Title: Association between physical multimorbidity and sleep problems in 46 low- and middle-income countries

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ABSTRACT

Background: Little is known on the association between multimorbidity (i.e., ≥2 chronic conditions) and sleep problems in the general adult population from low- and middle-income countries (LMICs). Thus, we aimed to assess this association among adults from 46 LMICs, and to quantify the extent to which anxiety, depression, stress, and pain explain this association.

Methods: Cross-sectional, predominantly nationally representative, community-based data of the World Health Survey were analyzed. Nine chronic physical conditions (angina, arthritis, asthma, chronic back pain, diabetes, edentulism, hearing problems, tuberculosis, visual impairment) were assessed. Sleep problems referred to past 30-day severe or extreme sleep problems (such as difficulties falling asleep, waking up frequently during the night or waking up too early in the morning). Multivariable logistic regression and mediation analyses were conducted to explore the associations.

Results: Data on 237,023 individuals aged ≥18 years [mean (SD) age 38.4 (16.0) years; 49.2% males] were analyzed. Compared to no chronic conditions, having 1, 2, 3, and ≥4 conditions were associated with 2.39 (95%CI=2.14, 2.66), 4.13 (95%CI=3.62, 4.71), 5.70 (95%CI=4.86, 6.69), and 9.99 (95%CI=8.18, 12.19) times higher odds for sleep problems. Pain (24.0%) explained the largest proportion of the association between multimorbidity and sleep problems, followed by anxiety (21.0%), depression (11.2%), and stress (10.4%).

Conclusions: Multimorbidity was associated with a substantially increased odds for sleep problems in adults from 46 LMICs. Future studies should assess whether addressing factors such as pain, anxiety, depression, and stress in people with multimorbidity can lead to improvement in sleep in this population.

Key Words: multimorbidity, sleep problems, sleep disorders, low- and middle-income countries, epidemiology

INTRODUCTION

Sleep problems (or disorders) is an umbrella term that refers to conditions that affect sleep quality, timing, or duration, and impact a person's ability to properly function while they are awake [1]. The global prevalence of sleep problems is high. For example, 'some insomnia problems' has been reported by ~30% of adults, and chronic insomnia by ~10% [2, 3], with studies showing that sleep problems affect high-income countries (HICs) and low- and middle-income countries (LMICs) to a similar degree [4]. One study found that among adults aged ≥50 years, the prevalence of severe/extreme sleep problems was as high as 43.9% in women from Bangladesh, while prevalence rates exceeding 25% have also been reported in Vietnam and South Africa, suggesting that sleep problems may be an emerging global epidemic [5]. Sleep problems have been associated with adverse health outcomes such as cognitive decline, low quality of life, mental health problems, and premature mortality [6-9]. Given the high prevalence of sleep problems as well as their associated adverse health outcomes, it is of prime importance to identify the correlates or risk factors of sleep problems to inform targeted intervention efforts.

One potentially important but understudied correlate is that of multimorbidity, which is often defined as the presence of two or more health conditions [10]. Multimorbidity is an important risk concept as it is associated with increased disability, poorer quality of life, polypharmacy, premature mortality, and increased health care costs [11, 12]. Multimorbidity may increase risk for sleep problems via factors such as anxiety, stress, depression, or pain [13-19], while sleep problems in turn, may also increase risk for multimorbidity via factors such as impairment in the hypothalamic–pituitary–adrenal (HPA) axis or inflammation, and this may lead to a vicious cycle where one condition may lead to the exacerbation of the other. Indeed, one study from Sweden found that moderate–severe sleep disturbances were associated with

a higher speed of chronic disease accumulation (ß/year = 0.142, p = 0.008) over nine years among older adults [20].

To date, several studies from HICs on the association between sleep problems and multimorbidity exist, but data from LMICs are scarce. This is an important research gap as disease profiles may differ between HICs and LMICs, while approximately 80% of all chronic diseases occur in LMICs [21]. It is also possible for some chronic conditions to be more likely to cause sleep problems in resource limited settings where symptoms cannot be adequately controlled (e.g., pain in arthritis), or where sleeping medication (e.g., benzodiazepines) is not readily available. Furthermore, the use of domestic and public lighting and other environmental factors related to the sleep site have been suggested to shape sleep patterns. Therefore, findings from HICs may not be applicable to LMICs, where the environment is distinct, with generally much higher proportions of rural populations [4].

To the best of our knowledge, to date, there are only three published studies on multimorbidity and sleep problems from LMICs. First, one multicountry study including adults aged ≥50 years from six LMICs found that a greater number of chronic conditions is associated with higher odds for sleep problems in China, Ghana, India, Russia, and South Africa [22]. Another study carried out in China among adults aged ≥60 years found that insomnia was associated with higher odds of multimorbidity [23]. Finally, in a study of 2637 individuals aged 18 years or older from Brazil, it was observed that the prevalence of short sleep duration was greater among individuals with three or more health conditions [24]. However, further studies from LMICs are necessary as two out of three of these studies were only on older populations, despite the fact that multimorbidity and sleep problems are common even in younger populations [25, 26], while even within LMICs, there can be a high

level of economic, demographic, environmental, and cultural diversity. Moreover, to date, no studies have identified potential mediators or influential factors in the multimorbidity-sleep problem relationship. Identifying such factors is important for intervention development as it provides information on potential mechanisms that can be targeted.

Given this background, the aim of the present study was to assess the association between multimorbidity and sleep problems in a sample of 237,023 individuals aged ≥18 years from 46 LMICs. Moreover, a further aim of this study was to investigate to what extent anxiety, depression, stress, and pain explain the multimorbidity-sleep problem relationship.

METHODS

The World Health Survey (WHS) was a cross-sectional survey carried out in 2002-2004. Survey details are available elsewhere (http://www.who.int/healthinfo/survey/en/). In brief, individuals with a valid home address aged ≥18 years were eligible to participate. Kish tables were used so that all household members had an equal chance of being selected. The questionnaire was subject to standard translation procedures to ensure comparability. Information was obtained through face-to-face interviews conducted by trained interviewers. Across all countries, the individual response rate was 98.5%. To adjust for non-response, sampling weights were generated using the population distribution as reported by the United Nations Statistical Division. Ethical approval for the survey was provided by ethical boards at each study site. All participants gave their informed consent.

Sleep problems

Sleep problems were assessed by the question "Overall in the last 30 days, how much of a problem did you have with sleeping, such as falling asleep, waking up frequently during the

night or waking up too early in the morning?" with answer options none, mild, moderate, severe, and extreme. Those who answered "severe" and "extreme" were considered to have sleep problems. This definition has been used in previous publications using the same survey question on sleep problems [5, 22, 27].

Physical multimorbidity

Nine chronic physical conditions were assessed in our study. *Arthritis*, *asthma*, and *diabetes* 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 [28]. *Chronic back pain* was defined as having had back pain (including disc problems) everyday during the last 30 days. *Visual impairment* was defined as having severe/extreme difficulty in seeing and recognizing a person that the participant knows from across the road (i.e., from a distance about 20 meters) [29]. The participant was considered to have *hearing problems* if the interviewer observed this condition. Those who have lost all their natural teeth were considered to have *edentulism*. A *tuberculosis* diagnosis was based on past 12-month symptoms and was defined as: (a) having had a cough that lasted for three weeks or longer; and (b) having had blood in phlegm or coughed up blood [30]. Multimorbidity was defined as having at least two chronic conditions, in line with previously used definitions [31]. The number of chronic conditions was also classified as 0, 1, 2, 3, and ≥4 conditions.

Influential factors

The influential factors (i.e., anxiety, depression, pain, stress) in the association between multimorbidity and sleep problems were selected based on past literature [13-19]. 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 answering "severe" or "extreme" were considered to

have anxiety [32]. Past 12-month depression was defined using the Diagnostic and Statistical Manual of Mental Disorders-IV algorithm [33]. Participants were asked "Overall in the last 30 days, how much of bodily aches or pains did you have?" with answer options being none, mild, moderate, severe, and extreme. Those who answered "mild" to "extreme" were considered to have pain. Stress over the month prior to the interview was assessed by two questions from the Perceived Stress Scale: "How often have you felt that you were unable to control the important things in your life?"; and "How often have you found that you could not cope with all the things that you had to do?" The answer options to these questions were: never (score=1), almost never (score=2), sometimes (score=3), fairly often (score=4), very often (score=5). The scores of the two questions were added to create a scale ranging from 2 to 10 [34]. Data on perceived stress were not available from Brazil, Hungary, and Zimbabwe.

Control variables

The control variables were selected based on past literature [35] and included age, sex, education (< or ≥Secondary), wealth, smoking (current smokers or else), heavy alcohol consumption, physical activity, and obesity. Principal component analysis based on 15-20 assets was conducted to create country-wise wealth quintiles. The question "Have you ever consumed a drink that contains alcohol (such as beer, wine, etc)?" with "yes" and "no" answer options was used to identify lifetime abstainers. Those who replied "yes" were then prompted to the next question on the amount of standard drinks of any alcoholic beverage the respondent had on each day of the past 7 days. The number of days in the past week in which 4 (female) or 5 (male) drinks were consumed was calculated. Heavy drinkers were defined as those who consumed the above amount of alcohol in two or more days of the past 7 days. We used the International Physical Activity Questionnaire to define low, moderate, and high levels of physical activity based on conventional cut-offs [36]. Based on self-reported weight

and height, body mass index (BMI) was calculated as weight (kg)/ [height (m)]^2. A BMI of ≥30kg/m^2 was considered to represent obesity.

Statistical analysis

The statistical analysis was done with Stata 14.2 (Stata Corp LP, College station, Texas). Data were publicly available for 69 countries. Of these, 10 countries were excluded due to a lack of sampling information. Furthermore, 10 high-income countries were excluded in order to focus on LMICs. Moreover, Turkey was deleted due to lack of data on education, while Morocco and Latvia were deleted due to lack of data on physical activity. Thus, the final sample consisted of 46 LMICs according to the World Bank classification at the time of the survey (2003). The data were nationally representative for all countries, with the exception of China, Comoros, the Republic of Congo, Ivory Coast, India, and Russia. The list of the included countries and their sample sizes are provided in **Table S1** of the Appendix.

The difference in sample characteristics between those with and without sleep problems were tested by Chi-squared tests and Student's *t*-tests for categorical and continuous variables, respectively. The associations between multimorbidity (i.e., ≥2 chronic conditions), number of chronic conditions, or individual chronic conditions (exposures) and sleep problems (outcome) were estimated by multivariable logistic regression using the overall sample. The analyses on multimorbidity and number of chronic conditions were also stratified by age groups (i.e., 18-44, 45-64, ≥65 years) and sex. To test whether the magnitude of the association between multimorbidity and sleep problems differ by age groups or sex, interaction analysis was conducted by including the product terms of age group X multimoribidty and sex X multimorbidity in the model. Next, in order to assess whether there is between-country heterogeneity in the association between multimorbidity and sleep

problems, we conducted country-wise analysis. The Higgins's I^2 statistic was calculated, which represents the degree of heterogeneity that is not explained by sampling error with values of 25%, 50%, and 75% often being considered low, moderate, and high level of heterogeneity, respectively [37]. A pooled estimate (overall and by region) was obtained by combining the estimates for each country into a random effect meta-analysis. Finally, using the overall sample, we conducted mediation analysis to assess the degree to which anxiety, depression, pain, and perceived stress explain the association between multimorbidity and sleep problems. We used the *khb* (Karlson Holm Breen) command in Stata [38] for this purpose. This method decomposes the total effect of a variable into direct and indirect effects. Using this method, the percentage of the main association explained by the influential factor can also be calculated (mediated percentage). Each potential influential factor was included in the model individually apart from the analysis where all these factors were included simultaneously in the model.

The regression and mediation analyses were all adjusted for age, sex, education, wealth, smoking, heavy alcohol consumption, physical activity, and country, with the exception of the sex-wise and country-wise analysis which were not adjusted for sex and country, respectively. Adjustment for country was done by including dummy variables for each country as in previous WHS publications [27, 30]. The analysis on the individual chronic conditions included these conditions individually in the model. The sample weighting and the complex study design were taken into account in all analyses. Results from the logistic regression models are presented as odds ratios (ORs) with 95% confidence intervals (CIs). The level of statistical significance was set at $P<0.05$.

RESULTS

The final sample included 237,023 individuals aged ≥18 years [mean (SD) age 38.4 (16.0) years; 49.2% males]. Overall, the prevalence of multimorbidity (i.e., ≥2 chronic conditions) and sleep problems were 14.0% and 7.5%, respectively. The sample characteristics are provided in **Table 1**. The prevalence of multimorbidity, female sex, <secondary education, lower levels of wealth, smoking, low levels of physical activity, and obesity were significantly higher among those with sleep problems. The prevalence of sleep problems increased sharply with increasing number of chronic conditions overall (**Figure 1**), and also in all age groups and both sexes (**Figure 2**). Adjusted analysis showed that all chronic conditions assessed were associated with significantly higher odds for sleep problems with the highest ORs being observed for visual impairment (OR=3.87), tuberculosis (OR=2.51), and angina (OR=2.50) (**Figure 3**). The association between multimorbidity or number of chronic conditions estimated by multivariable logistic regression is shown in **Table 2**. Compared to no chronic conditions, having 1, 2, 3, and ≥4 conditions were associated with 2.39 (95%CI=2.14, 2.66), 4.13 (95%CI=3.62, 4.71), 5.70 (95%CI=4.86, 6.69), and 9.99 (95%CI=8.18, 12.19) times higher odds for sleep problems in the overall sample. Interaction analysis showed that the magnitude of the association between multimorbidity and sleep problems is significantly more pronounced among those aged 18-44 years (OR=3.77) compared to those aged ≥65 years (OR=2.48), and also among males (OR=4.08) compared to females (OR=2.83). Country-wise analysis showed that multimorbidity is significantly associated with higher odds for sleep problems in all included countries, with the exception of Vietnam, Bosnia & Herzegovina, and Republic of Congo (**Figure 4**). The level of between-country heterogeneity was low to moderate (I^2=45.2%), while the pooled estimate based on a meta-analysis with random effects was 3.63 (95%CI=3.31, 3.99). The pooled estimates by region were similar. Finally, mediation analysis showed that pain (24.0%) and

anxiety (21.0%) explain >20% of the association between multimorbidity and sleep problems, while depression (11.2%) and stress (10.4%) also explained this association but to a lesser extent (**Table S2** of the Appendix). These four factors collectively explained 44.3% of the association between multimorbidity and sleep problems.

DISCUSSSION

Main findings

In the present large sample of adults from 46 LMICs, after adjustment for potential confounders, all nine individual chronic physical conditions were associated with higher odds for sleep problems (OR 1.19-3.87), and compared to having no chronic conditions, having 1, 2, 3, and ≥4 conditions were associated with 2.39 (95%CI=2.14, 2.66), 4.13 (95%CI=3.62, 4.71), 5.70 (95%CI=4.86, 6.69), and 9.99 (95%CI=8.18, 12.19) times higher odds for sleep problems. Interaction analysis showed that the magnitude of the association between multimorbidity (i.e., ≥2 chronic conditions) and sleep problems is significantly more pronounced among the youngest age group (vs. oldest) and males (vs. females). Country-wise analysis showed that multimorbidity was significantly associated with higher odds for sleep problems in 43 of the 46 countries studied, with a low to moderate level of between-country heterogeneity. The largest proportion of the association between multimorbidity and sleep problems was explained by pain (24.0%), followed by anxiety (21.0%), depression (11.2%), and stress (10.4%), with these four factors collectively explaining 44.3% of the association.

Interpretation of the findings

Our findings are in line with previous studies from LMICs which have shown that multimorbidity is positively associated with sleep problems [22-24]. Our study adds to the existing literature by showing that this association exists in a large sample of adults from 46

LMICs. Moreover, for the first time, we show that this association may be particularly pronounced among the younger population and males, while the present study has identified that anxiety, depression, stress, and pain partially explain the multimorbidity-sleep problem association.

In our study, all nine chronic conditions were associated with sleep problems. Vision impairment had the strongest association with sleep problems. Indeed, circadian rhythm sleep problems are common and manifest in those with visual impairment. These sleep problems are either free-running in which the circadian clock is no longer entrained to the 24-hour day or abnormally entrained either very late or very early [39]. The second strongest association was observed for tuberculosis. Sleep problems have often been reported as a common problem among those on treatment for tuberculosis. The quality of sleep may be affected directly or indirectly by various adverse drug reactions such as hepatitis and neuropathy or the disease symptoms such as pain, dyspnea, and nausea [40]. The third strongest association was observed for angina. The angina/sleep problem association is likely explained by psychological factors (e.g., higher levels of anxiety and depression), lifestyle factors (e.g., physical inactivity and high levels of sedentary time), and subclinical inflammation [41].

Thus, it is possible for multimorbidity to lead to sleep problems through the accumulation of the pathways mentioned above. Apart from this, the association may be explained by the influential factors identified in our study. First, in the case of pain, multimorbidity likely increases risk for chronic pain owing to symptom burden and increased functional impairment, while pain in turn may induce sleep problems via pain *per se* or increased discomfort from laying in certain positions [42]. Next, in terms of anxiety, depression, and stress, these conditions are known to be highly prevalent in multimorbidity possibly due to

factors such as symptom burden, functional impairment, and reduced quality of life [13]. Moreover, the complexity of treatment of multiple conditions and the associated high costs may also increase risk for anxiety and stress in people with multimorbidity. In turn, anxiety, depression, and stress may increase sleep problems owing to rumination when one is trying to sleep [43]. Moreover, almost all antidepressants have been found to influence sleep, notably by strongly suppressing REM sleep [44]. Finally, persistent hyperactivity in the basic ascending arousal system throughout the sleep-wake cycle in depression might be implicated in the experience of hyperarousal during waking and disturbed sleep continuity [44]. However, although these factors explained a substantial proportion of the multimorbidity-sleep relationship (44.3%), there are likely other factors which explain this association but could not be examined in our study due to lack of data. For example, multimorbidity is associated with increased sedentary time [45], and sedentary time has been implicated in poor sleep, potentially owing to elevated depression risk, increase in metabolic syndrome, and increased LED-backlit TV exposure [46]. Furthermore, multimorbidity is associated with polypharmacy to manage multiple chronic conditions, and polypharmacy may increase risk for sleep problems. For example, bronchodilators, beta-blockers, central nervous system stimulants, gastrointestinal drugs, and cardiovascular drugs have all been observed to increase sleep problems [47].

It should be noted that the strongest associations in the present study were observed for those aged 18 to 44 years and for males. Although the reasons for these findings can only be speculated, having multimorbidity at an age when this condition is not so common may increase risk for mental health conditions via factors such as shame, while not being able to work or study due to multimorbidity at young age may have a larger impact on mental health in terms of financial gains and future prospects [48]. Furthermore, having multimorbidity in

young age may lead to a particularly high risk for social isolation and loneliness as young adults are usually more active. All these factors may result in increased levels of anxiety, depression, and stress and thus amplify sleep problems in younger adults with multimorbidity. Similar pathways may exist in males who reside in LMICs since males in such settings often participate in paid work where females do the bulk of the housework [49]. However, it should be noted that the present finding that the strongest association between multimorbidity and sleep problems was observed in males contradicts some previous findings. For example, in one study carried out in older adults residing in Germany, it was found that multimorbidity was not associated with sleep problems in men but that it was in women [35]. This difference may be explained by social and cultural differences between HICs and LMICs such as that described above, and warrants further investigation.

Strengths and limitations

The use of a large predominantly nationally representative dataset from 46 LMICs is a clear strength of the present study. However, the study results should be interpreted in light of their limitations. First, multimorbidity and sleep problems were self-reported, and thus, study findings may be affected by self-reporting bias. Second, our list of chronic diseases included a variety of diseases which are highly prevalent in LMICs, but lacked some diseases such as cancer which is known to be related with high risk of sleep problems [50]. Finally, given the cross-sectional nature of our study, causality or temporal associations cannot be established. Relatedly, mediation and confounding are identical statistically and can only be distinguished on conceptual grounds [51]. Thus, our mediated percentage is likely to not only reflect mediation, and be an overestimation given the various ways in which multimorbidity, sleep problems, mental health problems, and pain can be intertwined.

Conclusion

We found that multimorbidity is associated with a substantially increased odds for sleep problems among adults in 46 LMICs. Future studies should examine sex and age differences in this association to assess whether the results can be replicated in other settings. Furthermore, future longitudinal or interventional studies should assess temporal associations and whether addressing anxiety, depression, stress, and pain among people with multimorbidity can lead to less sleep problems in this population. Clinicians should be aware of the high prevalence of sleep problems in people with multimoribidity, and address them as sleep problems in people with chronic conditions may worsen clinical outcomes via factors such as impaired immunity, inflammation, or distress [52, 53].

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Tables and Figures

Table 1 Sample characteristics (overall and by sleep problems)

			Sleep problems		
Characteristic		Overall	No	Yes	P-value[a]
Multimorbidity[b]	Yes	13.9	11.5	43.6	<0.001
Age (years)	Mean (SD)	38.4 (16.0)	37.6 (15.6)	48.4 (17.1)	<0.001
Sex	Male	49.2	50.3	35.3	<0.001
Education	≥Secondary	43.0	44.1	29.0	<0.001
Wealth	Poorest	20.1	19.6	26.2	<0.001
	Poorer	20.0	19.8	22.2	
	Middle	19.9	20.0	19.1	
	Richer	20.0	20.2	17.8	
	Richest	20.0	20.4	14.7	
Smoking	Yes	26.7	26.3	31.0	<0.001
Heavy alcohol consumption	Yes	4.9	4.9	4.7	0.742
Physical activity	High	63.2	64.1	51.9	<0.001
	Moderate	19.3	19.4	19.1	
	Low	17.4	16.5	29.0	
Obesity	Yes	9.0	8.7	12.9	<0.001

Abbreviation: SD Standard deviation

Data are column % unless otherwise stated.

[a] P-values were obtained by Chi-squared tests and Student's *t*-tests for categorical and continuous variables, respectively.

[b] ≥2 chronic conditions.

Table 2 Association between multimorbidity (i.e., ≥2 chronic conditions) or number of chronic conditions and sleep problems (outcome) estimated by multivariable logistic regression

			Age			Sex	
Exposure		Overall	18-44 years	45-64 years	≥65 years	Male	Female
Multimorbidity[a]	No	1.00	1.00	1.00	1.00	1.00	1.00
	Yes	3.23*	3.77*	3.20*	2.48*	4.08*	2.83*
		[2.92,3.57]	[3.23,4.41]	[2.75,3.72]	[2.04,3.00]	[3.43,4.86]	[2.53,3.18]
Number of	0	1.00	1.00	1.00	1.00	1.00	1.00
chronic conditions	1	2.39*	2.48*	2.10*	2.08*	2.53*	2.28*
		[2.14,2.66]	[2.16,2.85]	[1.73,2.56]	[1.53,2.84]	[2.14,3.00]	[1.99,2.61]
	2	4.13*	4.42*	3.80*	3.11*	4.94*	3.68*
		[3.62,4.71]	[3.68,5.31]	[3.03,4.76]	[2.28,4.24]	[3.98,6.14]	[3.13,4.34]
	3	5.70*	6.88*	5.49*	4.12*	7.48*	4.88*
		[4.86,6.69]	[5.21,9.07]	[4.28,7.04]	[3.01,5.64]	[5.68,9.86]	[4.05,5.87]
	≥4	9.99*	21.53*	9.95*	6.89*	13.72*	8.30*
		[8.18,12.19]	[13.55,34.23]	[7.17,13.81]	[4.86,9.78]	[10.00,18.82]	[6.48,10.63]

Data are odds ratio [95% confidence interval].

Models are adjusted for age, sex, education, wealth, smoking, heavy alcohol consumption, physical activity, obesity, and country, with the exception of the sex-stratified analysis which was not adjusted for sex.

[a] ≥2 chronic conditions.

* P<0.001

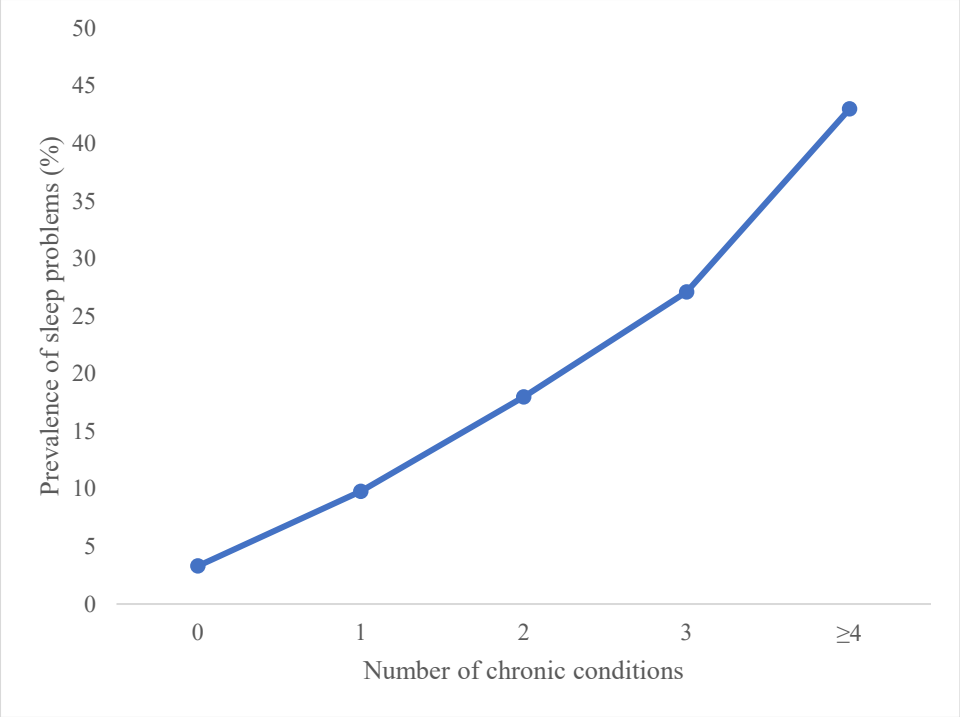
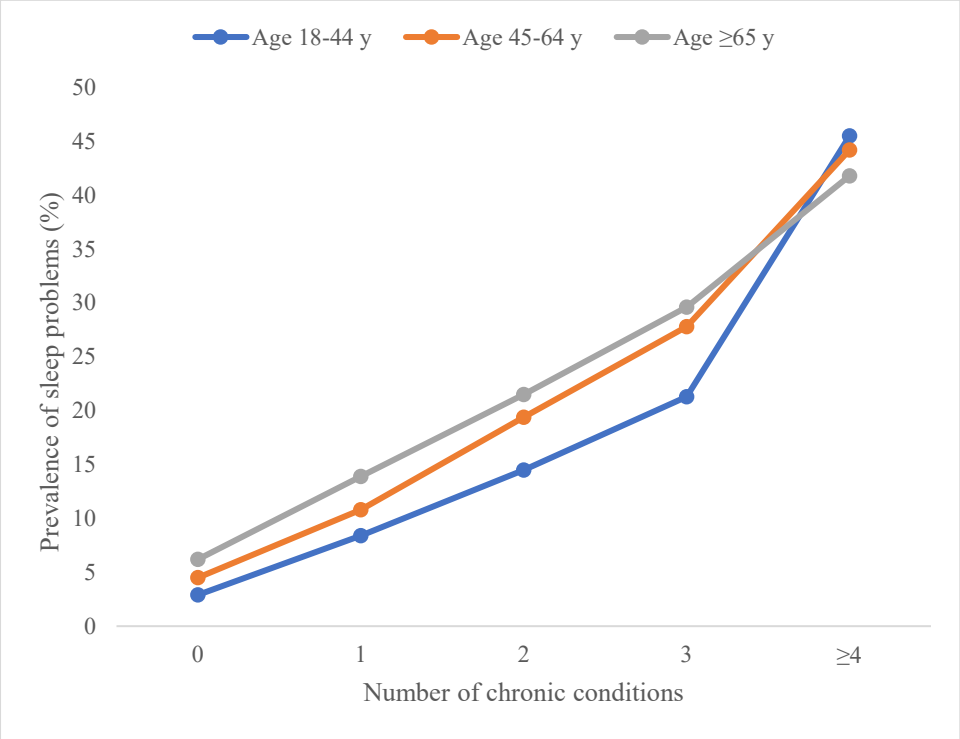


Figure 1 Prevalence of sleep problems by number of chronic conditions in the overall sample

(A) By age groups



(B) By sex

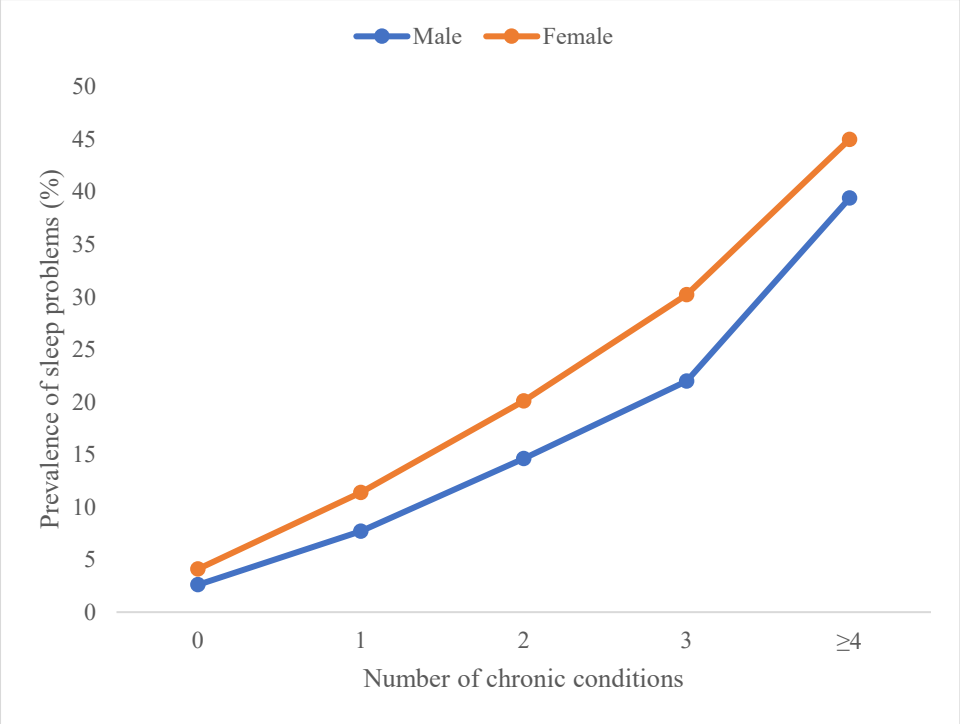


Figure 2 Prevalence of sleep problems by number of chronic conditions in (A) age group stratified samples, and (B) sex-stratified samples

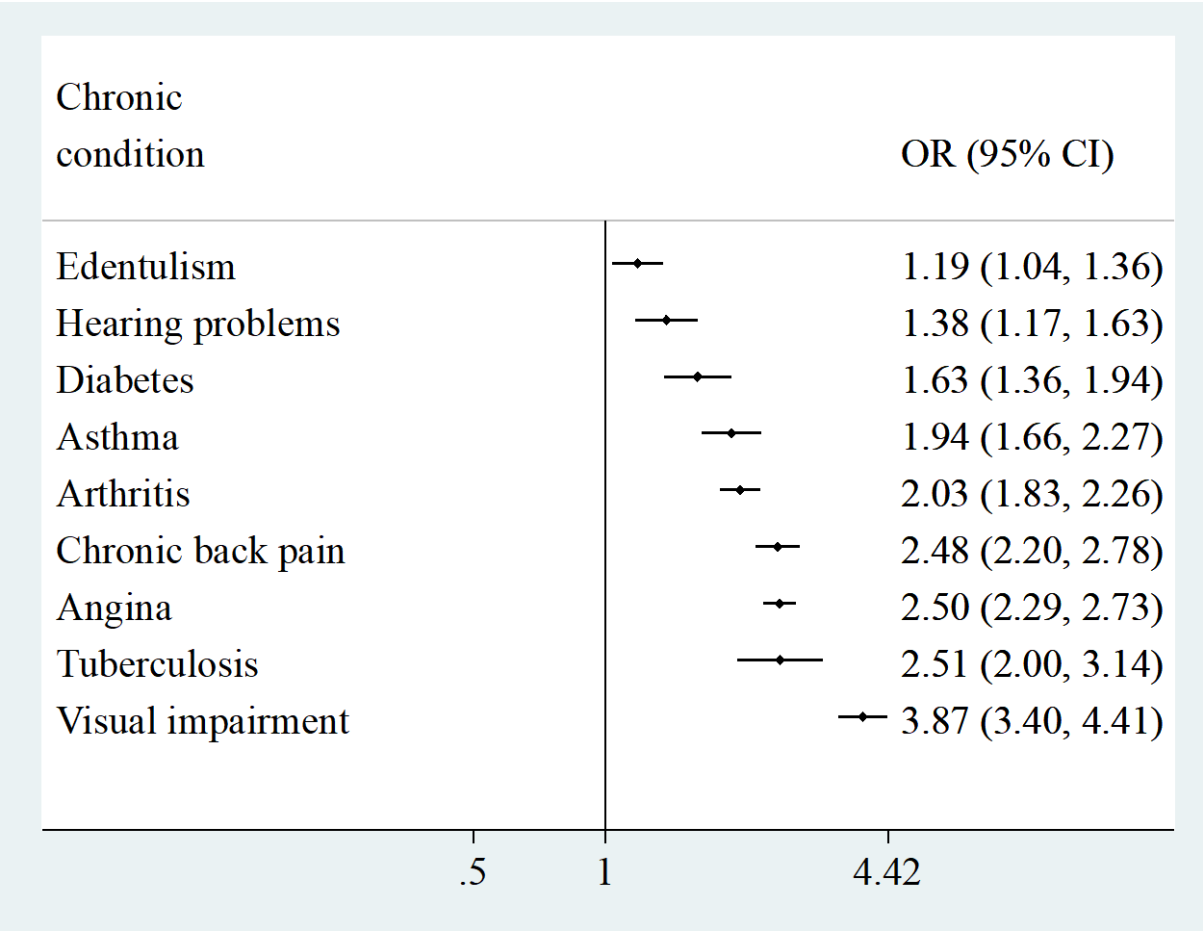


Figure 3 Association between individual chronic conditions and sleep problems (outcome) estimated by multivariable logistic regression

Abbreviation: OR Odds ratio; CI Confidence interval

Models are adjusted for age, sex, education, wealth, smoking, heavy alcohol consumption, physical activity, obesity, and country.

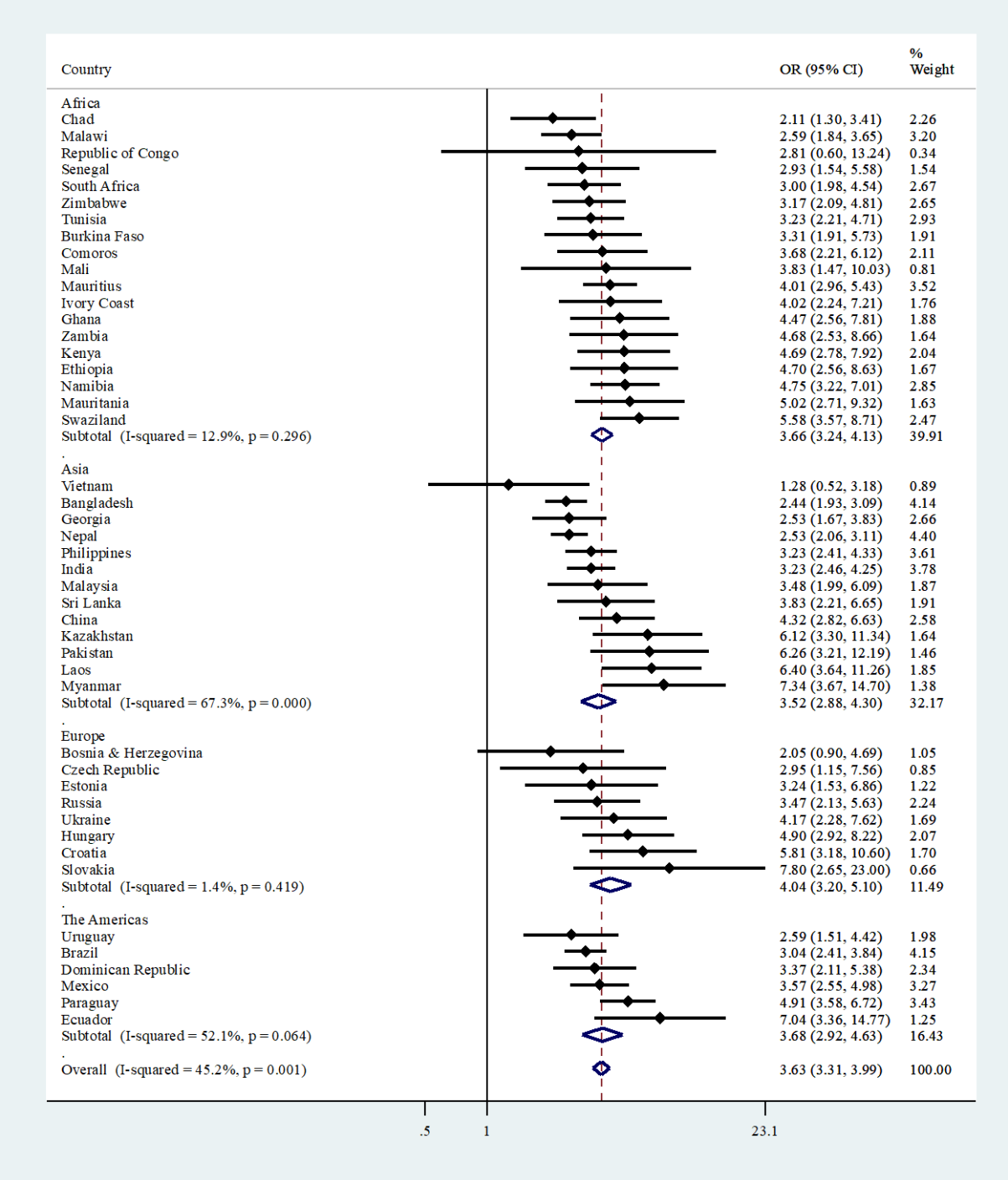


Figure 4 Country-wise association between multimorbidity (i.e., ≥2 chronic conditions) and sleep problems (outcome) estimated by multivariable logistic regression

Abbreviation: OR Odds ratio; CI Confidence interval

Models are adjusted for age, sex, education, wealth, smoking, heavy alcohol consumption, physical activity, and obesity.

Overall estimates were obtained by meta-analysis with random effects.

APPENDIX

Table S1 Included countries and sample size

Country	N
Burkina Faso	4,948
Bangladesh	5,942
Bosnia & Herzegovina	1,031
Brazil	5,000
China	3,994
Ivory Coast	3,251
Republic of Congo	3,075
Comoros	1,836
Czech Republic	949
Dominican Republic	5,027
Ecuador	5,675
Estonia	1,020
Ethiopia	5,089
Georgia	2,950
Ghana	4,165
Croatia	993
Hungary	1,419
India	10,687
Kazakhstan	4,499
Kenya	4,640
Laos	4,988
Sri Lanka	6,805
Mexico	38,746
Mali	4,886
Myanmar	6,045
Mauritania	3,902
Mauritius	3,968
Malawi	5,551
Malaysia	6,145
Namibia	4,379
Nepal	8,820
Pakistan	6,501
Philippines	10,083
Paraguay	5,288
Russia	4,427
Senegal	3,461
Slovakia	2,535
Swaziland	3,117
Chad	4,870
Tunisia	5,202
Ukraine	2,860
Uruguay	2,996
Vietnam	4,174
South Africa	2,629
Zambia	4,165
Zimbabwe	4,290

Table S2 Influential factors in the association between multimorbidity (i.e., ≥2 chronic conditions) and sleep problems

	Effect	OR [95%CI]	P-value	% Mediated
Stress[a]	Total	3.41 [3.04,3.82]	<0.001	10.4
	Direct	3.00 [2.68,3.36]	<0.001	
	Indirect	1.14 [1.11,1.16]	<0.001	
Depression	Total	3.29 [2.97,3.65]	<0.001	11.2
	Direct	2.88 [2.59,3.20]	<0.001	
	Indirect	1.14 [1.12,1.16]	<0.001	
Anxiety	Total	3.30 [2.98,3.66]	<0.001	21.0
	Direct	2.57 [2.32,2.85]	<0.001	
	Indirect	1.29 [1.25,1.32]	<0.001	
Pain	Total	3.59 [3.26,3.96]	<0.001	24.0
	Direct	2.64 [2.40,2.91]	<0.001	
	Indirect	1.36 [1.32,1.40]	<0.001	
All factors[a]	Total	3.91 [3.47,4.40]	<0.001	44.3
	Direct	2.14 [1.90,2.41]	<0.001	
	Indirect	1.83 [1.74,1.92]	<0.001	

Abbreviation: OR Odds ratio; CI Confidence interval

Models are adjusted for age, sex, education, wealth, smoking, heavy alcohol consumption, physical activity, obesity, and country.

[a] Brazil, Hungary, and Zimbabwe are not included due to lack of data on perceived stress.