

Sleep problems and mild cognitive impairment among adults aged ≥ 50 years from low- and middle-income countries

Lee Smith^{1*}, Jae Il Shin², Louis Jacob^{3,4}, Christina Carmichael¹, Guillermo F. López Sánchez⁵, Hans Oh⁶, Laurie T Butler¹, Yvonne Barnett¹, Damiano Pizzol⁷, Mark A Tully⁸, Pinar Soysal⁹, Nicola Veronese¹⁰, Ai Koyanagi^{3,11}

1. Centre for Health, Performance and Wellbeing, Anglia Ruskin University, Cambridge, UK
2. Department of Pediatrics, Yonsei University College of Medicine, Seoul, South Korea
3. Research and Development Unit, Parc Sanitari Sant Joan de Déu, CIBERSAM, Dr. Antoni Pujadas, 42, Sant Boi de Llobregat, Barcelona 08830, Spain
4. Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux 78180, France
5. Vision and Eye Research Institute, School of Medicine, Faculty of Health, Education, Medicine and Social Care, Anglia Ruskin University, Cambridge, UK
6. Suzanne Dworak Peck School of Social Work, University of Southern California, Los Angeles, CA 90007, USA
7. Italian Agency for Development Cooperation - Khartoum, Sudan
8. School of Health Sciences, Institute of Mental Health Sciences, Ulster University, Newtownabbey BT15 1ED, Northern Ireland
9. Department of Geriatric Medicine, Faculty of Medicine, Bezmialem Vakif University, Adnan Menderes Bulvarı (Vatan Street), 34093 Fatih, İstanbul, Turkey
10. Geriatric Unit, Department of Internal Medicine and Geriatrics, University of Palermo, 90133 Palermo, Italy
11. ICREA, Pg, Lluís Companys 23, 08010 Barcelona, Spain

* Corresponding author: Dr. Lee Smith. lee.smith@aru.ac.uk

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ABSTRACT

Background: The limited available literature suggests that sleep problems are linked to an increased risk of mild cognitive impairment (MCI). However, this association has been little studied to date in low-income settings.

Objective: To investigate the association between sleep problems and MCI in a large sample of adults from six low-and middle-income countries (LMICs).

Design: Cross-sectional.

Setting: Study on Global Ageing and Adult Health (SAGE).

Subjects: 32,715 individuals aged ≥ 50 years with preservation in functional abilities [age range 50-114 years; 51.7% females].

Methods: MCI was defined using the National Institute on Aging-Alzheimer's Association criteria. 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?" and categorized as "None", "Mild", "Moderate", "Severe/ Extreme". Multivariable logistic regression analysis and meta-analysis were conducted.

Results: Compared to no sleep problems, mild, moderate, and severe/extreme sleep problems were associated with significant 1.40, 1.83, and 2.69 times higher odds for MCI with similar associations being observed between age groups and sex. Severe/extreme sleep problems were positively associated with MCI (i.e., $OR > 1$) in the six countries studied with the overall estimate being $OR = 1.80$ ($95\%CI = 1.50-2.16$), and a low level of between-country heterogeneity was observed ($I^2 = 28.2\%$).

Conclusions: Sleep problems were associated with higher odds for MCI. Interventions to improve sleep quality among middle-aged and older adults in LMICs may be an effective strategy in reducing risk of MCI and dementia.

Key words: Mild cognitive impairment, dementia, sleep problems, low- and middle-income countries, middle-aged adults, older adults

BACKGROUND

Dementia is a syndrome characterized by impairments in memory, thinking, or decision-making that interferes with activities of daily living [1]. It has been estimated that approximately 50 million people have dementia, with nearly 60% of these individuals residing in low- and middle-income countries (LMICs) [2]. Importantly, the prevalence of dementia is projected to reach 82 million in 2030, and 152 million in 2050, predominantly owing to rising numbers of people with dementia living in LMICs [2].

This high current and rising global prevalence of dementia is of concern not only for the individuals affected by this condition and their caregivers and families, but for society in general. Indeed, the total global societal cost of dementia was estimated to be US\$ 818 billion in 2015, which is equivalent to 1.1% of global gross domestic product (GDP) [2]. Moreover, dementia is one of the major causes of disability and dependency among older adults globally [2]. However, since there are currently no drugs or other treatments to modify the clinical course or delay the onset of dementia [3], there is the need to identify modifiable risk factors for the preclinical transitional stages of dementia such as mild cognitive impairment (MCI). MCI is now considered to be a crucial stage for interventions to prevent or delay the onset of dementia, and has a high conversion rate to dementia, which has been reported to be 12%, 20%, and 50% at 1, 3, and 5 years, respectively [4].

A potentially important but understudied correlate of MCI is sleep problems, which involve problems with the quality, timing, and amount of sleep [5]. Sleep problems may increase the risk of MCI or dementia via the accumulation and impaired clearance of toxic metabolites in the brain [6] or inflammation [7]. One meta-analysis including 18 longitudinal studies all from high-income countries found that sleep problems were associated with a higher risk of

incident all-cause dementia and both Alzheimer's disease and vascular dementia subtypes [8]. In another meta-analysis of 5 prospective cohort studies and 4 cross-sectional studies involving 62937 individuals, and documenting 2718 MCI/dementia cases and 5596 cognitive decline cases, it was observed that individuals who accumulated an average of 7 hours of sleep tended to acquire the least risk of MCI/dementia or cognitive decline [9]. Importantly, all studies included in this review on MCI/ dementia were from high-income countries. It should also be noted here that in addition to the growing body of literature that suggests sleep problems are associated with an increased risk of MCI/dementia, literature has also shown that those with MCI/dementia are also at a higher risk of developing sleep problems compared to those without MCI/dementia [10, 11]. Thus, the sleep-MCI/dementia relationship is likely bidirectional, and this implies that sleep problems and cognitive impairment can mutually affect each other, potentially leading to an exacerbation of both conditions. Some studies focusing on sleep problems among those with MCI have been carried out in China, a middle-income country. These studies consisting of small and unrepresentative samples show that those with MCI have a higher risk of sleep problems [12, 13].

The existing literature on the association between sleep problems and MCI has an important limitation that should be noted. Specifically, almost all studies have utilized high-income single country samples. LMICs currently have the highest prevalence of dementia, and dementia is expected to rise considerably in such economic settings. As well as this, a third of the adult population in LMICs report disturbed sleep/poor sleep quality [14]. It is therefore of upmost importance to understand whether an association exists between sleep problems and MCI in such settings to inform targeted intervention efforts to aid in the prevention of MCI

and ultimately dementia [2]. Moreover, multi-country studies are required as they allow for the comparison of internationally comparable estimates.

Given this background, the aim of the present study was to investigate the association between sleep problems and MCI in a large sample of middle-aged and older adults from six LMICs.

METHODS

The survey

Data from the Study on Global Ageing and Adult Health (SAGE) were analyzed. These data are publicly available through <http://www.who.int/healthinfo/sage/en/>. This survey was undertaken in China, Ghana, India, Mexico, Russia, and South Africa between 2007 and 2010. These countries broadly represent different geographical locations and levels of socio-economic and demographic transition. Based on the World Bank classification at the time of the survey, Ghana was the only low-income country, and China and India were lower middle-income countries although China became an upper middle-income country in 2010. The remaining countries were upper middle-income countries.

Details of the survey methodology have been published elsewhere [15]. Briefly, to obtain nationally representative samples, a multistage clustered sampling design method was used. The sample consisted of adults aged ≥ 18 years with oversampling of those aged ≥ 50 years. Trained interviewers conducted face-to-face interviews using a standard questionnaire. Standard translation procedures were undertaken to ensure comparability between countries. The survey response rates were: China 93%; Ghana 81%; India 68%; Mexico 53%; Russia 83%; and South Africa 75%. Sampling weights were constructed to adjust for the population

structure as reported by the United Nations Statistical Division. Ethical approval was obtained from the WHO Ethical Review Committee and local ethics research review boards. Written informed consent was obtained from all participants.

Mild cognitive impairment

MCI was ascertained based on the recommendations of the National Institute on Aging-Alzheimer's Association [16]. We applied the identical algorithms used in previous SAGE publications to identify MCI [17, 18]. Briefly, individuals fulfilling all the following conditions were considered to have MCI:

- (a) Concern about a change in cognition: Individuals who replied 'bad' or 'very bad' to the question "How would you best describe your memory at present?" and/or those who answered 'worse' to the question "Compared to 12 months ago, would you say your memory is now better, the same or worse than it was then?" were considered to have this condition.
- (b) Objective evidence of impairment in one or more cognitive domains: was based on a <-1 SD cut-off after adjustment for level of education, age, and country. Cognitive function was assessed through the following performance tests: word list immediate and delayed verbal recall from the Consortium to Establish a Registry for Alzheimer's Disease [19], which assessed learning and episodic memory; digit span forward and backwards from the Weschler Adult Intelligence Scale [20], that evaluated attention and working memory; and the animal naming task [19], which assessed verbal fluency.
- (c) Preservation of independence in functional abilities: was assessed by questions on self-reported difficulties with basic activities of daily living (ADL) in the past 30 days [21]. Specific questions were: "How much difficulty did you have in getting dressed?" and "How much difficulty did you have with eating (including cutting up your food)?" The answer options were none, mild, moderate, severe, and extreme (cannot do). Those who answered

either none, mild, or moderate to both of these questions were considered to have preservation of independence in functional activities. All other individuals were deleted from the analysis (935 individuals aged ≥ 50 years).

(d) No dementia: Individuals with a level of cognitive impairment severe enough to preclude the possibility to undertake the survey were not included in the current study.

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”. For the analysis, we merged the “Severe” and “Extreme” categories as the number of individuals in the “Extreme” category was very small to create a four-category variable. Furthermore, for some analyses, we used a dichotomized variable of severe/extreme or not [22].

Control variables

The control variables were selected based on past literature [23] and included age, sex, wealth quintiles based on income, years of education received, physical activity, smoking (never, current, former), alcohol use, anxiety, depression, obesity, diabetes, hypertension, and stroke. Levels of physical activity were assessed with the Global Physical Activity Questionnaire and were classified as low, moderate, and high based on conventional cut-offs [24]. Consumers of at least four (females) or five drinks (males) of any alcoholic beverage per day on at least one day in the past week were considered to be ‘heavy’ drinkers. Those who had ever consumed alcohol but were not heavy drinkers were categorized as ‘non-heavy’ drinkers [25]. Those who claimed to have severe/extreme problems with worry or anxiety in

the past 30 days were considered to have anxiety [26]. Questions based on the World Mental Health Survey version of the Composite International Diagnostic Interview [27] were used for the endorsement of past 12-month DSM-IV depression [28]. Obesity was defined as a body mass index of $\geq 30 \text{ kg/m}^2$ based on measured weight and height [29]. Stroke and diabetes were based solely on self-reported lifetime diagnosis. Hypertension was defined as having at least one of: systolic blood pressure $\geq 140 \text{ mmHg}$; diastolic blood pressure $\geq 90 \text{ mmHg}$; or self-reported diagnosis.

Statistical analysis

The statistical analysis was performed with Stata 14.2 (Stata Corp LP, College station, Texas). The analysis was restricted to those aged ≥ 50 years. The middle-aged was also included in our study as from the viewpoint of prevention of dementia, intervening in middle-age is now considered important [30]. Differences in sample characteristics between those with and without severe/extreme sleep problems were tested by Chi-squared tests and Student's *t*-test for categorical and continuous variables, respectively. Multivariable logistic regression analysis was conducted to assess the association between sleep problems (exposure) and MCI (outcome). We used the four-category sleep problems variable (i.e., none, mild, moderate, severe/extreme) for the analysis using the overall sample, and conducted stratified analysis by age (i.e., 50-64 and ≥ 65 years) or sex. We also conducted test for trend by including the four-category sleep problems variable in the model as a continuous variable. In order to assess whether there is between-country heterogeneity in the association between extreme/severe sleep problems and MCI, country-wise analysis was also conducted. The Higgins's I^2 based on estimates from each country was also calculated to assess between-country heterogeneity. The Higgins's I^2 represents the degree of heterogeneity that is not explained by sampling error with a value of $<40\%$ often considered as negligible and 40-60%

as moderate heterogeneity [31]. A pooled estimate was obtained by fixed-effects meta-analysis.

All regression analyses were adjusted for age, sex, wealth, education, physical activity, smoking, alcohol use, anxiety, depression, obesity, diabetes, hypertension, stroke, and country with the exception of the sex- or country-stratified analyses, which were not adjusted for sex and country, respectively. Adjustment for country was done by including dummy variables for each country in the model as in previous SAGE publications [18]. Under 4.7% of the data were missing for the variables used in the analysis. Complete case analysis was done. The sample weighting and the complex study design were considered in the analyses. Results from the regression analyses 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 32,715 individuals (China $n=12815$; Ghana $n=4201$; India $n=6191$; Mexico $n=2070$; Russia $n=3766$; South Africa $n=3672$) aged ≥ 50 years with preservation in functional abilities [mean (SD) age 62.1 (15.6) years; 51.7% females]. The prevalence of MCI was 15.3%, while the prevalence of mild, moderate, and severe/extreme sleep problems were 28.2%, 15.2%, and 7.5%, respectively. The sample characteristics are shown in **Table 1**. Those with severe/extreme sleep problems were significantly more likely to have MCI, anxiety, depression, diabetes, stroke, and lower levels of wealth, education, and physical activity, while they were more likely to be older and be females. Greater severity of sleep problems was associated with higher prevalence of MCI in a linear fashion in both age groups and sexes (**Figure 1**). For example, in the overall sample, the prevalence of MCI was 12.8% in those without sleep problems, but this figure increased to 24.0% among those with severe/extreme sleep problems. After adjustment for a variety of potential confounders, in the

overall sample, compared to no sleep problems, mild, moderate, severe/extreme sleep problems were significantly associated with 1.40 (95%CI=1.20-1.63), 1.83 (95%CI=1.54-2.16), and 2.69 (95%CI=2.16-3.35) times higher odds for MCI (**Table 2**). The results were similar in the age- or sex-stratified samples. Finally, the country-wise analysis showed that severe/extreme sleep problems are positively associated with MCI in all countries (i.e., OR>1) with the overall estimate being OR=1.80 (95%CI=1.50-2.16), and a low level of between-country heterogeneity was observed (**Figure 2**).

DISCUSSION

Main findings

The present study in a large sample of middle-aged and older adults from LMICs found that the prevalence of MCI increases with increasing severity of sleep problems. In the adjusted model in the overall sample, compared to no sleep problems, mild, moderate, and severe/extreme sleep problems were independently associated with significant 1.40, 1.83, and 2.69 times higher odds for MCI with similar associations being observed between age groups and sex. Severe/extreme sleep problems were positively associated with MCI (i.e., OR>1) in all six countries included in the study with the overall estimate being OR=1.80 (95%CI=1.50-2.16), and a low level of between-country heterogeneity was observed ($I^2=28.2\%$).

Interpretation of the findings

Findings from the present study support those of previous meta-analytical works that have also observed an association between sleep problems and MCI or dementia in high-income countries using smaller samples [8, 9]. Moreover, the present findings add to this literature through showing that the association holds in a large representative sample of middle-aged and older adults from six LMICs.

There are several plausible pathways that likely explain an increased risk of MCI in those who have sleep problems. First, extended wakefulness leads to an accumulation and impaired clearance of toxic metabolites in the brain, which have been implicated in the pathogenesis of dementia [6]. Second, inflammation induced by chronic sleep deficiency may increase risk of MCI or dementia [7, 32]. For example, chronic inflammation has been associated with greater abnormalities in the brain's white matter, ultimately affecting cognitive function and possibly leading to MCI/dementia [33]. Third, sleep problems may disrupt sleep architecture, leading to a reduction in slow-wave sleep. Low levels of slow-wave sleep are associated with higher levels of cerebral spinal fluid amyloid beta, which may lead to brain amyloid plaque deposition that is toxic to neurons [34]. Fourth, sleep problems likely lead to excessive daytime sleepiness resulting in a reduction in intellectually stimulating activities and physical activity that may protect against MCI [35]. Fifth, sleep problems have been found to be associated with a poor quality diet, low in vegetable consumption [36], and a diet of low quality has been shown to increase risk of MCI or dementia. For example, a recent meta-analysis including nine studies concluded that increased consumption of fruit and vegetables is associated with a reduced risk of cognitive impairment and dementia [37]. Finally, the sleep problem-MCI/dementia association is likely bidirectional with several studies showing that those with MCI/dementia manifest sleep problems [10]. The manifestation of sleep problems among those with MCI/dementia may be due to neurophysiological sleep problems as a result of diminished sleep spindles that are key processes involved in overnight memory consolidation [10].

Public health and clinical implications

Findings from the present study suggest that improving sleep quality among middle-aged and older adults from LMICs may be an appropriate intervention to reduce risk of incident MCI

or dementia. It has been suggested that interventions to improve sleep should focus on relaxation techniques, sleep hygiene or reduce sleep interruptions and daytime bright light exposure [38]. Interestingly, physical activity promotion has been observed to improve sleep and aid in the prevention against MCI or dementia [39, 40]. For example, one study observed that the cognitive functions and sleep quality of elderly individuals improved when a 20-week Physical Activity Program was implemented [41]. Therefore, interventions that aim to promote physical activity in LMICs should be considered. Interventions should also aim to modify diet to reduce caffeine, foods that are high in fat and carbohydrates, and alcohol, which can disrupt sleep patterns while also contributing to risk for MCI. Along these lines, smoking cessation may also prove beneficial in improving sleep quality and reducing risk for MCI. Moreover, pharmacological interventions may be considered. For example, a recent systematic review that focused on sleep in MCI and mild Alzheimer's disease found that Suvorexant significantly increased total sleep time and sleep efficiency whilst reducing wake after sleep onset time. Furthermore, transcranial Stimulation enhanced cortical slow oscillations and spindle power during daytime naps, while melatonin significantly reduced sleep latency and sleep to wakefulness transitions [42].

Strengths and limitations

The large sample of middle-aged and older adults from six LMICs is a clear strength of the present paper. To the best of our knowledge, this is the first multi-country and nationally representative study from LMICs. However, findings must be interpreted in light of the study's limitations. First, the study is cross-sectional in nature, and it is not known whether sleep problems lead to MCI or vice versa, or where the covariates lie on the causal pathway. However, as previously discussed, the sleep problem-MCI/dementia relationship is likely to be bi-directional [43]. Second, owing to the measure of sleep in the present study, we were

not able to investigate the association between different symptoms (e.g., difficulty falling asleep, early morning awakenings, waking up in the middle of the night) or specific sleep disorders (e.g., insomnia, narcolepsy, obstructive sleep apnea) and their relations to MCI. It is possible that some sleep problems when compared to others may be more strongly associated with MCI. Future studies should aim to investigate such associations. Finally, participants with mild forms of dementia could have been included in our study sample as the study did not include a clinical assessment of dementia.

Conclusion

In this large representative sample of middle-aged and older adults from six LMICs, it was found that sleep problems were associated with higher odds for MCI. Interventions to improve sleep quality (e.g., through increasing levels of physical activity) among middle-aged and older adults in LMICs would be broadly beneficial to mental and physical health, and may be an effective strategy in reducing risk of MCI or dementia in this setting.

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Tables and Figures

Table 1 Sample characteristics (overall and by severe/extreme sleep problems)

Category		Total	Severe/extreme sleep problems		P-value ^a
			No	Yes	
Mild cognitive impairment	No	84.7	85.4	76.0	<0.001
	Yes	15.3	14.6	24.0	
Age (years)	Mean (SD)	62.1 (15.6)	61.9 (15.5)	64.9 (15.6)	<0.001
Sex	Male	48.3	49.6	32.6	<0.001
	Female	51.7	50.4	67.4	
Wealth	Poorest	16.9	16.2	25.3	<0.001
	Poorer	18.9	18.8	20.1	
	Middle	19.3	19.2	20.7	
	Richer	21.5	21.9	16.4	
	Richest	23.4	23.8	17.5	
Education (years)	Mean (SD)	6.1 (8.9)	6.2 (8.9)	4.4 (8.0)	<0.001
Physical activity	High	49.9	50.4	43.9	<0.001
	Moderate	23.0	23.1	21.9	
	Low	27.1	26.5	34.3	
Smoking	Never	58.6	58.8	56.0	0.058
	Current	35.0	34.9	35.3	
	Quit	6.4	6.2	8.7	
Alcohol consumption	Never	66.7	66.6	68.8	0.330
	Non-heavy	29.1	29.2	28.0	
	Heavy	4.2	4.3	3.1	
Anxiety	No	93.0	95.4	62.8	<0.001
	Yes	7.0	4.6	37.2	
Depression	No	94.5	95.7	80.2	<0.001
	Yes	5.5	4.3	19.8	
Obesity	No	88.5	88.6	87.1	0.323
	Yes	11.5	11.4	12.9	
Diabetes	No	93.3	93.5	89.7	<0.001
	Yes	6.7	6.5	10.3	
Hypertension	No	45.2	45.3	43.5	0.383
	Yes	54.8	54.7	56.5	
Stroke	No	97.2	97.5	93.8	<0.001
	Yes	2.8	2.5	6.2	

Abbreviation: SD Standard deviation

^a P-value calculated by Chi-squared tests and Student's *t*-tests for categorical and continuous variables, respectively.

Table 2 Association between sleep problems (exposure) and mild cognitive impairment (outcome) estimated by multivariable logistic regression

		Age			Sex	
		Overall	50-64 y	≥65 y	Female	Male
Sleep problems	None	1.00	1.00	1.00	1.00	1.00
	Mild	1.40**	1.68**	1.05	1.27*	1.57**
		[1.20,1.63]	[1.41,2.00]	[0.82,1.35]	[1.07,1.50]	[1.24,1.99]
	Moderate	1.83**	1.82**	1.70**	1.75**	1.85**
		[1.54,2.16]	[1.46,2.27]	[1.33,2.17]	[1.45,2.10]	[1.37,2.48]
	Severe/extreme	2.69**	2.61**	2.56**	2.23**	3.64**
		[2.16,3.35]	[1.88,3.64]	[1.86,3.53]	[1.68,2.96]	[2.52,5.25]

Data are odds ratio [95% confidence interval].

Models are adjusted for age, sex, wealth, education, physical activity, smoking, alcohol use, anxiety, depression, obesity, diabetes, hypertension, stroke, and country, with the exception of the sex-stratified analyses which were not adjusted for sex.

Test for trend significant for all samples (P<0.001).

** P<0.001, *P<0.01

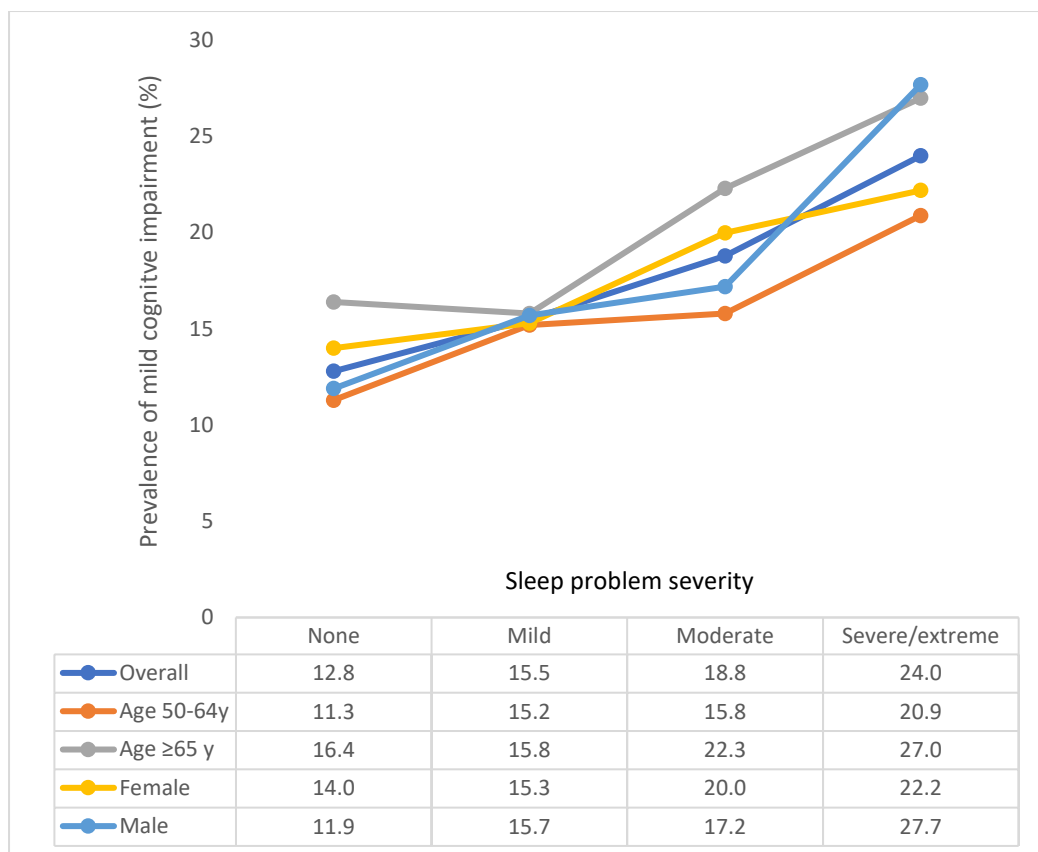


Figure 1 Prevalence of mild cognitive impairment by severity of sleep problems

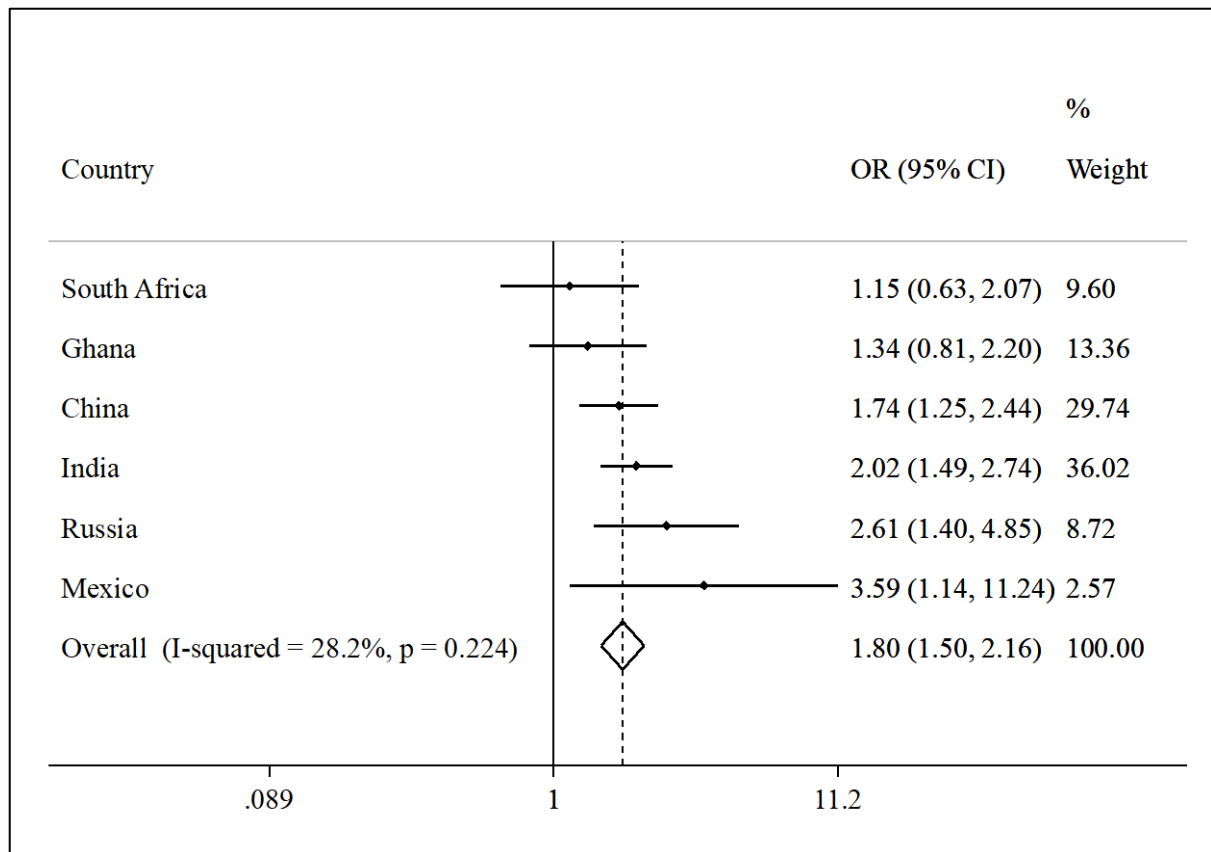


Figure 2 Country-wise association between extreme/severe sleep problems and mild cognitive impairment (outcome) estimated by multivariable logistic regression

Abbreviation: OR Odds ratio; CI Confidence interval

Models are adjusted for age, sex, wealth, education, physical activity, smoking, alcohol use, anxiety, depression, obesity, diabetes, hypertension, and stroke.

Overall estimate was obtained by meta-analysis with fixed effects.