Physical Multimorbidity and Sarcopenia among Adults Aged ≥65 Years in Low- and Middle-Income Countries

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Running head: Physical multimorbidity and sarcopenia among adults aged ≥65 years

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ABSTRACT

Introduction: Physical multimorbidity is plausibly linked to sarcopenia. However, to date, only a few studies exist on this topic, and none have examined this association in low- and-middle income countries (LMICs). Thus, we aimed to investigate the association between multimorbidity and sarcopenia in a sample of older adults from six LMICs (China, Ghana, India, Mexico, Russia, South Africa).

Methods: Cross-sectional, community-based data from the WHO Study on global Ageing and adult health (SAGE) were analysed. Sarcopenia was defined as having low skeletal muscle mass (SMM) and weak handgrip strength, while severe sarcopenia was defined as having low SMM, weak handgrip strength, and slow gait speed. A total of 11 physical chronic conditions were assessed and multimorbidity referred to ≥2 chronic conditions. Multivariable logistic regression analysis was conducted.

Results: Data on 14585 adults aged ≥65 years were analyzed (mean age 72.6 years, SD 11.5 years; 53.7% females). Adjusted estimates showed that compared to no chronic physical conditions, ≥2 conditions are significantly associated with 1.49 (95%CI=1.02-2.19) and 2.52 (95%CI=1.53-4.15) times higher odds for sarcopenia and severe sarcopenia, respectively.

Conclusions: In this large sample of older adults from LMICs, physical multimorbidity was significantly associated with sarcopenia and severe sarcopenia. Our study results tentatively suggest that targeting those with multimorbidity may aid in the prevention of sarcopenia, pending future longitudinal research.

Key words: Sarcopenia, Multimorbidity, Older adults, Low- and-middle income countries, Multi-country, Epidemiology

INTRODUCTION

Sarcopenia refers to "age-related muscle loss, affecting a combination of appendicular muscle mass, muscle strength, and/or physical performance measures" [1] and is now widely considered to be a disease since its introduction in the ICD-10-CM in 2016 [2]. The pathogenesis of sarcopenia likely involves genetic and environmental factors such as chronic inflammation, hormonal changes, oxidative stress, low physical activity, diet, and age-related chronic diseases [3].

Sarcopenia is one of the most prominent physiological changes associated with ageing, and is therefore highly prevalent among older adults. For example, a recent meta-analysis including community-dwelling adults aged ≥ 55 years reported a prevalence of at least 10% [4]. Furthermore, sarcopenia is associated with high risk for adverse health outcomes such as hospitalization, poor quality of life, dependency, falls, disability, and premature mortality [1,5]. Moreover, sarcopenia is associated with high healthcare costs [6]. Given the high prevalence of sarcopenia in the older population and related adverse health outcomes, and the fact that there are currently no effective pharmacological treatments for sarcopenia, there is an urgent need to identify the risk factors for sarcopenia to inform targeted interventions.

One potentially important but understudied risk factor is that of physical multimorbidity. Multimorbidity may be defined as the presence of two or more long-term health conditions [7] and its prevalence increases with age [8]. Physical multimorbidity may be feasibly linked to sarcopenia via factors such as a reduction in activities of daily living and consequent decrease in muscle mass [9], or chronic low-grade inflammation [10,11]. To date, two studies have focused specifically on the association between multimorbidity and sarcopenia. One cross-sectional study in a sample of 499 046 UK adults aged 40-70 years found that

multimorbidity was associated with nearly twice the odds of probable sarcopenia [OR 1.96 (95% CI: 1.91, 2.02)] [12]. In another cross-sectional study including 10,118 Korean adults aged ≥40 years, there were significant associations of sarcopenia (odds ratio, or OR, 1.49; 95% confidence interval, or CI, =1.31-1.70) and obesity (OR 1.63; 95% CI=1.45-1.84) with the risk of multimorbidity after adjustment for potential confounders. When examined as sarcopenia and obesity combined, a greater increase in the risk of multimorbidity was found (OR: 3.0, 95% CI: 2.60-3.40) compared with either sarcopenia (OR: 1.50, 95% CI: 1.18-1.77) or obesity (OR: 1.80, 95% CI: 1.39-2.30) alone [13]. However, to date, there are currently no studies on this topic from low- and middle-income countries (LMICs), from which a high prevalence of multimorbidity has been reported [14], and where there is a large increase in non-communicable diseases and multimorbidity due to factors such as changes in lifestyles and urbanization [15]. This is an important research gap as the proportion of the world population aged >60 years is projected to increase from 12% to 22% between 2015 and 2050, and in 2050, 80% of older people will be living in LMICs [16]. This is likely to be accompanied by an important increase in multimorbidity and sarcopenia in LMICs since both are age-related conditions. Furthermore, results from high-income countries may not be generalizable to LMICs owing to the different disease profiles and health system performance [17].

Given this background, the aim of the present study was to investigate the association between multimorbidity and sarcopenia in a sample of 14585 adults aged ≥65 years from six LMICs (China, Ghana, India, Mexico, Russia, and South Africa) using nationally representative data.

METHODS

Data from the 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. 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 [18]. Briefly, 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. 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.

Sarcopenia (dependent variable)

Following the criteria of the revised European consensus on the definition and diagnosis of sarcopenia [19], sarcopenia was defined as having low skeletal muscle mass (SMM) as reflected by lower skeletal mass index (SMI) and weak handgrip strength, while severe sarcopenia was defined as having low SMM, weak handgrip strength, and slow gait speed.

SMM was calculated based on the equation proposed by Lee and colleagues: SMM= 0.244*weight + 7.8*height + 6.6*sex – 0.098*age + race – 3.3 (where female=0 and male=1; race=0 –White and Hispanic–, race=1.4 –Black– and race=-1.2 –Asian–) [20]. SMM was further divided by body mass index (BMI) based on measured weight and height to create a SMI [21]. Low SMM was defined as the lowest quintile of the SMI based on sex-stratified values [22]. Country-specific cut-offs were used to determine low SMI, as this indicator is likely to be affected by racial differences in body composition [23]. Weak handgrip strength was defined as <27kg for men and <16kg for women using the average value of the two handgrip measurements of the dominant hand [19]. Gait speed was based on a 4m timed walk and was measured by asking the participant to walk at a normal pace. The interviewer recorded the time to completion of the 4m walk. Slow gait speed referred to ≤0.8m/s [19].

Chronic physical conditions and physical multimorbidity (independent variables)

We included all 11 chronic physical conditions (angina, arthritis, asthma, chronic back pain, chronic lung disease, diabetes, edentulism, hearing problems, hypertension, stroke, visual impairment) for which data were available in the SAGE. Chronic back pain was defined as having had back pain everyday during the last 30 days. Respondents who answered affirmatively to the question "Have you lost all of your natural teeth?" were considered to have edentulism. The participant was considered to have hearing problems if the interviewer observed this condition during the survey. Hypertension was defined as having at least one of the following: systolic blood pressure ≥140 mmHg; diastolic blood pressure ≥90 mmHg; or self-reported diagnosis. Visual impairment was defined as having severe/extreme difficulty in seeing and recognizing a person that the participant knows across the road [24]. Diabetes mellitus and stroke were solely based on lifetime self-reported diagnosis. For other conditions, the participant was considered to have the condition in the presence of either one

of the following: self-reported diagnosis; or symptom-based diagnosis based on algorithms. We used these algorithms, which have been used in previous studies using the same dataset, to detect undiagnosed cases [25,26]. Specifically, the validated Rose questionnaire was used for angina [27], and other previously validated symptom-based algorithms were used for arthritis, asthma, and chronic lung disease [25]. Further details on the definition of chronic physical conditions can be found in **Table S1** (supplementary material). The total number of chronic physical conditions was calculated and categorized as 0, 1, and ≥2. Multimorbidity was defined as ≥2 chronic physical conditions, in line with previously used definitions [26].

Control variables

The control variables were selected based on past literature [12], and included age, sex, highest level of education achieved (≤primary, secondary, tertiary), wealth quintiles based on income, physical activity, and body mass index (BMI). 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 [28]. BMI was calculated as weight in kilograms divided by height in meters squared. BMI was categorized as <18.5 kg/m^2 (underweight), 18.5-24.9 kg/m^2 (normal weight), 25.0-29.9 kg/m^2 (overweight), and ≥30.0 kg/m^2 (obesity) [29].

Statistical analysis

The statistical analysis was performed with Stata 14.2 (Stata Corp LP, College station, Texas). The analysis was restricted to those aged ≥65 years as sarcopenia is an age-related condition. Difference in sample characteristics by sarcopenia was tested with Chi-squared tests and Student's *t*-tests for categorical and continuous variables, respectively. Multivariable logistic regression was conducted to assess the association between

multimorbidity (exposure) and sarcopenia or severe sarcopenia (outcomes) using the overall sample. This analysis used the three-category multimorbidity variable (0, 1, ≥2 chronic physical conditions) as the exposure. Interaction analysis by sex was also conducted to assess whether there is effect modification by sex in the association between multimorbidity and sarcopenia or severe sarcopenia. This was done by including the interaction term of sex X multimorbidity in the model. Next, we also conducted country-wise analysis to assess whether there is between-country heterogeneity in the association between multimorbidity and sarcopenia or severe sarcopenia. The country-wise analysis used the dichotomized multimorbidity variable (i.e., ≥2 vs. ≤1 chronic condition) as the exposure variable. In order to assess the degree of between-country heterogeneity in the association between multimorbidity and sarcopenia or severe sarcopenia, 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 [30]. Overall estimates were obtained based on country-wise estimates by meta-analysis with fixed effects.

The regression analyses were adjusted for age, sex, education, wealth, physical activity, BMI, and country, with the exception of the country-wise analysis which was not adjusted for country. Adjustment for country was done by including dummy variables for each country in the model as in previous SAGE publications [31,32]. 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 sample consisted of 14585 adults aged ≥65 years (China n=5360; Ghana n=1975; India n=2441; Mexico n=1375; Russia n=1950; South Africa n=1484). The mean (SD) age was 72.6 (11.5) years and 53.7% were females. Overall, the prevalence of 1 and ≥2 chronic physical conditions was 26.2% and 60.2%, respectively, while 12.0% had sarcopenia, and 7.8% severe sarcopenia. The sample characteristics are provided in **Table 1**. Those with sarcopenia were significantly older, more likely to have lower levels of education, wealth, and physical activity, while they had higher prevalence of arthritis, chronic back pain, edentulism, hearing problems, visual impairment, and multimorbidity. The prevalence of sarcopenia among those with no (8.8%) or 1 (8.7%) chronic physical condition were similar but this figure increased substantially among those with ≥2 chronic physical conditions (14.4%) (**Figure 1**). The prevalence of severe sarcopenia increased with greater number of chronic physical conditions (i.e., no conditions 3.8%, 1 condition 4.9%, 2 conditions 10.3%). Adjusted estimates showed that compared to no chronic physical conditions, ≥2 conditions are significantly associated with 1.49 (95%CI=1.02-2.19) and 2.52 (95%CI=1.53-4.15) times higher odds for sarcopenia and severe sarcopenia, respectively (**Table 2**). No significant interactions by sex were found in the association between multimorbidity and sarcopenia or severe sarcopenia. Country-wise analysis showed that the level of between-country heterogeneity is low with the pooled estimate of multimorbidity (i.e., ≥2 vs. ≤1 chronic physical condition) being 1.55 (95%CI=1.31-1.83) and 1.97 (95%CI=1.60-2.42) for sarcopenia and severe sarcopenia, respectively (**Figure 2**).

DISCUSSION

Main findings

Findings from this large representative sample of older adults from six LMICs found that compared to no chronic physical conditions, ≥2 conditions are significantly associated with

1.49 and 2.52 times higher odds for sarcopenia and severe sarcopenia, respectively. Moreover, country-wise analysis showed that the level of between-country heterogeneity in the association between multimorbidity and sarcopenia or severe sarcopenia is low.

Interpretation of the findings

Findings from the present study add to and support the previous literature on multimorbidity and sarcopenia, which has been carried out in single high-income countries [12,13]. Our findings add to this literature through showing that a positive association also exists between multimorbidity and sarcopenia among older adults from six LMICs. Several mechanisms may explain the association between physical multimorbidity and sarcopenia. For example, we found that single chronic conditions such as arthritis, chronic back pain, edentulism, hearing problems, and visual impairment are significantly more frequent among those with sarcopenia. Arthritis and chronic back pain are likely associated with sarcopenia owing to these conditions increasing levels of low-grade inflammation and reducing levels of physical activity [33,34]. In terms of vision and hearing problems, an increase in sarcopenia among these populations may again be owing to a low level of physical activity and high sitting time [35]. The association between multimorbidity and sarcopenia may be explained by the accumulative effect of single chronic conditions and their increased risk for sarcopenia.

Apart from this, the frequent coexistence of sarcopenia and chronic conditions may be the result of their shared pathophysiological pathways involving altered nutrient intake and absorption, inflammatory processes, as well as metabolic and autonomic disturbances. For instance, a systematic review including 49 articles concluded that vitamin D deficiency was among the main risk factors for sarcopenia [36], while, vitamin D deficiency increases the risk of developing multiple chronic conditions [37-39]. In LMICs, altered nutrient intake may

be a key driving force for chronic conditions and sarcopenia owing to the high prevalence of food insecurity in these settings [40]. Next, inflammatory processes have been implicated in the onset of sarcopenia as such processes can affect both muscle protein breakdown and synthesis through several signaling pathways [10]. Meanwhile, systemic chronic low-grade inflammation has been found to be longitudinally associated with sarcopenia and multimorbidity [41,42].

Furthermore, other potential mechanisms include factors such as disability, polypharmacy, sleep problems, poverty, and obesity. For example, physical multimorbidity reduces activities of daily living [9], and this has been observed to be associated with a reduction in muscle mass and strength [43]. Next, polypharmacy is common in individuals with multimorbidty to treat multiple chronic conditions [44], and polypharmacy in turn, may increase risk for sarcopenia [45]. Indeed, multiple medications affect and interfere with various metabolic processes and circulatory homeostasis. Several molecular, metabolic, and vascular alterations are suspected to play central roles in the development of sarcopenia, and thus may account for polypharmacy-associated sarcopenia [45]. Importantly, multimorbidity is associated with sleep problems [46], and sleep problems have been implicated in an increased risk of sarcopenia via the impact of impaired sleep on the function of endocrine factors and consequent reduction in muscle health [47,48]. Next, it is possible for poverty to lead to both physical multimorbidity and sarcopenia via factors such as risky lifestyles (e.g., poor nutrition) and inadequate health care [49,50]. Finally, obesity is a known risk factor for a variety of chronic conditions [51], while obesity may increase risk for sarcopenia via higher levels of low-grade inflammation [52]. In our study, while we did adjust for current levels of wealth and obesity, it is possible that the association observed may still be driven by these factors as we were unable to adjust for past trajectories of these due to lack of data.

Public health implications

Findings from the present study suggest that targeting intervention efforts among those with multimorbidity to aid in the prevention of sarcopenia may be fruitful. Such interventions may wish to consider implementing exercise plus nutritional supplementation if not contraindicated. In a review of nine studies, it was concluded that exercise could be used as anti-sarcopenic strategies, and nutritional interventions (e.g., protein and vitamin D supplement) when combined with exercise might play a compensated or perhaps a comprehensive role among community-dwelling older people [53]. Clinicians should be aware of the higher risk for sarcopenia in those with multimorbidity and attempt to address sarcopenia when identified. Furthermore, exercise promotion in the general population may be important to prevent both multimorbidity and sarcopenia in those who have not yet developed these conditions as low physical activity is a risk factor for both conditions [54,55].

Strengths and limitations

The large representative samples from six LMICs, which represent nearly half of the global population, is a clear strength of the present study. However, findings must be considered in light of the studies limitations. First, the study is cross-sectional in nature and thus it is not known whether multimorbidity increases risk of sarcopenia or vice versa. Second, the survey did not include a robust dietary assessment, and thus the role of diet could not be considered in the investigated associations. Third, our list of chronic diseases included a variety of diseases which are highly prevalent in older populations, but we lacked some diseases such as cancer, Parkinson's disease, congestive heart failure, peripheral arterial disease, kidney failure, and hip fracture, which may be related with higher risk of sarcopenia [56,57]. Thus,

the results could have differed with a different list of chronic diseases. Finally, ASM was based on a population equation and not direct assessment. However, this has been validated against gold standard methods such as magnetic resonance imaging and dual-energy X-ray absorptiometry [20].

Conclusion

In this large sample of older adults from six LMICs, multimorbidity was found to be significantly associated with sarcopenia and severe sarcopenia. Although our study could not assess temporal associations due to the cross-sectional design, the finding that sarcopenia and multimorbidity co-exist is an important finding as both individual conditions are associated with multiple adverse health outcomes including premature mortality [58,59]. Future studies should study this association longitudinally in order to understand the temporal association and potential mediators in this association. Moreover, future studies are now needed to elucidate further on the main mechanisms that drive the relationship between multimorbidity and sarcopenia in LMICs, for example, the high prevalence of food insecurity in these settings or the potential role of low-grade inflammation. This information may aid in the prevention of sarcopenia among those with multimorbidity.

STATEMENTS

Acknowledgment: None.

Statement of Ethics: The Study on Global Ageing and Adult Health (SAGE) obtained ethical approval from the WHO Ethical Review Committee and local ethics research review boards. For the present study ethical approval was not required as this study was based on publicly available data.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Data Availability Statement: The data that support the findings of this study are available via the WHO website subject to approval. Further enquiries can be directed to the corresponding author.

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Figure 1 Prevalence of sarcopenia and severe sarcopenia by number of chronic physical conditions
Bars denote 95% confidence interval.

Figure 2 Country-wise association between multimorbidity (i.e., ≥2 vs. ≤1 chronic physical condition) and (A) sarcopenia or (B) severe sarcopenia (outcomes) estimated by multivariable logistic regression
Abbreviation: OR Odds ratio; CI Confidence interval
Models are adjusted for age, sex, education, wealth, physical activity, and body mass index.
Overall estimate was obtained by meta-analysis with fixed effects.