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Chronic physical conditions, multimorbidity, and mild cognitive impairment in low- and middle-income countries

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Abstract

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Supplementary material

Title: Details of variables and additional analyses

Background/Objectives—Chronic physical conditions and multimorbidity may be modifiable risk factors for dementia. However, data from low- and middle-income countries (LMICs) are lacking. This study thus assessed the association of chronic physical conditions and multimorbidity with mild cognitive impairment (MCI) in LMICs.

Design—Nationally representative, cross-sectional, community-based.

Setting—Six countries which participated in the World Health Organization's Study on Global Ageing and Adult Health.

Participants—32,715 adults aged ≥50 years [mean (SD) age 62.1 (15.6) years; 51.7% females].

Measurements—The definition of MCI was based on the recommendations of the National Institute on Ageing-Alzheimer's Association. Ten chronic conditions (angina, arthritis, asthma, cataract, chronic lung disease, diabetes, edentulism, hearing problems, hypertension, stroke) were assessed. Multivariable logistic regression analysis was conducted to assess the association between chronic physical conditions, multimorbidity (i.e., ≥2 chronic conditions), and MCI.

Results—The prevalence (95%CI) of multimorbidity and MCI were 49.8% (48.1%–51.5%) and 15.3% (14.4%–16.3%), respectively. After adjustment for potential confounders, edentulism (OR=1.24), arthritis (OR=1.24), chronic lung disease (OR=1.29), cataract (OR=1.33), stroke (OR=1.94), hearing problems (OR=2.27), and multimorbidity (OR=1.40) were significantly associated with higher odds for MCI. Compared to those with no chronic conditions, there was a gradual increase in the odds for MCI ranging from one condition (OR=1.21; 95%CI=1.03–1.42) to ≥4 conditions (OR=2.07; 95%CI=1.70–2.52).

Conclusion—These results highlight the need to investigate the underlying mechanisms linking chronic conditions and MCI, and whether the prevention or treatment of chronic conditions or multimorbidity can reduce the onset of cognitive decline and subsequent dementia especially in LMICs.

Keywords

Mild cognitive impairment; chronic physical conditions; multimorbidity; low- and middle-income countries

Introduction

The world population is aging at an unprecedented speed due to increasing life expectancy. The number of individuals aged ≥65 years is projected to increase from 524 million in 2010 to 1.5 billion by 2050, with most of the increase occurring in low- and middle-income countries (LMICs).[1] This demographic change will inevitably be accompanied by increases in non-communicable diseases (NCDs) such as heart disease, cancer, and diabetes,[1] as well as neuropsychiatric disorders such as dementia.[2] In particular, dementia is projected to increase sharply as the incidence of dementia doubles with every 6.3 years increase in age in the older population.[3] Indeed, the number of people living with dementia is projected to increase from current figures of 46 million to 131.5 million by 2050.[3] Among people with dementia, the proportion of those residing in LMICs are expected to increase from current rates of 58% to 68% in 2050.[3]

Dementia is one of the major causes of disability and dependency in the older population and also has significant social and economic impacts.[4] However, there are currently no drugs to cure dementia or to modify its clinical course, and symptomatic medication only has modest effects.[5, 6] Thus, identifying modifiable risk factors of the precursory stage of dementia to establish interventions to prevent or delay the onset of dementia is a priority. Specifically, mild cognitive impairment (MCI) is considered to be a preclinical transitional state of dementia[7] for which targeted interventions may be feasible. The conversion rate of MCI to dementia has been estimated to be 12%, 20%, and 50% at 1, 3, and 5 years, respectively.[8] Previously reported potentially modifiable risk factors for MCI include factors such as low physical activity, obesity, diabetes, and hypertension.[9]

In terms of single chronic physical diseases, most previous studies have focused on cardio-metabolic diseases,[10] but studies on other chronic conditions are limited. Furthermore, there is a notable paucity of data on the association between multimorbidity (i.e., coexistence of ≥2 chronic conditions) and MCI. Multimorbidity is highly prevalent in the older population, and 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]

To our knowledge, as yet, only a few studies have specifically focused on the association between multimorbidity and MCI in the general population.[13, 14] One U.S. longitudinal study found that multimorbidity is associated with a 1.38 (95%CI=1.05–1.82) times higher risk for MCI or dementia among individuals aged ≥70 years (n=2176). Another cross-sectional study from Sweden found that compared to no chronic conditions, 2–3 conditions are associated with 3.03 (95%CI=1.20–7.64) times higher odds for MCI among individuals aged ≥75 years (n=1435).[14] However, these studies were conducted in a limited location in single high-income countries with a focus only on the elderly. Thus, it is unknown whether these results are applicable to other age groups or settings. Assessment of cognitive function and its risk factors at earlier ages is important from the point of view of prevention of dementia as cognitive dysfunction appears up to 10 years before the actual dementia diagnosis,[15] and the importance of intervening in mid-life has been emphasized.[16–18] Also, data on this topic from LMICs are particularly important given that increasing trends in cardiovascular diseases coupled with epidemics of obesity and increasing hypertension can result in upward trends in dementia prevalence and incidence in this setting.[3] Furthermore, the association between multimorbidity and MCI may differ in LMICs due to different disease profiles, population age structure, and health care systems as well as higher prevalence of poverty and low education, and suboptimal treatment for chronic conditions.[19]

Thus, the main aim of the current study was to assess the association between multimorbidity and MCI among adults aged ≥50 years in six LMICs using data from the WHO Global Ageing and Adult Health study (SAGE).

Methods

The survey

Data from the SAGE were analyzed. This survey was undertaken in China, Ghana, India, Mexico, Russia, and South Africa between 2007 and 2010. Based on the World Bank

classification at the time of the survey, all of these countries were LMICs. Details of the survey methodology have been published elsewhere.[20] In brief, in order 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. Those who were unable to undertake the interview because of limited cognitive function were not included in the current study. 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) (Outcome)

MCI was ascertained based on the recommendations of the National Institute on Aging-Alzheimer's Association.[21] We applied the identical algorithms used in previous publications using a dataset with the same survey questions to identify MCI.[9, 22] Briefly, individuals fulfilling all of 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 then 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,[23] which assessed learning and episodic memory; digit span forward and backwards from the Weschler Adult Intelligence Scale,[24] that evaluated attention and working memory; and the animal naming task,[23] which assessed verbal fluency.

c. Preservation of independence in select functional abilities [absence of severe/extreme difficulties in performing activities of daily living (ADL)]: was assessed by questions on self-reported difficulties with basic ADL, which has been suggested to be a measure of individuals' functional status, in the past 30 days.[25] 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 ADL. Although these questions were on difficulty with ADL rather than dependence, we assumed that those with severe or extreme levels of difficulty in performing these tasks are highly unlikely to have preservation of independence in functional

abilities. 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.

Chronic conditions and multimorbidity (Exposures)

We included all ten chronic physical conditions (angina, arthritis, asthma, cataract, chronic lung disease, diabetes, edentulism, hearing problems, hypertension, stroke), assessed by self-report of diagnosis, symptoms, interviewer observation, or blood pressure measurement (See Supplementary Table S1 for details), for which data were available in the SAGE. These conditions have been reported to be associated with poor cognitive performance.[9, 26–33] The total number of chronic conditions was calculated and categorized as 0, 1, 2, 3, and ≥4. Multimorbidity was defined as ≥2 chronic conditions.[34]

Control variables

The analysis adjusted for a number of potential confounders which have been reported to be linked with both MCI and chronic physical conditions.[9, 35, 36] Sociodemographic control variables included age, sex, education (no formal, at least some primary, ≥secondary completed), and wealth quintiles based on country-specific income. Other variables included health behavior [smoking (never, current, former), alcohol consumption (never, non-heavy, heavy), physical activity], body mass index (BMI) based on measured weight and height (<18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m^2), and depression (See Supplementary Table S2 for details on these variables).

Statistical analysis

The statistical analysis was performed with Stata 14.1 (Stata Corp LP, College station, Texas). The analysis was restricted to those aged ≥50 years. The difference in the prevalence of multimorbidity or MCI by sample characteristics was tested by Chi-squared tests. Tetrachoric correlations between each chronic condition was calculated among those with MCI.

We conducted multivariable logistic regression analysis to assess the association between the number of chronic conditions including multimorbidity (≥2 chronic conditions) or each of the 10 individual chronic conditions (exposure variables) and MCI (outcome) using the overall sample (age ≥50 years) and by age groups (50–64 and ≥65 years) as previous studies have shown that the risk factors of MCI may differ between mid-life and late-life.[9, 37] Finally, in order to assess the degree of between-country heterogeneity in the association between multimorbidity and MCI, we calculated the Higgin's I^2 based on country-wise estimates. This represents the degree of heterogeneity that is not explained by sampling error with values of 25%, 50%, and 75% often being considered as low, moderate, and high levels of heterogeneity.[38]

The regression analyses were all adjusted for age, sex, education, wealth, smoking, alcohol consumption, physical activity, BMI, depression, and country with the exception of the

country-wise analysis which did not adjust for country. When the individual chronic conditions were the exposure variable, the models were also adjusted for the presence of other chronic illness to account for comorbid chronic conditions. This variable included information on whether the individual had any of the other nine chronic conditions (Y/N). Country adjustment was done by including dummy variables for each country. Under 5% of the data were missing for the variables used in the analysis. All variables were included in the models as categorical variables with the exception of age when used as a continuous variable. Complete-case analysis was done. The sample weighting and the complex study design were taken into account 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 analytical sample consisted of 32,715 individuals (China n=12,815; Ghana n=4201; India n=6191; Mexico n=2070; Russia n=3766; South Africa n=3672) aged ≥50 years. The mean (SD) age was 62.1 (15.6) years and 51.7% were females. The prevalence (95%CI) of multimorbidity and MCI were 49.8% (48.1%–51.5%) and 15.3% (14.4%–16.3%), respectively. The country-wise prevalence of individual chronic physical conditions are provided in Supplementary Table S3. Older age, female sex, lower levels of education and wealth, former smoking, low physical activity, BMI ≥30 kg/m^2, and depression were factors associated with higher prevalence of multimorbidity (Table 1).

Compared to not having the condition, all single chronic conditions assessed were significantly associated with higher prevalence of MCI with the exception of angina, cataract, and diabetes (Table 2). There was a linear increase in the prevalence of MCI with increasing numbers of chronic conditions. Among individuals with MCI, there was a particularly strong correlation between: angina and asthma; angina and chronic lung disease; asthma and chronic lung disease; diabetes and hypertension; edentulism and hearing problems; stroke and hypertension (See Supplementary Table S4).

In the overall sample, the multivariable regression analysis showed that all individual chronic conditions are associated with higher odds for MCI but statistical significance was only reached for arthritis (OR=1.24), cataract (OR=1.33), chronic lung disease (OR=1.29), edentulism (OR=1.24), hearing problems (OR=2.27), and stroke (OR=1.94), while the OR (95%CI) for multimorbidity was 1.40 (95%CI=1.23–1.58) (Table 3). These associations were similar in the two age groups with the exception of angina and chronic lung disease which were only significantly associated with MCI in the younger age group. The association between MCI and multimorbidity showed a moderate level of between-country heterogeneity [Higgin's I^2 64% (95%CI=12%–85%)] (See Supplementary Figure S1). Compared to no chronic conditions, there was a gradual increase in the odds for MCI ranging from one condition (OR=1.21; 95%CI=1.03–1.42) to ≥4 conditions (OR=2.07; 95%CI=1.70–2.52) in the overall sample (Table 4). In terms of other potentially modifiable risk factors for MCI, in the overall sample, smoking, low physical activity, and obesity (BMI ≥30kg/m^2) were also associated with higher odds for MCI independent of the number of

chronic conditions although some of these factors were not significantly associated with MCI in one of the age groups (Table 4).

Discussion

In this study, several chronic conditions and multimorbidity were significantly associated with a higher odds for MCI. There was also a gradual increase in the odds for MCI with increasing number of chronic conditions. The strength of the study includes the large sample size and the use of nationally representative samples from six countries, which comprise nearly half of the worldwide population.[20] Our study results expand the understanding of the effects of modifiable risk factors on the development of MCI/dementia, by showing for the first time that multimorbidity is associated with MCI in mid-life and in LMICs. This is an important finding since previous studies have suggested that strategies to address risk factors for dementia should take place in midlife.[16–18] Furthermore, our study has important implications for public health in LMICs, as in this context, MCI/dementia is often underdiagnosed,[39] health care is suboptimal,[19] and there is an urgent need for the development of strategies to address and manage the growing epidemic of chronic diseases [40] which also constitute risk factors for MCI/dementia.

We found that angina (only 50–64 years), edentulism, arthritis, chronic lung disease, cataract, stroke, and hearing problems are significantly associated with higher odds for MCI. All these factors have been observed to be associated with poor cognitive performance, even in study populations from LMICs,[26, 28–30, 32, 33, 41–43] although with mixed results for some conditions.[32, 44, 45] Similar to some previous studies, we did not observe a significant association between diabetes or hypertension and MCI.[46, 47] these two conditions have been recognized as potentially modifiable risk factors for dementia.[16] Thus, further studies from LMICs are warranted to assess whether our results are corroborated. In particular, the results on diabetes may have differed if objective data such as blood glucose were available.

Our study results are in line with previous studies reporting a high risk for MCI among those with multiple chronic conditions.[13, 14, 48] Of note, one study found that a faster accumulation of chronic conditions was associated with greater decline in cognitive function.[48] Multimorbidity may reflect an age-related multisystem failure which can also be accompanied by neurodegeneration or cognitive decline.[48] Some combinations of chronic conditions may act synergistically to accelerate cognitive decline as in the case of heart disease and cerebrovascular disease, while polypharmacy and drug interactions may also increase the risk for cognitive decline in individuals with multimorbidity.[13] One study found that several health problems not individually recognized as risk factors for dementia are associated with increased risk for dementia when combined into a frailty index.[49] This finding, together with increasing evidence that multimorbidity is related to poor cognitive performance, reinforces the notion that promoting overall health of the population might mitigate the burden of late-life dementia.[50] Finally, a moderate level of between-country heterogeneity in the association between multimorbidity and MCI was found. Although the reason for this heterogeneity is not clear, it may be related to factors such as access to health care and quality of care (e.g., availability of drugs). This is an area for future research.

If confirmed with longitudinal and interventional studies, the key to prevention of MCI and subsequent dementia may be to strengthen a multidisciplinary approach simultaneously targeting both lifestyle factors and physical health outcomes (e.g., chronic diseases, multimorbidity). Health promotion can specifically target the risk factors contributing to chronic physical conditions and ultimately multimorbidity which might entail diet, exercise, and smoking cessation, all of which are also considered to be important for dementia prevention even in the absence of chronic physical conditions.[16]

To address chronic diseases in LMICs, the Innovative Care for Chronic Conditions framework developed by the World Health Organization provides a health systems roadmap but it still lacks incorporation of the complexity associated with multimorbidity [51] In LMICs, there is a particular need to enhance integration of care, capacity building, and improve quality of services to address multimorbidity.[52]

The study results should be interpreted in the light of several limitations. First of all, although we included a wide variety of important chronic conditions, we lacked data on diseases such as hypercholesterolemia and HIV. Second, symptom-based algorithms were used to define some chronic conditions to minimize under-diagnosis but some level of misclassification may still exist, while under-diagnosis is likely to have occurred for diseases based solely on self-report (i.e., diabetes, stroke). For example, chronic lung diseases and asthma are not easy to differentiate for the overlapping symptoms especially in older populations.[53] Third, because the study was not designed to generate clinical diagnoses of dementia, some individuals with mild dementia may have been included in our analytical sample. However, the prevalence of MCI in our study was within previously reported figures.[54] Furthermore, in line with previous publications,[9, 22] we used a definition for preservation of independence in functional abilities which was only based on two ADL domains so as not to overexclude MCI cases with disability not related with their cognitive ability. There is currently no consensus in terms of the acceptable level of functional impairment that individuals with MCI could present[55] but it is reassuring that the results were similar even when applying a different definition for disability (i.e., impairment in all six domains of ADL[25]). Furthermore, we lacked data on dietary factors, medication, and past alcohol drinking patterns which may also explain the chronic condition-MCI link. Next, the response rate for the SAGE survey was comparable to or higher than that of other national surveys on ageing in most of the countries included in our study. Nevertheless, there was some between-country variability and the response rate for Mexico was low. Finally, because this was a cross-sectional study, causality cannot be inferred and the possibility of reverse causality cannot be dismissed.

In conclusion, these results show that several chronic conditions and multimorbidity are associated with MCI. Our study results highlight the need to investigate the underlying mechanisms linking chronic conditions and MCI, and whether the prevention or treatment of chronic conditions or multimorbidity can reduce the onset of cognitive decline and subsequent dementia especially in LMICs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of interest: None.

Author's contributions: AK conceived the study idea. AK, EL, BS, DV analysed and interpreted the data, and AK wrote the main body of the text. All authors contributed to the drafting of the manuscript, interpreted the data, and commented for intellectual content. All authors read and approved the final manuscript.

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Impact statement

We certify that this work is novel or confirmatory of recent novel clinical research (Vassilaki M, Aakre JA, Cha RH, et al. Multimorbidity and Risk of Mild Cognitive Impairment. J Am Geriatr Soc. 2015;63: 1783–1790).

The potential impact of this research on clinical care of health policy includes the following:

- Edentulism, arthritis, chronic lung disease, cataract, stroke, and hearing problems, as well as multimorbidity were associated with higher odds for mild cognitive impairment in six low- and middle-income countries.
- Independent of the number of chronic conditions, lifestyle factors such as low physical activity, obesity, and smoking were also associated with mild cognitive impairment.
- If confirmed with longitudinal and intervention studies, the key to prevent mild cognitive impairment and subsequent dementia may be a multidisciplinary approach simultaneously targeting both lifestyle factors and physical health outcomes.

Table 1

Sample characteristics and prevalence of multimorbidity by each characteristic

Characteristic	Category	%[a]	% with multimorbidity	P-value
Age (years)	50–59	47.3	37.6	<0.001
	60–69	30.2	53.1	
	70–79	17.7	70.2	
	≥80	4.8	74.6	
Sex	Female	51.7	54.9	<0.001
	Male	48.3	44.4	
Education	No formal	28.5	54.3	<0.001
	At least primary	28.2	46.6	
	≥Secondary completed	43.3	49.0	
Wealth	Poorest	16.9	53.2	0.005
	Poorer	18.9	53.1	
	Middle	19.4	50.0	
	Richer	21.5	48.0	
	Richest	23.3	46.3	
Smoking	Never	58.7	51.0	<0.001
	Current	34.9	46.4	
	Former	6.4	57.4	
Alcohol consumption	Never	66.7	49.0	<0.001
	Non-heavy	29.1	52.6	
	Heavy	4.2	39.8	
Low physical activity	No	77.6	47.8	<0.001
	Yes	22.4	56.8	
BMI (kg/m^2)	<18.5	16.2	52.1	
	18.5–24.9	47.8	44.2	<0.001
	25.0–29.9	24.5	51.4	
	≥30	11.5	67.5	
Depression	No	94.5	48.3	<0.001
	Yes	5.5	76.5	

Abbreviation: BMI Body mass index

Percentage is based on weighted sample.

[a]Denominator ranges from 31179 to 32715.

Table 2

Prevalence of chronic conditions and the proportion of individuals with mild cognitive impairment by presence or absence of chronic conditions

Characteristic	Category	%[a]	% with MCI	P-value
Angina	No	82.8	15.1	0.286
	Yes	17.2	16.3	
Arthritis	No	71.0	14.2	<0.001
	Yes	29.0	17.9	
Asthma	No	92.5	15.1	0.032
	Yes	7.5	17.9	
Cataract	No	73.6	14.9	0.074
	Yes	26.4	16.5	
Chronic lung disease	No	85.0	14.5	<0.001
	Yes	15.0	19.6	
Diabetes	No	93.3	15.3	0.703
	Yes	6.7	15.8	
Edentulism	No	87.8	14.7	<0.001
	Yes	12.2	20.0	
Hearing problems	No	94.7	14.2	<0.001
	Yes	5.3	32.0	
Hypertension	No	45.2	13.3	<0.001
	Yes	54.8	17.0	
Stroke	No	97.3	15.0	<0.001
	Yes	2.7	27.6	
No. of chronic conditions	0	19.2	10.7	<0.001
	1	31.0	14.0	
	2	23.6	15.4	
	3	13.8	18.0	
	≥4	12.5	21.2	

Abbreviation: MCI Mild cognitive impairment

Percentage is based on weighted sample.

[a]Denominator ranges from 31940 to 32662.

Table 3

Associations of physical health conditions and multimorbidity with mild cognitive impairment estimated by multivariable logistic regression

	Overall (Age ≥50 years)		Age 50–64 years		Age ≥65 years	
Chronic physical condition	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**
Angina	1.14	[0.98,1.33]	1.34**	[1.09,1.63]	0.98	[0.77,1.24]
Arthritis	1.24***	[1.10,1.40]	1.24**	[1.06,1.44]	1.30**	[1.09,1.54]
Asthma	1.18	[0.96,1.45]	1.13	[0.85,1.50]	1.22	[0.91,1.63]
Cataract	1.33***	[1.15,1.55]	1.44**	[1.15,1.79]	1.28**	[1.06,1.55]
Chronic lung disease	1.29**	[1.10,1.52]	1.46***	[1.17,1.83]	1.14	[0.91,1.44]
Diabetes	1.13	[0.90,1.42]	1.32	[0.93,1.89]	1.05	[0.80,1.38]
Edentulism	1.24*	[1.03,1.48]	1.23	[0.95,1.58]	1.21	[0.95,1.55]
Hearing problems	2.27***	[1.84,2.78]	2.86***	[2.10,3.89]	1.91***	[1.50,2.43]
Hypertension	1.08	[0.96,1.20]	1.04	[0.91,1.19]	1.15	[0.97,1.37]
Stroke	1.94***	[1.49,2.53]	2.35***	[1.57,3.52]	1.65**	[1.14,2.39]
Multimorbidity	1.40***	[1.23,1.58]	1.43***	[1.25,1.64]	1.42***	[1.16,1.73]

Abbreviation: OR Odds ratio; CI Confidence interval

Multimorbidity was defined as ≥2 physical health conditions.

Models are adjusted for age, sex, education, wealth, body mass index, smoking, alcohol consumption, physical activity, depression, other physical illness, and country with the exception of multimorbidity which was not adjusted for other physical illness.

* p<0.05,

** p<0.01,

*** p<0.001

Table 4

Association between number of chronic physical conditions and other modifiable factors with mild cognitive impairment estimated by multivariable logistic regression

		Overall (Age ≥50 years)		Age 50–64 years		Age ≥65 years	
Characteristic	**Category**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**
No. of chronic conditions	0	1.00		1.00		1.00	
	1	1.21*	[1.03,1.42]	1.23*	[1.02,1.48]	1.14	[0.83,1.55]
	2	1.37***	[1.14,1.63]	1.40**	[1.14,1.73]	1.33	[0.91,1.95]
	3	1.75***	[1.43,2.14]	1.91***	[1.45,2.51]	1.66**	[1.21,2.27]
	≥4	2.07***	[1.70,2.52]	2.41***	[1.76,3.29]	1.85***	[1.36,2.50]
Smoking	Never	1.00		1.00		1.00	
	Current	1.20*	[1.01,1.43]	1.23*	[1.00,1.50]	1.24	[0.91,1.69]
	Former	1.20	[0.97,1.50]	1.16	[0.86,1.58]	1.22	[0.88,1.69]
Alcohol consumption	Never	1.00		1.00		1.00	
	Non-heavy	0.97	[0.82,1.15]	1.03	[0.85,1.26]	0.95	[0.73,1.23]
	Heavy	1.22	[0.93,1.61]	1.18	[0.81,1.72]	1.31	[0.86,2.00]
Low physical activity	No	1.00		1.00		1.00	
	Yes	1.24**	[1.08,1.43]	0.83	[0.69,1.00]	1.72***	[1.40,2.11]
BMI (kg/m^2)	<18.5	1.21	[1.00,1.47]	1.44**	[1.11,1.87]	0.95	[0.67,1.34]
	18.5–24.9	1.00		1.00		1.00	
	25.0–29.9	0.93	[0.81,1.06]	1.07	[0.90,1.27]	0.78*	[0.64,0.95]
	≥30.0	1.30*	[1.02,1.65]	1.54**	[1.12,2.11]	1.06	[0.76,1.49]
Depression	No	1.00		1.00		1.00	
	Yes	0.93	[0.69,1.24]	0.87	[0.61,1.25]	0.90	[0.57,1.44]

Abbreviation: OR odds ratio; CI confidence interval; BMI Body mass index

The model is mutually adjusted for all variables in the Table, sociodemographic variables (age, sex, education, wealth), and country.

* p<0.05,

** p<0.01,

*** p<0.001