**Associations between handgrip strength and mild cognitive impairment in middle-aged and older adults in six low- and middle income countries**

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**Abstract**

**Objectives:** A number of small scale, single country studies have suggested that muscular weakness may be a biomarker for cognitive health, mild cognitive impairment (MCI) and dementia. However, multinational, representative studies are lacking, particularly from low- and middle-income countries (LMICs). Thus, we assessed the association between muscular strength (measured by maximal handgrip) and MCI in six LMICs (China, Ghana, India, Mexico, Russia, South Africa), using nationally representative data.

**Methods:** Cross-sectional, community-based data on individuals aged ≥50 years from the World Health Organization’s Study on Global Ageing and Adult Health were analyzed. MCI was defined according to the National Institute on Ageing-Alzheimer’s Association criteria. Weak handgrip strength was defined as <30kg for men and <20 kg for women using the average value of two handgrip measurements of the dominant hand. Multivariable logistic regression analysis was conducted to assess the association between muscular strength and MCI.

**Results:** 32,715 participants were included (mean age 62.± SD 15.6 years and 51.7% female). The prevalence of MCI and weak handgrip strength were 15.3% (95%CI=14.4%-16.3%) and 46.5% (95%CI=43.6%-49.5%) respectively. After adjustment for potential confounders, weak handgrip strength was associated with 1.41 (95%CI=1.23-1.61) times higher odds for MCI. The corresponding figures for those aged 50-64 years and ≥65 years were 1.35 (95%CI=1.14-1.60) and 1.54 (95%CI=1.27-1.86) respectively.

**Conclusions:** Muscular weakness may provide a clinically useful indicator of MCI risk. Increasing our understanding of the connection between muscular and cognitive function could ultimately lead to the development and broader implementation of resistance-training interventions targeting both physical and cognitive health.

**Keywords:** dementia; physical fitness; muscular strength; low- and middle-income countries

**Introduction**

Dementia is one of the most important causes of dependency and disability in the global adult population (Wimo, et al. 2017). It is estimated that currently almost 50 million people are diagnosed with dementia, and this figure is projected to increase to 132 million by 2050 (Prince 2015). The prevalence of dementia in low- and middle-income countries (LMICs) is rapidly growing owing to an increase in life expectancy. This evolution places pressure on the socio-economic systems in these countries (Wimo et al. 2017). Specifically, the proportion of those with dementia residing in LMICs is expected to rise from 58% in 2015 to 68% in 2050 (Alzheimer's Disease International 2015). As there are at present no effective treatments for dementia (Cummings 2004; Kaduszkiewicz, et al. 2005), there is an increasing emphasis on intervening in the precursory stage of dementia such as mild cognitive impairment (MCI). The identification of modifiable risk factors for cognitive decline among people with MCI can serve as a target for prevention of later onset dementia. As a next step, evidence for the efficacy and (cost-)effectiveness of prevention programs that focus on local contexts and modifiable risk factors needs to be strengthened in order to design effective interventions and appropriate public health policies. This may be particularly relevant in the context of LMICs where availability of health care for dementia may be limited.

An emerging body of evidence shows that non-cognitive features such as muscular weakness and slow gait speed (measures of physical functioning) may be useful biomarkers to predict the incidence of cognitive decline (Boyle, et al. 2010; Fritz, et al. 2017; Veronese, et al. 2016). Changes in the performance of motor tasks (e.g., handgrip strength and gait) have been associated with changes in cognition and are a harbinger of impending cognitive decline (Cohen, et al. 2016; Fritz et al. 2017). This may be due to several mechanisms. First, both cognitive and motor performance rely upon the nervous system to execute physical activities, thus, any deficit in the nervous system may result in deficits in cognitive and motor functioning (Boyle et al. 2010). Second, white matter hyperintensities, which are a common neuropathological characteristic of MCI (Boyle, et al. 2016), have been associated with greater cognitive (Boyle et al. 2016) and muscular mass decline (Kohara, et al. 2017) and slowing of gait speed (Ghanavati, et al. 2018). Finally, participation in physical activity improves muscular fitness (Opdenacker, et al. 2011) while it may be usefulfor maintaining neuronal health (Engeroff, et al. 2018), indicating that a person’s lifestyle serves as a mediating factor to offset potential cognitive decline and physical frailty. From a public health and clinical perspective, the assessment of handgrip strength is of particular relevance as it is an objective measure of muscular fitness which is easily measurable at a low cost (Leong, et al. 2015). Stronger handgrip strength is also related to a better ability to perform self-care tasks (Gopinath, et al. 2017). Although it is well established that increasing age is associated with a decline in physical and cognitive abilities, the association between these abilities has most often been reported in normal aging studies and less in people with MCI (Fritz et al. 2017). Additionally, whereas multiple population-scale studies have shown associations between weak handgrip and cognitive impairments in high-income countries (Firth, et al. 2018; Fritz et al. 2017; Moon, et al. 2016), this is currently under-explored in LMICs. To the best of our knowledge, the only population-based study from a LMIC exploring the association between handgrip strength and cognitive impairment demonstrated that in 564 older Colombian adults (i.e. 65 years of age or older) in Bogota, having cognitive impairment is significantly associated with weak handgrip strength (OR=2.25; 95%CI=1.52-3.33) (Garcia-Cifuentes, et al. 2017). Whilst novel, the lack of nationally representative population-based studies investigating the associations between handgrip strength and cognitive impairment in LMICs is an important research gap given the rapid increase of people with dementia and other cognitive impairment in these countries. Furthermore, this study from Colombia was not specifically on MCI which may be more strongly related with risk for future dementia. More research in LMICs is needed as the association between hand grip strength and MCI may differ in LMICs due to suboptimal health care systems (Chow, et al. 2013; Patel, et al. 2007) and differences in knowledge regarding the risks of being sedentary and its associated decrease in muscular strength (Pengpid, et al. 2015) compared to people in high-income countries.

Given the aforementioned, the aim of the current study was to assess associations between MCI and handgrip strength among community-dwelling middle-aged and older adults using nationally representative data from six LMICs which represent different geographical locations and levels of socio-economic transition.

**Methods**

*The survey*

Data from the World Health Organization’s Study on Global Ageing and Adult Health (SAGE) were analyzed. These data are publically 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. 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 (Kowal, et al. 2012). 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. If a respondent was unable to undertake the interview because of limited cognitive function, then a separate questionnaire was administered to a proxy respondent. These individuals 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 (outcome)*

MCI was ascertained based on the recommendations of the National Institute on Aging-Alzheimer’s Association (Albert, et al. 2011). We applied the identical algorithms used in previous SAGE publications to identify cases of MCI (Koyanagi, et al. 2018a; Vancampfort, et al. 2018; Vancampfort, et al. 2017b). 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 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 (Morris, et al. 1989), which assessed learning and episodic memory; digit span forward and backwards from the Weschler Adult Intelligence Scale (The Psychological Corporation 2002), that evaluated attention and working memory; and the animal naming task (Morris et al. 1989), 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 (Katz, et al. 1963). 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.

*Handgrip strength (exposure)*

Grip strength was measured twice by trained research assistants for both hands with the use of the Smedley’s hand dynamometer. If the participant had any surgery in the last three months or arthritis or pain in the hand/wrist/arm, grip strength was not measured for that hand. Weak handgrip strength was defined using standard cut-offs of <30kg for men and <20 kg for women (Cruz-Jentoft, et al. 2010), using the mean average of the two handgrip measurements of the dominant hand

*Control variables*

The selection of control variables was based on past literature and included age, sex, wealth quintiles based on country-specific income, years of education, physical activity, obesity, number of chronic physical conditions, and depression (Lara, et al. 2016; Veronese et al. 2016). Physical activity levels were assessed with the Global Physical Activity Questionnaire (Bull, et al. 2009). The total amount of moderate to vigorous physical activity in a typical week was calculated based on self-report. Those scoring ≥150 minutes of moderate to high intensity physical activity were classified as meeting the recommended guidelines (coded=0), and those scoring <150 minutes (low physical activity) were classified as not meeting the recommended guidelines (coded=1) (Organization 2010). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared based on measured weight and height. Obesity was defined as BMI≥30kg/m2 (World Health Organization). The total number of 11 chronic physical conditions (angina, arthritis, asthma, chronic back pain, chronic lung disease, diabetes, edentulism, hearing problems, hypertension, stroke, visual impairment) was summed per individual. These conditions were assessed by self-report of diagnosis, symptoms, or blood pressure measurement (See eTable 1 of the Appendix). Questions based on the World Mental Health Survey version of the Composite International Diagnostic Interview (Kessler and Ustun 2004) were used for the endorsement of DSM-IV depression.

*Statistical analysis*

The statistical analysis was done with Stata 14.1 (Stata Corp LP, College station, Texas). The analysis was restricted to individuals aged ≥50 years due to the age-related nature of MCI. The difference in sample characteristics by handgrip strength was tested by Chi-squared tests and Student’s *t*-tests for categorical and continuous variables respectively. We assessed the association between weak handgrip strength (exposure) and MCI (outcome) with multivariable logistic regression. Analyses using the overall sample and analyses stratifying by age (50-64 years and ≥65 years) and country were done. The regression analyses were adjusted for age, sex, wealth, education, physical activity, obesity, number of chronic physical conditions, and depression. To assess the level of between-country heterogeneity, the Higgins’ *I2*statisticwas calculated. This 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 (21). A pooled estimate was obtained by combining the estimates for each country into a random-effect meta-analysis. Analyses using the overall sample were also adjusted for country by including dummy variables for each country. All variables were included in the models as categorical variables with the exception of age, years of education, and number of chronic conditions (continuous variables). The sample weighting and the complex study design were taken into account in all 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 consisted of 32,715 individuals (n China = 12,815; n Ghana = 4201; n India = 6191; n Mexico = 2070; n Russia = 3766; n South-Africa = 3672), aged ≥50 years with preserved independence in functional abilities. The mean (SD) age of the sample was 62.1 (15.6) years and 49.0% were males (**Table 1**). Individuals with weak handgrip strength were significantly more likely to be older, female, poorer, have lower education, engage in lower levels of physical activity, and have depression and higher numbers of chronic physical conditions, while they were less likely to be obese. The prevalence of MCI and weak handgrip strength were 15.3% (95%CI=14.4%-16.3%) and 46.5% (95%CI=43.6%-49.5%) respectively. The prevalence of MCI was higher among those with weak handgrip strength compared to those without this condition in the overall sample (18.7% vs. 12.6%) and country-wise samples (**Figure 1**). After adjustment for potential confounders, weak handgrip strength was associated with 1.41 (95%CI=1.23-1.61) times higher odds for MCI. The corresponding figures for those aged 50-64 years and ≥65 years were 1.35 (95%CI=1.14-1.60) and 1.54 (95%CI=1.27-1.86) respectively (**Table 2**). Country-wise analyses showed that weak handgrip strength is associated with MCI in all countries although statistical significance was reached only in Ghana and China (**Figure 2**). The Higgin’s *I2* showed that there was no between-country heterogeneity in the association between weak handgrip strength and MCI.

**Discussion**

*General findings*

The current study shows that the prevalence of MCI is higher among those with weak handgrip strength. More specifically, a weak handgrip strength was associated with an almost 1.5 times higher odds of having MCI after adjustment for age, sex, wealth, years of education, physical activity, obesity, number of chronic physical conditions, and depression. The current study therefore extends the limited prior work on muscular weakness and cognitive decline in LMICs and suggests that handgrip measures may help to identify persons who are likely to have MCI and who are most likely to benefit from interventions to improve or maintain their current cognitive function. Given the increase in risk factors for dementia (e.g., low physical activity, chronic diseases such as diabetes, obesity) (Lara et al. 2016), rapid aging, and the potentially heighted risk for stress in LMICs due to factors such as poverty, our study results highlight the need to further investigate muscle weakness as a potential risk factor for dementia in this setting.

The exact nature of the relationship between handgrip strength and cognition is unclear. For instance, some studies have shown that weak handgrip strength precedes cognitive decline (Alfaro-Acha, et al. 2006; Jeong and Kim 2018; Veronese et al. 2016; Viscogliosi, et al. 2017). A four year longitudinal study with just over 3000 community dwelling adults compared four objective performance tests as a predictor of developing cognitive decline (MMSE decline below 24 or decline in 3 points) and the authors found that after adjusting for multiple confounders (and excluding those with cognitive impairment at baseline), weaker handgrip strength was a robust predictor of incident cognitive decline and impairment (Veronese et al. 2016). Vice versa, there is evidence that cognitive decline precedes declines in handgrip strength as greater cognitive loss is associated with weaker grip strength (Taekema, et al. 2012). Support for the proposition that cognitive decline precedes declines in handgrip strength may be based on the understanding that motor skill learning and motor output are dependent on the activity of the frontal and parietal brain regions and the interconnection between these regions are related to motor output (Taekema et al. 2012). Nonetheless, a recent study with a longer follow up period assessed 708 adults at six time points over a 20-year period, and concluded that the strength and stability of the connections between handgrip strength and cognition indicate bi-directionality and/or third-factor causality (Sternäng, et al. 2015). With regards to third-factor causality, both lower muscle strength and cognitive impairment occur in concert with a higher risk for chronic diseases (Koyanagi, et al. 2018b) and low physical activity participation (Koyanagi, et al. 2017; Vancampfort, et al. 2017a) which are on their turn risk factors for further cognitive decline. However, the association between weak handgrip strength and MCI remained significant in our study even after controlling for chronic conditions, depression and physical inactivity indicating that the relationship is likely to be explained by underlying biological mechanisms, which were not assessed in the current study. However, the biological basis of the association remains largely unknown. It may be that weak muscle strength and cognitive impairments may share an underlying pathogenesis. It is nowadays well known that skeletal muscles are the target of numerous hormones, and recent evidence has shown that skeletal muscles have a role as a secretory organ of cytokines, peptides, cytokines such as brain-derived neurotrophic factor (BDNF), and several interleukins (IL-6, IL-8, IL-15) (Pedersen 2013; Pedersen and Febbraio 2008, 2012). In addition, recent research has suggested that sarcopenia (Bano, et al. 2017) and frailty (Soysal, et al. 2016) are associated with an adverse inflammatory and oxidative stress profile (Soysal, et al. 2017), both of which are associated with cognitive decline (Crichton, et al. 2013; Lai, et al. 2017). Decline in muscle mass and strength may reduce expression of BDNF which is thought to play a role in brain health (Pedersen 2013; Pedersen and Febbraio 2012). Thus, examination of serum-biomarkers such as BDNF in addition to cognition and strength may be an important addition to future longitudinal work. Another biological factor which should be considered is vitamin D deficiency. Evidence indicates that serum 25-hydroxyvitamin D (25(OH)D) may impact brain health (Aspell, et al. 2017) as epidemiological evidence supports associations between low serum 25(OH)D concentrations and poorer cognitive performance in community-dwelling older populations (Toffanello, et al. 2014). Next to this, associations between low serum 25(OH)D concentrations and handgrip strength have also been found (Dhanwal, et al. 2013; Haslam, et al. 2014). However, longitudinal and interventional studies are needed to confirm or refute the vitamin D deficiency hypothesis.

Beyond considering grip strength as a marker of cognitive and functional capacities, further work should also investigate how increasing muscular fitness may be a therapeutic target for improving cognitive and functional outcomes of those with MCI in LMICs. There is now compelling evidence from randomized controlled trials in aging populations that strength training exercise interventions significantly improve cognitive functioning (Cassilhas, et al. 2007; Liu-Ambrose, et al. 2010). The beneficial effects of resistance training may be mediated through exercise-induced increases in grey matter and attenuation of aging-related white matter abnormalities (Suo, et al. 2016).

*Limitations*

Although the strength of the study includes the large sample size and the use of nationally representative samples from six countries, our results should be interpreted in the light of several limitations. First, because the study was not designed to generate clinical diagnoses of dementia nor MCI, some individuals with mild dementia may have been included in our analytical sample. However, the prevalence of MCI in our study was well-aligned with population estimates(Petersen, 2016)*.* Second, there is currently no consensus in terms of the an acceptable level of functional impairment that individuals with MCI could present (Lindbergh, et al. 2016). In the current study, and in accordance with previous publications (Lara, et al. 2017; Lara et al. 2016), a rather conservative definition for preservation of independence in functional abilities was used in order to not exclude people with MCI with disability not related with their cognitive ability. Third, because this was a cross-sectional study, causality cannot be inferred. Although our data provides some potential hypotheses to address the weak muscle strength and MCI relationship, longitudinal studies are required to better disentangle the relationships we observed.

In conclusion, despite these limitations the current study shows that the prevalence of MCI is higher among those with weak handgrip strength. Future research should explore whether grip strength may be an early indirect non-cognitive marker of subsequent cognitive decline, as it has many advantages over other biological measurements which make it very attractive to use within LMIC settings. Handgrip dynamometers are inexpensive, easily portable, non-invasive, fast, reliable, and do not require extensive training. Additionally, increasing our understanding of the connection between muscular and cognitive function could ultimately lead to the development and broader implementation of resistance-training interventions targeting both physical and cognitive health.

**Competing interests**

None.

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**Author’s contribution**

AK and DV conceived the study idea, analyzed and interpreted the data, and wrote the main body of the text. BS, LS, JF and NS 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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**References**

Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, et al. 2011 The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association* **7** 270-279.

Alfaro-Acha A, Snih SA, Raji MA, Kuo Y-F, Markides KS & Ottenbacher KJ 2006 Handgrip strength and cognitive decline in older Mexican Americans. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* **61** 859-865.

Alzheimer's Disease International 2015 World Alzheimer Report.

Aspell N, Lawlor B & O'Sullivan M 2017 Is there a role for vitamin D in supporting cognitive function as we age? *Proceedings of the Nutrition Society* 1-11.

Bano G, Trevisan C, Carraro S, Solmi M, Luchini C, Stubbs B, Manzato E, Sergi G & Veronese N 2017 Inflammation and sarcopenia: A systematic review and meta-analysis. *Maturitas* **96** 10-15.

Boyle PA, Buchman AS, Wilson RS, Leurgans SE & Bennett DA 2010 Physical frailty is associated with incident mild cognitive impairment in community‐based older persons. *Journal of the American Geriatrics Society* **58** 248-255.

Boyle PA, Yu L, Fleischman DA, Leurgans S, Yang J, Wilson RS, Schneider JA, Arvanitakis Z, Arfanakis K & Bennett DA 2016 White matter hyperintensities, incident mild cognitive impairment, and cognitive decline in old age. *Annals of clinical and translational neurology* **3** 791-800.

Bull FC, Maslin TS & Armstrong T 2009 Global physical activity questionnaire (GPAQ): nine country reliability and validity study. *Journal of physical activity & health* **6** 790-804.

Cassilhas RC, Viana VA, Grassmann V, Santos RT, Santos RF, Tufik S & Mello MT 2007 The impact of resistance exercise on the cognitive function of the elderly. *Med. Sci. Sports Exerc.* **39** 1401-1407.

Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, Bahonar A, Chifamba J, Dagenais G & Diaz R 2013 Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *Jama* **310** 959-968.

Cohen JA, Verghese J & Zwerling JL 2016 Cognition and gait in older people. *Maturitas* **93** 73-77.

Crichton GE, Bryan J & Murphy KJ 2013 Dietary antioxidants, cognitive function and dementia-a systematic review. *Plant foods for human nutrition* **68** 279-292.

Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, et al. 2010 Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age and ageing* **39** 412-423.

Cummings JL 2004 Treatment of Alzheimer's disease: current and future therapeutic approaches. *Reviews in neurological diseases* **1** 60-69.

Dhanwal DK, Dharmshaktu P, Gautam V, Gupta N & Saxena A 2013 Hand grip strength and its correlation with vitamin D in Indian patients with hip fracture. *Archives of osteoporosis* **8** 158.

Engeroff T, Vogt L, Fleckenstein J, Füzéki E, Matura S, Pilatus U, Schwarz S, Deichmann R, Hellweg R & Pantel J 2018 Lifespan leisure physical activity profile, brain plasticity and cognitive function in old age. *Aging & mental health* 1-8.

Firth J, Stubbs B, Vancampfort D, Firth JA, Large M, Ward PB, Rosenbaum S, Sarris J & Yung AR 2018 Grip strength is associated with cognitive performance in schizophrenia and the general population: a UK Biobank study of 476,559 participants. *Schizophrenia Bulletin*.

Fritz NE, McCarthy CJ & Adamo DE 2017 Handgrip strength as a means of monitoring progression of cognitive decline–A scoping review. *Ageing research reviews* **35** 112-123.

Garcia-Cifuentes E, David-Pardo D, Borda M, Perez-Zepeda M & CANO C 2017 TWO-WAY BRIDGE BETWEEN MUSCULAR DYSFUNCTION AND COGNITIVE IMPAIRMENT: SECONDARY ANALYSES OF SABE–BOGOTA STUDY. *Age (years)* **71** 8.05.

Ghanavati T, Smitt MS, Lord SR, Sachdev P, Wen W, Kochan NA, Brodaty H & Delbaere K 2018 Deep white matter hyperintensities, microstructural integrity and dual task walking in older people. *Brain imaging and behavior* 1-9.

Gopinath B, Kifley A, Liew G & Mitchell P 2017 Handgrip strength and its association with functional independence, depressive symptoms and quality of life in older adults. *Maturitas* **106** 92-94.

Haslam A, Johnson MA, Hausman DB, Cress ME, Houston DK, Davey A, Poon LW & Study GC 2014 Vitamin D status is associated with grip strength in centenarians. *Journal of nutrition in gerontology and geriatrics* **33** 35-46.

Jeong S & Kim J 2018 Prospective Association of Handgrip Strength with Risk of New-Onset Cognitive Dysfunction in Korean Adults: A 6-Year National Cohort Study. *The Tohoku journal of experimental medicine* **244** 83-91.

Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP & van den Bussche H 2005 Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. *Bmj* **331** 321-327.

Katz S, Ford AB, Moskowitz RW, Jackson BA & Jaffe MW 1963 Studies of illness in the aged. The index of ADL: A standardized measure of biological and psychosocial function. *Jama* **185** 914-919.

Kessler RC & Ustun TB 2004 The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *International journal of methods in psychiatric research* **13** 93-121.

Kohara K, Okada Y, Ochi M, Ohara M, Nagai T, Tabara Y & Igase M 2017 Muscle mass decline, arterial stiffness, white matter hyperintensity, and cognitive impairment: Japan Shimanami Health Promoting Program study. *Journal of cachexia, sarcopenia and muscle* **8** 557-566.

Kowal P, Chatterji S, Naidoo N, Biritwum R, Fan W, Lopez Ridaura R, Maximova T, Arokiasamy P, Phaswana-Mafuya N, Williams S, et al. 2012 Data resource profile: the World Health Organization Study on global AGEing and adult health (SAGE). *International journal of epidemiology* **41** 1639-1649.

Koyanagi A, Lara E, Stubbs B, Carvalho AF, Oh H, Stickley A, Veronese N & Vancampfort D 2018a Chronic Physical Conditions, Multimorbidity, and Mild Cognitive Impairment in Low- and Middle-Income Countries. *Journal of the American Geriatrics Society*.

Koyanagi A, Lara E, Stubbs B, Carvalho AF, Oh H, Stickley A, Veronese N & Vancampfort D 2018b Chronic Physical Conditions, Multimorbidity, and Mild Cognitive Impairment in Low‐and Middle‐Income Countries. *Journal of the American Geriatrics Society*.

Koyanagi A, Stubbs B & Vancampfort D 2017 Correlates of low physical activity across 46 low-and middle-income countries: A cross-sectional analysis of community-based data. *Preventive medicine*.

Lai KSP, Liu CS, Rau A, Lanctôt KL, Köhler CA, Pakosh M, Carvalho AF & Herrmann N 2017 Peripheral inflammatory markers in Alzheimer's disease: a systematic review and meta-analysis of 175 studies. *J Neurol Neurosurg Psychiatry* jnnp-2017-316201.

Lara E, Koyanagi A, Domenech-Abella J, Miret M, Ayuso-Mateos JL & Haro JM 2017 The Impact of Depression on the Development of Mild Cognitive Impairment over 3 Years of Follow-Up: A Population-Based Study. *Dementia and geriatric cognitive disorders* **43** 155-169.

Lara E, Koyanagi A, Olaya B, Lobo A, Miret M, Tyrovolas S, Ayuso-Mateos JL & Haro JM 2016 Mild cognitive impairment in a Spanish representative sample: prevalence and associated factors. *International journal of geriatric psychiatry* **31** 858-867.

Leong DP, Teo KK, Rangarajan S, Lopez-Jaramillo P, Avezum A, Orlandini A, Seron P, Ahmed SH, Rosengren A & Kelishadi R 2015 Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. *The Lancet* **386** 266-273.

Lindbergh CA, Dishman RK & Miller LS 2016 Functional Disability in Mild Cognitive Impairment: A Systematic Review and Meta-Analysis. *Neuropsychology review* **26** 129-159.

Liu-Ambrose T, Nagamatsu LS, Graf P, Beattie BL, Ashe MC & Handy TC 2010 Resistance training and executive functions: a 12-month randomized controlled trial. *Arch. Intern. Med.* **170** 170-178.

Moon J, Kim K, Choi S, Lim S, Park K, Kim KW & Jang HC 2016 Sarcopenia as a predictor of future cognitive impairment in older adults. *The journal of nutrition, health & aging* **20** 496-502.

Morris JC, Heyman A, Mohs RC, Hughes JP, van Belle G, Fillenbaum G, Mellits ED & Clark C 1989 The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology* **39** 1159-1165.

Opdenacker J, Delecluse C & Boen F 2011 A 2‐Year Follow‐Up of a Lifestyle Physical Activity Versus a Structured Exercise Intervention in Older Adults. *Journal of the American Geriatrics Society* **59** 1602-1611.

Organization WH 2010 *Global recommendations on Physical Activity for health*: World Health Organization.

Patel V, Araya R, Chatterjee S, Chisholm D, Cohen A, De Silva M, Hosman C, McGuire H, Rojas G & van Ommeren M 2007 Treatment and prevention of mental disorders in low-income and middle-income countries. *The Lancet* **370** 991-1005.

Pedersen BK 2013 Muscle as a secretory organ. *Comprehensive Physiology*.

Pedersen BK & Febbraio MA 2008 Muscle as an endocrine organ: focus on muscle-derived interleukin-6. *Physiological reviews* **88** 1379-1406.

Pedersen BK & Febbraio MA 2012 Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nature Reviews Endocrinology* **8** 457.

Pengpid S, Peltzer K, Kassean HK, Tsala JPT, Sychareun V & Müller-Riemenschneider F 2015 Physical inactivity and associated factors among university students in 23 low-, middle-and high-income countries. *International journal of public health* **60** 539-549.

Prince MJ 2015 *World Alzheimer Report 2015: the global impact of dementia: an analysis of prevalence, incidence, cost and trends*: Alzheimer's Disease International.

Soysal P, Isik AT, Carvalho AF, Fernandes BS, Solmi M, Schofield P, Veronese N & Stubbs B 2017 Oxidative stress and frailty: A systematic review and synthesis of the best evidence. *Maturitas* **99** 66-72.

Soysal P, Stubbs B, Lucato P, Luchini C, Solmi M, Peluso R, Sergi G, Isik AT, Manzato E & Maggi S 2016 Inflammation and frailty in the elderly: A systematic review and meta-analysis. *Ageing research reviews* **31** 1-8.

Sternäng O, Reynolds CA, Finkel D, Ernsth-Bravell M, Pedersen NL & Dahl Aslan AK 2015 Grip strength and cognitive abilities: associations in old age. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences* **71** 841-848.

Suo C, Singh MF, Gates N, Wen W, Sachdev P, Brodaty H, Saigal N, Wilson GC, Meiklejohn J, Singh N, et al. 2016 Therapeutically relevant structural and functional mechanisms triggered by physical and cognitive exercise. *Mol. Psychiatry* **21** 1633-1642.

Taekema DG, Ling CH, Kurrle SE, Cameron ID, Meskers CG, Blauw GJ, Westendorp RG, de Craen AJ & Maier AB 2012 Temporal relationship between handgrip strength and cognitive performance in oldest old people. *Age and ageing* **41** 506-512.

The Psychological Corporation 2002 The Psychological Corporation: The WAIS III-WMS III Updated Technical Manual. San Antonio.

Toffanello ED, Coin A, Perissinotto E, Zambon S, Sarti S, Veronese N, De Rui M, Bolzetta F, Corti M-C & Crepaldi G 2014 Vitamin D deficiency predicts cognitive decline in older men and women The Pro. VA Study. *Neurology* **83** 2292-2298.

Vancampfort D, Koyanagi A, Ward PB, Rosenbaum S, Schuch FB, Mugisha J, Richards J, Firth J & Stubbs B 2017a Chronic physical conditions, multimorbidity and physical activity across 46 low-and middle-income countries. *International Journal of Behavioral Nutrition and Physical Activity* **14** 6.

Vancampfort D, Lara E, Stubbs B, Swinnen N, Probst M & Koyanagi A 2018 Physical activity correlates in people with mild cognitive impairment: findings from six low- and middle-income countries. *Public health* **156** 15-25.

Vancampfort D, Stubbs B, Lara E, Vandenbulcke M, Swinnen N & Koyanagi A 2017b Mild cognitive impairment and physical activity in the general population: Findings from six low- and middle-income countries. *Experimental gerontology* **100** 100-105.

Veronese N, Stubbs B, Trevisan C, Bolzetta F, De Rui M, Solmi M, Sartori L, Musacchio E, Zambon S, Perissinotto E, et al. 2016 What physical performance measures predict incident cognitive decline among intact older adults? A 4.4year follow up study. *Experimental gerontology* **81** 110-118.

Viscogliosi G, Di Bernardo M, Ettorre E & Chiriac I 2017 Handgrip strength predicts longitudinal changes in clock drawing test performance. An observational study in a sample of older non-demented adults. *The journal of nutrition, health & aging* **21** 593-596.

Wimo A, Guerchet M, Ali GC, Wu YT, Prina AM, Winblad B, Jonsson L, Liu Z & Prince M 2017 The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimer's & dementia : the journal of the Alzheimer's Association* **13** 1-7.

World Health Organization <http://apps.who.int/bmi/index.jsp?introPage=intro_3.html> [Accessed 12 Sep 2014].

World Health Organization 2010 *Global recommendations on Physical Activity for health*. Geneva:

World Health Organization.

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| **Table 1** Sample characteristics (overall and by handgrip strength) |
|   |   |   | Weak handgrip strength |   |
| Characteristic | Category | Total | No | Yes | P-valuea |
| Age (years) |  | 62.1 (15.6) | 59.8 (14.5) | 64.2 (15.9) | <0.001 |
| Sex | Male | 49.0 | 50.2 | 47.6 | 0.013 |
|  | Female | 51.0 | 49.8 | 52.4 |  |
| Wealth | Poorest | 17.0 | 14.2 | 20.3 | <0.001 |
|  | Poorer | 18.6 | 17.2 | 20.1 |  |
|  | Middle | 19.5 | 19.2 | 19.9 |  |
|  | Richer | 21.8 | 23.7 | 19.6 |  |
|  | Richest | 23.1 | 25.7 | 20.0 |  |
| Education (years) |  | 6.1 (8.9) | 6.9 (9.4) | 4.6 (8.1) | <0.001 |
| Low physical activity | No | 78.7 | 82.9 | 73.8 | <0.001 |
|   | Yes | 21.3 | 17.1 | 26.2 |   |
| Obesity | No | 89.4 | 86.1 | 93.1 | <0.001 |
|  | Yes | 10.6 | 13.9 | 6.9 |  |
| No. of chronic diseases |  | 1.6 (2.4) | 1.4 (2.3) | 1.7 (2.4) | <0.001 |
| Depression | No | 94.3 | 96.4 | 92.0 | <0.001 |
|   | Yes | 5.7 | 3.6 | 8.0 |   |

Data are % or mean (standard deviation).

a P-values were calculated with Chi-squared tests and Student’s *t*-tests for categorical and continous variables respectively.

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| --- |
| **Table 2** Association between weak handgrip strength and mild cognitive impairment (outcome) estimated by multivariable logistic regression |
|   |   | Overall | Age 50-64 years | Age ≥65 years |
| Characteristic | Category | OR | 95%CI | OR | 95%CI | OR | 95%CI |
| Weak handgrip strength | Yes vs. No | 1.41\*\*\* | [1.23,1.61] | 1.35\*\*\* | [1.14,1.60] | 1.54\*\*\* | [1.27,1.86] |
| Age (years) |  | 1.01\*\* | [1.00,1.02] | 1.02 | [1.00,1.04] | 1.04\*\*\* | [1.03,1.06] |
| Sex | Female vs. Male | 1.05 | [0.92,1.19] | 1.20\* | [1.02,1.41] | 0.89 | [0.72,1.09] |
| Wealth | Poorest | 1.00 |  | 1.00 |  | 1.00 |  |
|  | Poorer | 0.95 | [0.79,1.13] | 0.94 | [0.75,1.18] | 0.90 | [0.68,1.19] |
|  | Middle | 0.97 | [0.80,1.19] | 0.85 | [0.67,1.07] | 1.10 | [0.79,1.53] |
|  | Richer | 0.68\*\*\* | [0.56,0.82] | 0.68\*\* | [0.53,0.85] | 0.59\*\*\* | [0.45,0.77] |
|  | Richest | 0.39\*\*\* | [0.32,0.48] | 0.33\*\*\* | [0.25,0.43] | 0.45\*\*\* | [0.33,0.62] |
| Education (years) |  | 0.98\* | [0.96,1.00] | 0.97\*\* | [0.95,0.99] | 0.99 | [0.96,1.02] |
| Low physical activity | Yes vs. No | 1.24\*\* | [1.07,1.44] | 0.85 | [0.71,1.02] | 1.70\*\*\* | [1.35,2.14] |
| Obesity | Yes vs. No | 1.24 | [0.97,1.58] | 1.50\*\* | [1.13,1.99] | 0.95 | [0.64,1.40] |
| No. of chronic diseases |  | 1.20\*\*\* | [1.15,1.25] | 1.24\*\*\* | [1.16,1.32] | 1.17\*\*\* | [1.10,1.24] |
| Depression | Yes vs. No | 0.86 | [0.64,1.16] | 0.84 | [0.58,1.20] | 0.83 | [0.51,1.34] |

Abbreviation: OR Odds ratio; CI Confidence interval

Models are adjusted for all variables in the Table and country.

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

**Figure 1** Prevalence of mild cognitive impairment by presence or absence of weak handgrip strength (overall and by country)



**Figure 2** Country-wise association between weak handgrip strength 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, obesity, number of chronic physical diseases, and depression.

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