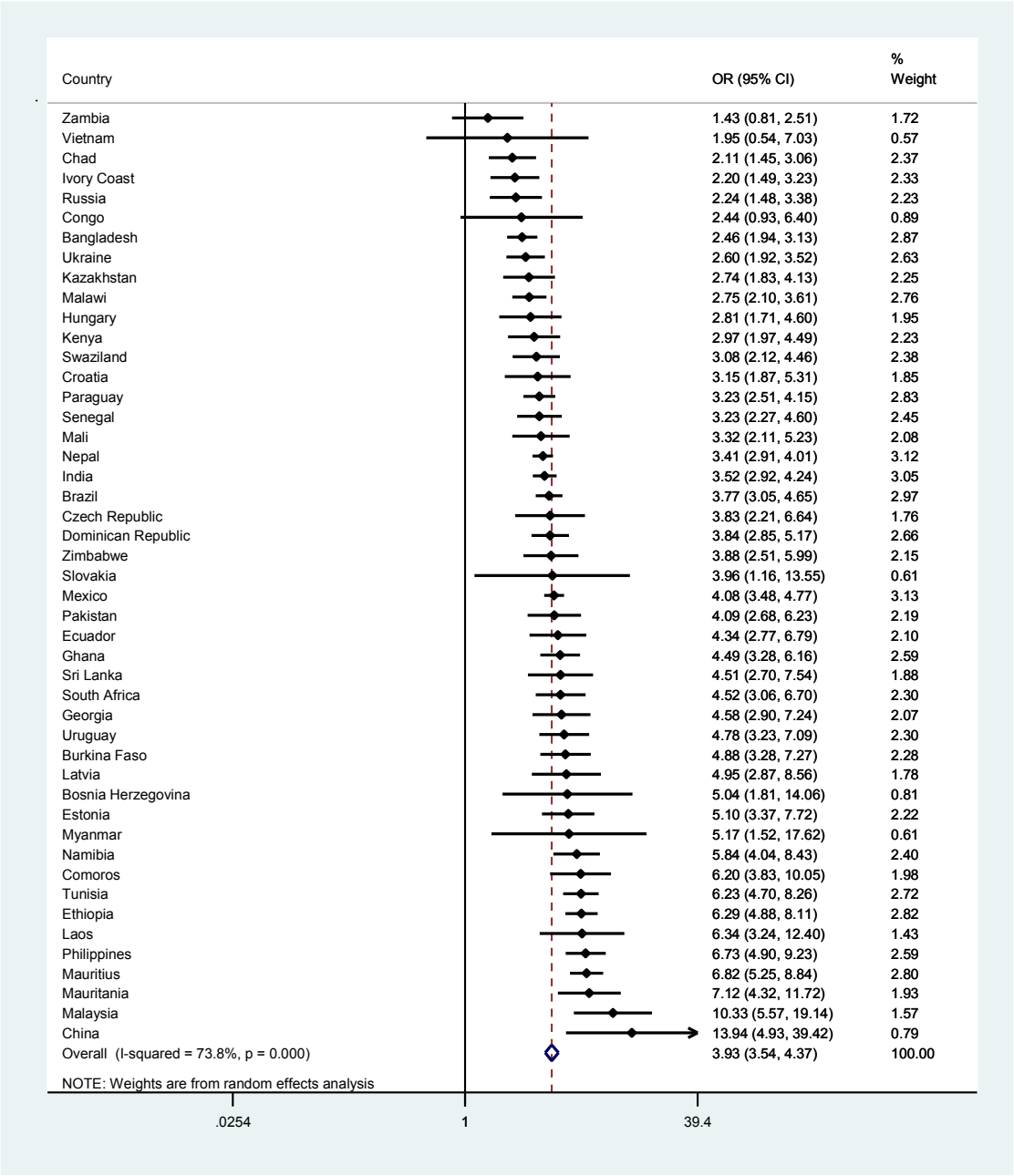

Figure 2 Country-wise association between any depression (independent variable) and severe pain (dependent variable) estimated by logistic regression adjusted for sex and age

Any depression refers to having subsyndromal depression or brief depressive episode or depressive episode.

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