Title: Association between dynapenia and multimorbidity: A systematic review

Running title: Dynapenia and multimorbidity

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Title

Association between dynapenia and multimorbidity in community-dwelling older adults: A
systematic review

Abstract

Dynapenia and multimorbidity are common health problems affecting older adults. However,
few studies have systematically reviewed the association between dynapenia and
multimorbidity. Therefore, this systematic review aimed to provide a comprehensive overview
of studies on the association between these conditions. We searched four electronic databases
for relevant articles published in July 2023. The main inclusion criteria were the following: (1) a
description of dynapenia, which indicates loss of muscle strength and (2) a description of
multimorbidity with two or more chronic diseases. Five studies met these inclusion criteria. In
all five of these studies, the participants were community-dwelling older adults. All the studies
showed an association between dynapenia and multimorbidity. The prevalence of dynapenia and
multimorbidity ranged from 16% to 25.9%. The results of our systematic review demonstrated
that dynapenia in older adults increases the risk of multimorbidity. We propose that
interventions and reversible changes in dynapenia can prevent multimorbidity.

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Key words: Dynapenia, Multimorbidity, Multi disease, Older adults, Systematic review
Introduction

The world's aging population is rapidly increasing, and it is expected to reach 16.4% by 2050, posing a societal challenge. The physical changes associated with aging are categorized into sarcopenia and dynapenia. Sarcopenia is defined as a decrease in skeletal muscle mass, muscle strength, or physical performance, whereas dynapenia is defined as a loss of muscle strength despite a normal skeletal muscle mass. Dynapenia impairs physical function, leading to reduced physical activity and impaired mobility. Dynapenia development involves the transmission of cerebral excitability and age-related changes, which suggests that sarcopenia and dynapenia may be conceptually distinct. Furthermore, dynapenia reduces quality of life and increases mortality risk. In some cases, dynapenia can also coexist with chronic diseases, such as diabetes, cancer, and dementia, affecting health outcomes and worsening symptoms.

The presence of two or more chronic diseases is commonly called multimorbidity. Multimorbidity increases with age and is associated with the increased use of inpatient and outpatient care and high mortality rates. A previous systematic review showed that the prevalence of multimorbidity in older adults ranges from 55% to 98%. Consequently, many older adults with multimorbidities have negative health outcomes. Additionally, although most healthcare provisions and medical research to date have focused on individual diseases, a multidimensional approach is essential for older adults with multimorbidities. As a multidimensional approach, healthcare providers should promote understanding and provide better support for diseases to reduce the burden of treatment, polypharmacy, and polyphysician.

However, to our knowledge, no systematic reviews have investigated the association between dynapenia and multimorbidity. The concept of dynapenia is similar to that of frailty. Dynapenia focuses on the loss of muscle strength with aging, whereas frailty describes the
decline in physical, cognitive, and social functions with aging, indicating overall physical and psychological vulnerability. A review of frailty and multimorbidity in older adults found that 70% of frail older adults have multimorbidity, suggesting an interaction between the two factors. In their review of sarcopenia and comorbidity, Pacifico et al. reported that patients with cardiovascular and respiratory diseases, dementia, and diabetes developed sarcopenia more frequently, compared with patients without these conditions. Thus, the relationships and characteristics of age-related conditions and multimorbidity in older adults have been demonstrated. Therefore, we aimed to review the association between dynapenia and multimorbidity and consider potential medical interventions for adults with these two conditions.

Materials and Methods

This systematic review was guided by an a priori defined protocol consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The protocol for this systematic review was registered with PROSPERO (ID: CRD42023443282). The electronic databases searched included PubMed, EBSCO CINAHL, Cochrane Library (Wiley), and Web of Science for relevant articles published through July 7, 2023. The search strategy was created in consultation with a medical librarian, using search terms that primarily included derivatives of the terms: dynapenia and multimorbidity. Supplemental Material 1 presents the PubMed search strategy.

HO searched for articles, and all results from the complete search were imported into Rayyan online software for screening and reading. HO and SY independently assessed the titles and abstracts of the studies identified through the search of electronic databases. If the title and abstract did not provide sufficient information to determine the eligibility of a study, the full text of the article was reviewed. HO and SY then independently assessed the full texts of the articles to arrive at a final list of eligible articles. In case of any disagreement regarding
inclusion during the screening of titles and abstracts or full-text evaluation of the articles, a third reviewer was consulted for making the final decision.

Eligibility criteria

We included studies that 1) described dynapenia; 2) described multimorbidity with two or more chronic diseases; 3) were original articles written in English; and 4) were randomized controlled trials, cohort studies, observational studies, qualitative studies, or systematic reviews. The exclusion criteria were the following: 1) studies not investigating the aims of the review; 2) protocols and case reports; and 3) studies not designed for human participants.

Data extraction

Following the PRISMA guidelines, we recorded the number of articles retrieved, number of articles excluded, reasons for their exclusion, and number of articles included. We also created a data form to extract data relevant to the research question. HO independently extracted the data and SY checked the extracted data. Any disagreements regarding the extracted data were discussed and resolved. We planned to perform a meta-analysis if we identified three or more studies with similar definitions of dynapenia and multimorbidity.

Quality assessment

We assessed the risk of bias in the included studies using the Critical Appraisal Checklist for Analytical Cross-Sectional Studies from the Joanna Briggs Institute (JBI). The checklist comprised eight items with possible reviewer responses of “yes,” “no,” or “unclear”. The sum of the number of “yes” responses was defined as the overall score for each study, which ranged from 0 to 8. We assigned the studies as having low, moderate, and high risk of bias based on “yes” scores >70%, between 50% and 69%, and <49%, respectively. We used RevMan 5.4 (Review Manager 5.4; The Cochrane Collaboration) to generate Figure 2. The two reviewers independently examined the quality assessment process, checked the collected information, and discussed cases of disagreement.
The results of screening of the studies based on the eligibility criteria are shown in Figure 1. This review included five studies. A summary of these five eligible studies is presented in Table 1. Four studies were conducted in Brazil and one in the United Kingdom. In all the included studies, the target population consisted of older community-dwelling adults. The number of participants differed between studies, ranging from 247 to 8,396.

A summary of the risk of bias assessment is shown in Figure 2. Based on the criteria of the JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies, we ranked four of the five eligible studies as having a low risk of bias. One study was ranked as medium quality (“yes” score of 62.5%). Table 2 summarizes the relationship between dynapenia and multimorbidity reported in the eligible studies. The criteria for dynapenia were mainly measured and assessed based on grip strength; however, the values differed between studies. For example, the grip strength of participants was classified into tertiles, with the lower third of ≤18 kg classified as dynapenia, or cutoffs of ≤27 kg for men and ≤16 kg for women. The prevalence of dynapenia tended to increase with age, with overall rates ranging from 11.1% to 17.2% in studies of participants aged ≥50 years and from 25.9% to 33.2% in studies of participants aged ≥60 years.

The multimorbidity criteria included studies that selected participants with hypertension and diabetes with two or more chronic diseases, including heart disease, stroke, and cancer, and five or more chronic diseases. The prevalence of multimorbidity ranged from 35.4% to 64.6%, depending on the age of the participants. The association between dynapenia and multimorbidity was relevant in all five included studies. The prevalence of multimorbidity among participants with dynapenia
ranged from 16% to 25.9%. Similarly, Borges et al. showed that the odds ratio for multimorbidity was 1.2-fold higher in participants with dynapenia than in those without dynapenia. Additionally, Montes et al. measured handgrip strength and the quartile criteria for dynapenia and showed that the prevalence of multimorbidity increased with decreasing handgrip strength. Komatsu et al. also showed that dynapenia, which indicates low muscle strength, is a mediating variable that leads to increased mortality in association with multimorbidity. To successfully conduct a meta-analysis, we required at least three studies with the same definitions for dynapenia and multimorbidity, respectively. Among the included studies, only two—those by Borges et al. and Veronese et al.—met this criteria; therefore, we could not perform a meta-analysis.

Discussion

Our findings were as follows: 1) studies on dynapenia and multimorbidity were mainly cross-sectional studies in community settings; 2) participants with dynapenia were at a higher risk of multimorbidity; and 3) intervention studies on dynapenia and multimorbidity have not been reported.

Studies on dynapenia and multimorbidity have primarily been conducted in Brazil. In a study by Borges et al. on community-dwelling adults aged ≥50 years, almost one-fifth of them were found to have dynapenia. In recent years, the Brazilian Government has developed the Financial and Family Health Program as a strategy to address health promotion and disease prevention. The increasing prevalence of age-related disabilities and diseases is a global challenge and a topic of health promotion. Thus, research on dynapenia and multimorbidity is important in the current aging society. In their review, Komatsu et al. found that dynapenia increased the prevalence of multimorbidity, in a path analysis. In contrast, diseases found in older adults, such as dementia and cancer, can influence the prevalence of dynapenia.
Therefore, future studies should longitudinally examine the changes in risk and the interactions between dynapenia and multimorbidity.

Interventions for patients with dynapenia and multimorbidity should include preventive measures. Dynapenia is a risk factor for multimorbidity. In our review, cross-sectional studies reported an increased risk of multimorbidity associated with dynapenia. Komatsu et al. demonstrated that dynapenia was a mediating variable in the increase in multimorbidity and subsequent mortality. Therefore, early medical interventions for dynapenia may prevent multimorbidity. Such interventions improve physical activity and muscle strength. For example, in an intervention study on dynapenia, a combined intervention of low-impact resistance training and protein intake improved muscle strength and homogeneity. Similarly, systematic reviews of interventions for sarcopenia and dynapenia have demonstrated the benefits of resistance training. We propose that dynapenia is a reversible condition and that medical interventions are likely to prevent the worsening of multimorbidity. Aoki et al. reported five patterns of multimorbidity, including the combination of skeletal and gastrointestinal diseases. For example, the loss of muscle mass in dynapenia can lead to knee osteoarthritis, and the use of nonsteroidal anti-inflammatory drugs for pain can lead to gastric ulcers. Thus, the treatment of musculoskeletal disorders may allow symptom control; however, the side effects of these drugs may lead to the occurrence of new comorbidities, resulting in multimorbidity. Additionally, muscle weakness in dynapenia can cause a negative cycle of poor physical function and nutrition. The key to breaking this negative cycle is a reversible change through interventions for muscle weakness in dynapenia. Improved muscle strength through medical interventions may contribute to the maintenance or improvement of physical activity. Therefore, screening for dynapenia among community-dwelling older adults to select those in need of intervention may prevent the risk of developing multimorbidity due to muscle weakness and maintain physical function. In the future, we...
must continue to evaluate the effects of early assessment and intervention on dynapenia in older adults.

However, a balancing model has been proposed as a useful way to intervene in multimorbidity.\textsuperscript{17,19} The balancing model aims to increase the understanding of the disease, social support, and resilience of the patient, as well as to reduce the multiple challenges of polypharmacy, polyphysician, and lifestyle, which can be burdens to treatment.\textsuperscript{18} Thus, medical interventions for adults with dynapenia and multimorbidity should include not only resistance training for dynapenia but also multimodal interventions. Additionally, multidisciplinary interventions can improve outcomes in older adults.\textsuperscript{39} However, none of the studies included in our systematic review involved medical interventions. Further research is warranted to investigate the effects of multidisciplinary interventions in communities.

\textit{Limitation}

We conducted this systematic review to identify the relationship between dynapenia and multimorbidity and also considered medical interventions. However, this study has some limitations. First, most of the included studies used a cross-sectional design, and only one used a longitudinal design. Given this, we could not determine causal associations because of the lack of longitudinal evidence. Second, the definitions of dynapenia and multimorbidity were inconsistent across the included studies. Dynapenia is a condition in which both men and women experience age-related loss of muscle strength while maintaining muscle mass. The cutoff values for dynapenia were discussed and described using the cutoff values for sarcopenia. The European Working Group on Sarcopenia in Older People criteria are a grip strength <30 kg for men and <20 kg for women and skeletal muscle mass <10.76 kg/m\textsuperscript{2} for men and <6.76 kg/m\textsuperscript{2} for women, based on bioelectrical impedance analysis.\textsuperscript{40} The Asian Working Group for Sarcopenia criteria are a handgrip strength <28.0 kg for men and <18.0 kg for women and
skeletal muscle mass <7.0 kg/m$^2$ for men and <5.7 kg/m$^2$ for women, based on bioelectrical impedance analysis.\textsuperscript{41} The studies included in this review used only the lower third of grip strength or loss of grip strength as the criteria for dynapenia, and the maintenance of muscle mass was unclear.\textsuperscript{26-30} Similarly, multimorbidity was often defined as the comorbidity of two or more chronic diseases\textsuperscript{27, 29, 30}, however, one study defined it as the comorbidity of five or more chronic diseases.\textsuperscript{28} Therefore, although the impact of dynapenia may differ depending on the degree of multimorbidity, this relationship could not be considered in our review. The association between dynapenia and the degree of multimorbidity must be clarified in future studies. However, we systematically reviewed and defined the eligibility criteria and screened studies to clarify this relationship. Further research is warranted to establish a consensus definition of dynapenia and multimorbidity.

Conclusions

In conclusion, this systematic review identified an association between dynapenia and multimorbidity in five studies that met the eligibility criteria. All the selected studies involved community-dwelling older adults. Additionally, dynapenia increased the risk of multimorbidity in all the included studies. However, we found no intervention studies on dynapenia and multimorbidity. Further research is needed to establish the interaction between dynapenia and multimorbidity and the changes in prevalence with medical interventions.