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Aims and Scope

Annals of Geriatric Medicine and Research (Ann Geriatr Med Res, AGMR) is a peer-reviewed journal that aims to introduce new knowledge related to geriatric medicine and to provide a forum for the analysis of gerontology, broadly defined. As a leading journal of geriatrics and gerontology in Korea, one of the fastest aging countries, AGMR offers future perspectives on policymaking for older adults, clinical and biological science in aging researches especially for Asian emerging countries. Original manuscripts relating to any aspect of geriatrics, including clinical research, aging-related/basic research, and policy research related to senior health and welfare will be considered for publication. Professionals from a wide range of geriatric specialties, multidisciplinary areas, and related disciplines are encouraged to submit manuscripts for publication.

General Information

The official journal title has been Annals of Geriatric Medicine and Research since September 2016 which followed the Journal of the Korean Geriatrics Society (1997-2016, pISSN: 1229-2397, eISSN: 2288-1239). It is the official journal of the Korean Geriatrics Society (http://www.geriatrics.or.kr/eng/) and the Korean Society for Gerontology (http://www.korea-biogerontology.co.kr). It is published in English quarterly on the last days of March, June, September, and December. The journal publishes original research articles, case reports, reviews, special contributions, and commentaries. Review board consists of members in 7 different countries. Articles are welcome for submission from all over the world. The contents of this Journal are indexed in Web of Science, Scopus, PubMed, PubMed Central (PMC), EBSCO, DOAJ, KoreaMed, KoMCI, KCI, DOIs/Crossref, and Google Scholar. It is accessible without barrier from Korea Citation Index (https://www.kci.go.kr) or National Library of Korea (http://nl.go.kr) in the event a journal is no longer published.

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Annals of Geriatric Medicine and Research Indexed in PubMed Central: An Important Milestone toward the Leading Journal

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We are excited to announce that Annals of Geriatric Medicine and Research (AGMR) has passed the evaluations required by PubMed Central (PMC) and has been officially accepted for inclusion in PubMed/PMC, an extensive digital repository of biomedical and life science journals. The contents of AGMR published since 2018 are now available in PubMed. By leveraging the PubMed networks and user base, a primary literature resource used by most researchers globally, the inclusion of AGMR in PMC ensures greater visibility of the research published in AGMR. This is an important milestone for AGMR, not only in our efforts to increase the recognition of AGMR worldwide but also in our journey toward becoming a high-impact journal in the fields of geriatrics and gerontology. We extend our sincere appreciation for the enthusiastic support and contributions of our editorial board members, reviewers, authors, and readers and also acknowledge the perseverance and commitment of our editorial staffs.

AGMR, formerly the Journal of the Korean Geriatrics Society, has grown as a representative journal in the fields of Korean geriatrics and gerontology over the last 20 years.\textsuperscript{1,2} Since the successful launch of the newly-named AGMR in September 2016, continuous efforts have been made to improve the scientific and editorial quality of the articles published in this journal. The scope of the journal was broadened to include an international readership, and the journal started to receive more scientifically competent papers from diverse countries. Thus, in March 2018, our journal was listed in the Emerging Sources Citation Index database included in the Web of Science Core Collection, which lists journals under evaluation for inclusion in impact factor databases such as Science Citation Index Expanded.\textsuperscript{3} In October 2019, Elsevier announced the exciting news that AGMR was accepted for coverage in Scopus, a comprehensive abstract and citation database; research materials published 2016 onwards were to be covered.\textsuperscript{3} AGMR was included in the 2019 Q3 journal ranking released by Elsevier with a CiteScore of 1.1, a meaningful achievement for a journal that had entered Scopus for the first time.

In the multifaceted process of reforming AGMR into a multidisciplinary, globalized, high-quality journal, we have revised the journal’s aims and scope statement to be more specific and straightforward. In this statement, we emphasize the role of AGMR as a growing platform offering future perspectives on the research needs related to geriatrics and gerontology in emerging countries with rapidly growing aging populations.\textsuperscript{3} As the name implies, AGMR’s comprehensive aims and scope not only cover clinical studies on geriatric medicine but also cover basic science, pre-clinical, and translational studies in the field of gerontology. To bolster competencies in basic and translational research on aging, the Korean Society for Gerontology endorsed AGMR as its official journal in 2019; thus, AGMR is now officially backed by two leading academic societies of geriatrics and gerontology in Korea. To expand globalized readership and promote the quantitative and qualitative growth of the academic content of the journal, we have been recruiting academic experts as editorial and reviewer board members. To date, 44 outstanding scholars in the fields of geriatrics and gerontology from 12 countries have joined our journal as editors.

We have made efforts to improve our standards in terms of the editorial process and ethical guidelines, such as the Principle of Transparency and Best Practice in Scholarly Publishing, a Joint Statement by the Committee on Publication Ethics. We also aim to improve the editorial process to ensure the timeliness of articles by reducing the step-wise processes of reviewing, editing, and publishing using lean approaches. To enhance user experience, the journal website has been upgraded, as the function of browsing through the articles has been enhanced with the metric information of the journal such as journal hits, downloads, and cross-refer-
ence citations. These efforts and achievements have resulted in a growth rate of more than 100% in page views and content downloads in this year compared to that in previous years.

Together with our board members and authors, the editorial team is improving the journal into an even more rigorous platform to meet the expectations of clinicians, researchers, policymakers, and readers in the fields of geriatrics and gerontology. Being indexed in PubMed/PMC is an important step toward achieving this goal. We look forward to taking the journal to the next level in 2021 and beyond.

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CONFLICT OF INTEREST

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REFERENCES


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Understanding Muscle Protein Dynamics: Technical Considerations for Advancing Sarcopenia Research

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Sarcopenia, which is the loss of muscle mass and strength that occurs with aging, involves imbalanced muscle protein turnover (i.e., protein breakdown exceeding synthesis), which in turn exacerbates other clinical conditions such as type 2 diabetes mellitus, obesity, osteoporosis, and cancer, thereby worsening the quality of life in older adults. This imbalance is attributed in part to the resistance of aged muscle to anabolic stimuli such as dietary protein/amino acids and resistance exercise known as anabolic resistance. Despite research efforts, no practical therapeutics have been successfully discovered possibly because of a lack of understanding of the dynamic nature of muscle protein, and the use of indirect assessments of muscle mass. Herein, we briefly discuss the regulation of protein turnover in response to the abovementioned anabolic stimuli with respect to anabolic resistance and optimal protein intake, followed by methodological considerations for advancing sarcopenia research, including assessments of muscle mass and dynamics.

Key Words: Sarcopenia, Metabolism, Essential amino acids, Stable isotope labeling

INTRODUCTION

Sarcopenia, the age-related degenerative loss of muscle mass and function, is considered a muscle disease (i.e., muscle failure) and is central to functional and metabolic alterations in various clinical conditions such as critical illness (e.g., burn injury and cancer), chronic diseases (e.g., heart failure), insulin resistance, obesity, and osteoporosis. Therefore, discovering effective therapeutic means to counteract sarcopenia progression is of utmost importance to improve the quality of life in older adults and is a major target for drug development; however, efforts have not yet led to clinically meaningful success. The etiology of sarcopenia is multifactorial, including alterations in hormones and sex steroids, physical inactivity, and comorbidities. It is, therefore, difficult to understand the underlying mechanism(s) at molecular and cellular levels, which may explain the lack of meaningful success in the development of effective drugs to treat sarcopenia. Regardless of the complexity of etiology, sarcopenia is the direct result of dysregulation in muscle proteostasis that is maintained through orchestrated changes in the rates of protein synthesis and breakdown in response to various physiological challenges. While it is important to appreciate the dynamic nature of the proteome, most previous studies largely depend on "snap-shot" information obtained through molecular and cellular biological tools or -omics data that lack information on the actual rates of muscle protein kinetics. Furthermore, the invasiveness of muscle biopsy required to assess muscle protein dynamics is a burden that impedes subjects participating in sarcopenia research. In this regard, stable isotope tracer techniques are helpful as they provide information on protein dynamics in vitro and in vivo in both.
animal and human studies.\textsuperscript{6,9} Furthermore, it is important to accurately determine muscle mass to evaluate the efficacy of therapeutic candidates (e.g., nutrition, exercise, and/or drugs) using minimally invasive techniques; however, no commonly used methods (such as dual-energy X-ray absorptiometry [DEXA]) directly assess muscle mass.\textsuperscript{10,11} Therefore, this short review discusses the following topics: (1) regulation of muscle protein dynamics in response to anabolic stimuli such as resistance exercise and amino acid (AA)/protein nutrition, (2) anabolic resistance to those anabolic stimuli in older adults, (3) importance of dietary protein or balanced essential AAs (EAA) for effective muscle protein synthesis (MPS), and (4) methodological considerations for advancing medical research in sarcopenia, including the critical role of stable isotope tracer methodologies to assess muscle protein dynamics and muscle mass.

\textbf{REGULATION OF MUSCLE PROTEIN KINETICS: EFFECTS OF RESISTANCE EXERCISE AND DIETARY PROTEINS/ AMINO ACIDS}

The muscle protein pool is in a constant state of turnover (i.e., protein synthesis and protein breakdown). Thus, the muscle protein pool (mass) is determined by the balance between rates of protein synthesis and breakdown. As long as the two rates are constant, muscle mass will not change, regardless of the actual rates. If the MPS rate exceeds that of breakdown, muscle mass will hypertrophy over time. In contrast, muscle atrophy will occur in the opposite state (i.e., protein breakdown > synthesis) (Fig. 1).

Resistance exercise and dietary EAA/protein are the two most prominent anabolic stimuli. In the resting fasted state, muscle protein breakdown (MPB) typically exceeds MPS, implying a net negative protein balance.\textsuperscript{12,13} Resistance exercise stimulates muscle protein turnover, with MPS increasing to a greater extent than MPB, leading to an improvement in the net protein balance. However, the net protein balance remains negative (MPB > MPS) because MPB remains greater than MPS. Moreover, resistance exercise alone does not lead to a net positive protein balance (i.e., muscle hypertrophy) until the provision of nutrients, particularly high-quality dietary protein or balanced EAAs.\textsuperscript{15-18} In contrast, dietary protein alone can induce a net positive protein balance (i.e., anabolic response: MPS > MPB) even without resistance exercise, although the anabolic effect is relatively transient (approximately 2–3 hours post-feeding).\textsuperscript{19} The anabolic response to dietary protein or AAs is achieved by stimulating MPS with no apparent change in MPB\textsuperscript{20-22} after the intake of AAs/proteins. This may not be the case following the intake of mixed meals containing proteins; however, no definite evidence with respect to MPB is currently available.\textsuperscript{23-25} The stimulatory effect of dietary protein consumption on MPS is attributable to the EAA component because the consumption of non-essential AAs (NEAAs) alone or with EAAs failed to further stimulate MPS.\textsuperscript{26} Resistance exercise can amplify\textsuperscript{15} and prolong anabolic responses to dietary protein/EAA.\textsuperscript{14}

\textbf{Fig. 1.} Muscle (protein) mass is regulated by the balance between muscle protein synthesis (MPS) and muscle protein breakdown (MPB). The pool size of the muscle protein (i.e., mass) is represented as the volume in the water tank. Muscle hypertrophy is defined as MPS > MPB and muscle atrophy as MPS < MPB.
Anabolic Resistance to Dietary Protein/EAA and Resistance Exercise in Older Adults with Sarcopenia

It was once believed that age-related sarcopenia resulted from alterations in protein kinetics in the basal fasted state. However, using state-of-the-art stable isotope tracer methodologies with muscle biopsy and arteriovenous balance techniques, it was demonstrated that no difference in basal fasted protein kinetics between older adults with sarcopenia and normal healthy young adults exists. Instead, the efficiency of stimulation of net muscle protein synthetic response to a small EAA intake was attenuated in older adults compared with that in healthy young adults (intake of 6.7 g EAA), a phenomenon termed anabolic resistance. However, the attenuated response to dietary protein/ EAA was rescued when the amount of EAA intake (contained in beef steak) was doubled. Similarly, anabolic resistance occurs in response to resistance exercise in older adults with sarcopenia. For example, Kumar et al. determined MPS after resistance exercise at a wide range of intensities while holding the volume of exercise constant in young and older subjects. They found that MPS increased linearly as a function of intensity until 60% repetition maximum (a maximal weight to be lifted once) in both age groups, but to a greater extent in young subjects than in older subjects at all intensities. Anabolic resistance could be partly because of the attenuated activation of mammalian target of rapamycin complex 1 (mTORC1) in response to anabolic stimuli such as dietary protein/EAA or resistance exercise. Consistent with this notion, increasing the proportion of leucine in AA mixtures overcomes the blunted anabolic response in rest and post-exercise conditions in older adults. Although leucine may have a therapeutic potential to counteract muscle wasting owing to its potency in activating mTORC1, the activation of mTORC1 is only one of several important components required for the complete synthesis of new proteins, including the availability of precursor AAs.

All AAs Work Together to Make New Proteins

Appreciation of the process of protein synthesis makes clear the requirement that all AA precursors must be present in adequate quantities to produce a protein. The requirement for all AAs can be envisioned with the following analogy. If you bought a sports car, you can drive at 100 mph as long as you have gasoline in the tank. However, you cannot go without gasoline (i.e., no AAs) despite having a powerful engine (i.e., a fully activated mTORC1). In short, to make new proteins, all AAs required for protein synthesis need to be available. As discussed above, because the consumption of NEAAs does not lead to the stimulation of MPS and because they are sufficiently produced endogenously, the consumption of balanced EAA should be mainly considered. Consistent with this notion, no clinical studies have shown the positive effects of leucine supplementation on lean body mass and strength, particularly in older adults. In contrast, EAA or protein supplementation improved lean body mass in older adults, with or without exercise training. Moreover, at the whole-body level, the consumption of balanced EAA was more effective in inducing a greater anabolic response than that of protein in young and older adults. However, leucine alone could have nutraceutical potential in counteracting sarcopenia if the following two criteria are met: (1) acceleration of protein breakdown drives loss of muscle mass and (2) leucine effectively inhibits protein breakdown. First, the underlying kinetic mechanism may vary depending on muscle-wasting conditions (e.g., sarcopenia vs. cachexia). Cachexia is a much stronger driver of accelerated MPB than sarcopenia. Thus, it is important to determine protein kinetics to understand if the underlying mechanisms reside in the alteration of protein breakdown or synthesis. Second, an anti-proteolytic potential of leucine that involves mTORC1 activation, which in turn suppresses autophagy through the phosphorylation of an important autophagy initiating kinase, Unc-51-like autophagy-activating kinase 1 (ULK1), has been reported. However, its quantitative contribution to muscle wasting remains to be determined.

Optimal Dietary Protein Intake for Maximal Anabolic Response

Protein dose-response studies in older adults have largely been conducted with protein or AA alone. However, most of these studies only quantified the synthesis side of the protein balance equation. In this respect, the optimal amount of protein, i.e., the minimum amount of protein that induces a maximal anabolic response, ranges from 20 to 35 g per meal or more specifically 0.24 g protein/kg body weight per meal for healthy young adults. The corresponding amount for healthy older adults is 0.40 g protein/kg body weight per meal, reflecting 70% anabolic resistance. Based on these data, distributing the total amount of protein evenly throughout the day rather than the more conventional approach of consuming one large meal containing most of the dietary protein (typically dinner) may provide a near-maximal anabolic response per meal. For example, if an older adult weighing 70 kg consumes 1.2 g protein/kg/day (84 g/day), corresponding to 1.5 times the recommended dietary allowance (0.8 g/kg/day) a typical distribution pattern might be 20% (0.24 g/kg or 16.8 g per meal) at breakfast, 30% (0.36 g/kg or 25.2 g per meal) at lunch, and 50% (0.6 g/kg or 42 g per meal) at dinner. With this uneven pattern of protein intake, a near-maximal anabolic response can occur only at dinner (above 0.4 g/kg per meal).
However, if consumed evenly throughout the day (one-third per meal), the same person can achieve maximal anabolic response by consuming the optimal 0.4 g/kg at every meal. While this theory appears to be logical, the optimal dose (0.4 g/kg per meal) may be underestimated in the real world for several reasons. First, the optimal protein dose was based on the assessment of the anabolic response to increasing doses of high-quality (animal source) protein, whereas a normal diet contains proteins with varying degrees of quality. Second, for most (> 95%) older adults to achieve maximal anabolic response, they need to consume approximately 0.6 g protein/kg/meal (3 meals × 0.6 g/kg/meal = approximately 1.8 g/kg/day). Third, and most importantly, people consume most protein in the context of mixed meals and not in isolation, which induces different physiological responses such as higher insulin and lower EAA responses in the blood for a given amount of protein or AA consumed. Consistent with this notion, we showed an increased whole-body anabolic response following the consumption of protein above the amount considered optimal. Furthermore, the response was dose dependent (dose range: approximately 6.4–91.7 g per meal), with an increasing protein intake in the context of mixed meals largely improving the net protein balance by suppressing protein breakdown via insulin-dependent and insulin-independent pathways. The results of a 12-week chronic study support our findings by showing a close correlation between lean body mass and the amount of protein intake within a wide range of protein intake. However, the role of the suppression of protein breakdown in inducing an anabolic response in muscle remains to be confirmed because the rate of MPB with increasing amounts of protein or EAA intake has not been directly measured. Furthermore, despite its major role in inducing an anabolic response, it is still unclear if inducing an anabolic response by slowing protein turnover, as shown in our previous studies, is optimal for muscle health and the quality of life in older adults. A high rate of protein turnover presumably replaces older proteins with new functional proteins. Thus, further investigations of the optimal total amount of dietary protein intake and the pattern of consumption are warranted.

METHODOLOGICAL CONSIDERATIONS FOR ADVANCING MEDICAL RESEARCH IN SARCOPENIA: A ROLE FOR STABLE ISOPIPE TRACER METHODOLOGIES

To better understand the pathological alterations in sarcopenic skeletal muscle and test the efficacy of potential therapeutics developed to counteract sarcopenia, two important variables need to be accurately assessed, namely (1) muscle protein kinetics and (2) muscle mass. However, quantifying these parameters presents several challenges. First, the assessment of muscle protein turnover requires a minimum of one, and often several, muscle biopsies, which is invasive and may limit participant recruitment. Second, despite the critical importance of an accurate assessment of changes in muscle mass owing to therapeutic interventions (nutrition, exercise, and/or drugs), the approaches commonly utilized in clinical research such as DEXA are indirect measurements of muscle mass, which are highly susceptible to errors. However, these challenges can be overcome by recent technological advancements with minimal invasiveness, including (1) a deuterium-labeling method combined with “virtual” biopsy (no muscle biopsy) to determine muscle protein dynamics and (2) a D$_3$-creatine dilution method to directly determine muscle mass. In the following section, we will briefly discuss (1) the basic principles of determining muscle protein turnover, (2) the deuterium oxide labeling method combined with virtual biopsy, and (3) the D$_3$-creatine dilution method.

Exploration of Protein Turnover Dynamics

To maintain proteostasis in the body, all proteins are in varying rates of turnover, resulting in a dynamic balance between protein synthesis and breakdown (Fig. 1). In normal conditions, muscle mass is maintained through a close match between the rates of protein synthesis and breakdown in a daily basis. That is, the portion of the day in which protein balance is positive as the result of anabolic stimuli, such as exercise and nutritional intake, is closely balanced with the portion of the day in which protein balance is negative as the result of catabolic stimuli such as overnight fasting and/or post-absorptive periods. However, in muscle-wasting conditions such as sarcopenia, negative protein balance (i.e., loss of muscle mass) predominates owing to protein breakdown exceeding protein synthesis over time. Hence, an understanding of the dynamic nature of protein turnover in the body is of critical importance for elucidating in vivo proteostasis, which can be assessed by stable isotope tracers.

The MPS rate is generally assessed using stable isotope tracers and is reported as a fractional term, namely the fractional synthetic rate (FSR, %/unit time). Briefly, following the administration of a tracer AA (i.e., phenylalanine tracer) that monitors the fate of the trace AA into the body (typically intravenously), muscle protein FSR is estimated by determining the rate of tracer phenylalanine incorporation into muscle protein over time. To obtain the absolute rate of MPS, the muscle protein FSR is multiplied by the pool size (i.e., muscle protein mass), which underpins another reason to correctly determine muscle (protein) mass. In contrast, the rate of
MPB is determined similarly in principle, except that the precursor of free AAs is muscle protein. More comprehensive information regarding the principles of stable isotope tracer methodology is available elsewhere.\(^{49-50}\)

### Assessment of Muscle Dynamics: Deuterium Oxide and Virtual Biopsy Method

The assessment of muscle protein FSR using the stable isotope tracer methodology typically requires muscle tissue obtained by needle biopsy. However, muscle biopsy is invasive, thus limiting subjects’ willingness to participate. Furthermore, obtaining muscle tissue by biopsy may be difficult in older adults with sarcopenia owing to their greatly reduced muscle mass. The heavy water labeling method combined with “virtual biopsy” allows researchers to avoid problems of obtaining muscle samples.\(^{49,50}\) The method comprises two parts (Fig. 2), namely (1) heavy water labeling of muscle proteins and (2) measurement of labeling of a circulating protein almost exclusively released from skeletal muscle into the blood (e.g., muscle creatine kinase, mCK). To assess the MPS rate using this method, individuals consume a small amount (approximately 100 mL) of heavy water (deuterium oxide, \(\text{D}_2\text{O}\)) daily from a few days to months. Deuterium from heavy water rapidly equilibrates with the existing body water pool, both of which are then rapidly exchanged with free AAs via transamination and deamination reactions\(^{41}\) and then incorporated into muscle proteins, including mCK. The advantages of measuring mCK include (1) consistent detection in the blood, (2) exclusive derivation from muscle (\(>90\%\)), and (3) a shorter half-life than that in muscle (approximately 2 months) (Fig. 1).\(^{53,54}\) Therefore, circulating mCK levels reflect the levels in muscle with respect to deuterium labeling and thus the protein FSR of mCK.\(^{49}\) Furthermore, mCK FSR is well equated with the muscle contractile protein FSR.\(^{49}\)

#### Direct Assessment of Skeletal Muscle Mass: The D\(_{3}\)-Creatine Dilution Method

The accurate measurement of changes in muscle mass is crucial for assessing the efficacy of potential therapeutics for sarcopenia. DEXA, electrical impedance, computed tomography, and magnetic resonance imaging have been commonly utilized\(^{10}\) to measure muscle mass. However, none of these techniques directly measures skeletal muscle mass because muscle mass is not distinguished from bone and tendon-like connective tissues and the results are significantly affected by hydration status.\(^{50}\) The recently described D\(_{3}\)-creatine dilution method more directly estimates muscle mass via the dilution principle of deuterium-labeled creatine (i.e., D\(_{3}\)-creatine). The basic principle of the method is based on the calculation of the magnitude of the dilution of D\(_{3}\)-creatine in all skeletal muscles in the body (reflected in urine creatinine enrichment) following the oral consumption of a known small amount of D\(_{3}\)-creatine.\(^{53,54}\) Briefly, orally consumed creatine mostly enters skeletal muscle via a creatine transporter against a concentration gradient. In muscles, creatine is converted to creatinine by irreversible, non-enzymatic dehydration, whereupon the creatinine is released into the blood and is excreted by the urinary system (Fig. 3). The advantage of using the D\(_{3}\)-creatine dilution method to measure muscle mass is that approximately 98% of the total creatine pool is found in skeletal muscle and that creatine is exclusively turned over in muscle and converted to creatinine. Thus, urine enrichment of creatinine reflects creatine enrichment in muscle, enabling the calculation of the total creatine pool size, which is directly related to muscle mass.\(^{50}\)

In summary, the heavy water labeling method combined with virtual biopsy and D\(_{3}\)-creatine dilution method provided precise,

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**Fig. 2.** Heavy water labeling combined with virtual biopsy method. Heavy water (\(\text{H}_2\text{O}, \text{D}_2\text{O}, \text{or DDO}\)) that is consumed rapidly equilibrates with water in the body (\(\text{H}_2\text{O} \text{or } \text{H}^\text{H} \text{HO}\)) for hydrogen, resulting in deuterium-labeled AAs (the number of deuterium labels vary depending on AAs and thus protein) that are incorporated into muscle proteins, including the muscle isoform of creatine kinase (mCK), which is released into the blood. Circulating mCK is extracted for measuring the amount of deuterium-labeled AA incorporation over time using mass spectrometry. The muscle fractional synthesis rate of mCK is a direct reflection of the total muscle protein fractional synthesis rate. AA, amino acid; PB, protein breakdown; PS, protein synthesis.
accurate, and convenient tools to analyze protein turnover and muscle mass, respectively, with minimal invasiveness. The application of these techniques can facilitate and advance clinical muscle research, particularly in the field of sarcopenia.

SUMMARY AND CONCLUSIONS

Sarcopenia, which is the progressive loss of muscle mass and strength with aging, is a public health problem affecting the quality of life of older adults. While research efforts to reverse sarcopenia progression have heavily focused on “static” molecular and cellular mechanisms, improved understanding of “kinetic” mechanisms is needed as the muscle protein pool is in a dynamic state of constant turnover. The determination of muscle protein kinetics traditionally requires muscle biopsy, which slows sarcopenia research. In this regard, heavy water labeling combined with “virtual” biopsy is an important tool for determining muscle protein kinetics in free-living conditions without requiring an actual muscle biopsy. Furthermore, the accurate assessment of muscle mass is required to determine the efficacy of potential therapeutics. To date, muscle mass has been indirectly estimated using methods such as DEXA. These indirect methods can be replaced by a direct muscle mass assessment using the D$_3$-creatine dilution method. The virtual biopsy and D$_3$-creatine methods can use stable isotope tracers to quantify the dynamic nature of the muscle proteome and accurately measure muscle mass. These new methods will allow the development of therapeutics based on a quantitative understanding of the physiological basis of sarcopenia.

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AUTHOR CONTRIBUTIONS

Conceptualization, IYK; Funding acquisition, IYK; Writing-original draft, IYK, SP, JWJ; Writing-review & editing, SP, JWJ, IYK, RRW.

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INTRODUCTION

The current pandemic caused by the newly described severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to spread, with devastating effects on the functioning of society and the world economy. By June 4, 2020, 6,416,828 people had been infected, with 382,867 deaths worldwide. While new cases are declining in some countries in the European region, the disease continues to spread, almost unchanged, in the United States, and a steady increase in the number of infections in the African region has been reported. The first case of coronavirus disease 2019 (COVID-19) was reported in Wuhan in the Hubei province of China on December 12, 2019, the origin of which was traced to the Huanan seafood market in Wuhan; moreover, genomic studies confirmed that the causative organism to be of bat origin. COVID-19 mainly spreads via droplets from saliva and nasal discharge of infected people, and its common symptoms include fever, dry cough, shortness of breath, diarrhea, and vomiting. COVID-19 is predominantly observed in young and middle-aged people with no significant sex difference. Most infections are either asymptomatic or paucisymptomatic and do not require hospitalization or specific treatment. Some patients, however, gradually deteriorate, with the involvement of internal organs such as the lungs, kidneys, and heart.

Pandemics lead to social disruption and economic downturns both regionally and globally, as well as uncertainty and anxiety among populations. The effect of pandemics on economies and healthcare systems is enormous. Furthermore, pandemics are associated with overcrowding of healthcare facilities, as well as health care staff exhaustion and burnout, resulting in the disruption of routine care provided to patients with other illnesses. Pandemics affect individuals differently; the resultant negative effect may be more pronounced on marginalized populations, including older adults, refugees, and people living in slums. However, the effect of pandemics on these marginalized populations has not been adequately studied.

Older adults are considered a vulnerable population for a multitude of reasons. Besides age, multiple diseases; long-term drug use; and poor social habits, nutrition, and living conditions increase the vulnerability of older adults to infection. Policy decisions and ac-

Key Words: COVID-19, Aged, Pandemics
tions to curb pandemics may aggravate these conditions, resulting in poor access to healthcare, drug shortages, limited food supplies, and movement restrictions.

The special needs of older populations during critical periods of pandemics should be a focus of healthcare and other services. It is intuitive to believe that the effects of pandemics are globally uniform and vary according to ethnicity and geography. Therefore, interventions to safeguard older people should be country or ethnicity specific and must be adjusted and modified according to the beliefs, attitudes, behaviors, health, etc., of older people. This assessed the effect of the COVID-19 pandemic on older people based on the interactions among the virus, patients, and environment to suggest possible interventions. This study is a more general review and not specific to a particular ethnic group or geographical area. We searched the PubMed, Ovid, and World Health Organization (WHO) COVID-19 databases for current scientific information, as well as other sources such as printed media from countries, including the UK and the United States, to collect general information. We found a rapid increase in scientific literature during recent months; this review includes only studies available through June 4, 2020.

OLDER ADULTS AS A VULNERABLE GROUP

In general, older adults are prone to both acute and chronic infections owing to reduced immunity. Immune senescence, which is the downregulation of the immune system at multiple levels, is mainly attributed to aging and makes this population vulnerable to a multitude of infections and leads to reduced cell-mediated immunity and poor antibody response to immunogens. In addition to this acquired immunity insufficiency, other factors such as reduced cough and gag reflexes, urine and fecal incontinence, and reduced skin barrier also contribute to high infection susceptibility among older adults. Furthermore, comorbidities such as diabetes, chronic renal failure, and neuromuscular disorders and the long-term use of medications such as glucocorticoids and proton pump inhibitors make older adults more vulnerable to infections.

In addition to host-related factors, environmental or social factors contribute to the high infection risk among older adults. These include poor living conditions, nutrition, ventilation, sanitation, and overcrowding, especially among older adults in long-term care.

The interactions between host and environmental factors that make older adults susceptible to infections are complex. These factors, apart from making older adults susceptible to infections, also interfere with the clinical recovery of patients. Yamamoto et al. reported that severe underlying disease, poor general condition, aspiration, bacterial resistance to drugs, superinfection, and poly-microbial infection were associated with treatment failure and poor clinical recovery in older patients with hospital-acquired pneumonia. Also, negative effects of comorbidities on the clinical outcomes of both acute and chronic diseases is well known. Comorbidities may alter clinical symptomatology, leading to delays in seeking treatment and diagnosis, especially during the pandemic where respiratory involvement predominates and clinicians rely on respiratory symptoms to identify patients. Further underlying diseases such as renal and liver diseases may interfere with management protocols.

COVID-19 AND OLDER ADULTS

Older adults are a highly vulnerable group during the pandemic. The effect of COVID-19 on older adults has been assessed in terms of percentage infected and rates of hospitalization and mortality. The proportions infected or hospitalized may not reflect the true disease effect on older people because they may not be considered a priority group for screening and hospitalization during the pandemic. When healthcare facilities are overburdened during the pandemic, it may not be possible to equally cater to all patients; moreover, reports indicate that some countries adopted an age-based triage during the current pandemic, in which younger patients were given priority over older adults to receive healthcare. Furthermore, older adults may be underrepresented in screening programs owing to poor communication and restricted mobility. During pandemics, systematically documented mortality rates may be a better reflection of the disease effect on older populations.

Analyses of age-dependent mortality rates have consistently shown an exponential increase in mortality of COVID-19 patients aged more than 50 years. Reanalysis of combined data of the WHO–China joint mission on February 28, 2020, which included 55,924 confirmed cases, and data from the Chinese Center for Disease Control and Prevention report from February 17, 2020, based on 72,314 confirmed, suspected, or asymptomatic cases, showed mortality rates below 0.4% among patients aged < 50 years, with an exponential increase in those older than 50 years. In this analysis, the mortality rates among the 50–59, 60–69, 70–79, and 80 or above age groups were 1.3%, 3.6%, 8.0%, and 14.8%, respectively.

Furthermore, analysis of COVID-19-related deaths in the United States between February 1 and April 11, 2020 according to patient age showed that only 746 of the 8,259 deaths during the study period occurred in patients aged < 55 years. The number of deaths in patients aged > 55 years, however, increased substantially, at 1,086 for those aged 55–64 years, 1,821 for those aged 65–
74 years, 2,248 for those aged 75–84 years, and 2,358 for those aged 85 years or above. While most of these deaths (6,120) occurred in inpatient healthcare settings, a substantial number (830) occurred in nursing homes/long-term care facilities, most likely in older patients.14

Apart from higher mortality, older adults have a high risk of hospitalization during epidemics. An analysis of COVID-19-associated hospitalization rates among patients admitted during March 2020 in the United States showed that among 1,482 patients hospitalized, 74.5% were aged ≥ 50 years and 54.4% were male. While the hospitalization rate among all patients during this period was 4.6 per 100,000 population, a higher rate of hospitalization (13.8) was observed among those aged ≥ 65 years.15 Furthermore, 89.3% of adults aged ≥ 65 years had one or more underlying conditions. While hypertension was the most common comorbidity observed in 49.7% of cases, 48.3% were obese, 34.6% had chronic lung disease, 28.3% had diabetes mellitus (28.3%), and 27.8% had cardiovascular disease (27.8%).15

The poor clinical outcomes observed among older adults during the COVID-19 pandemic prompted the Centers for Disease Control and Prevention (CDC) to categorize this population, especially those with multiple diseases, as a high-risk group4 and prescribe special precautionary measures for them. According to the CDC, 8 out of 10 deaths reported in the United States were adults aged 65 years or above.

**CLINICAL FEATURES AND INVESTIGATIONS**

Older adults, in general, tend to have atypical presentations, especially those with infectious diseases. They often have blunted fever responses even in the presence of overwhelming infections. Studies comparing clinical presentations and disease progressions of COVID-19 between older and other age groups are sparse. Liu et al.15 compared the clinical course of 18 older patients to that of 38 young or middle-aged COVID-19 patients and observed more severe disease and higher mortality in the former patient group. Although presenting symptoms were similar in the two groups, older patients had a higher Pneumonia Severity Index (PSI) than young and middle-aged patients. Furthermore, the proportion of patients with PSI grade 4 or 5 was higher among older patients. In addition, they had more multilobar involvement, lower lymphocyte proportion, and lower C-reactive protein concentration than young and middle-aged patients.

In an update in Military Medical Journal, Guo et al.27 highlighted differences between older and younger COVID-19 patients. COVID-19 is mainly affecting young and middle-aged patients, with the median age of affected patients being 47–59 years. However, infection is highly transmissible among older adults, particularly among those with comorbidities. Furthermore, the rapid deterioration of the clinical condition leading to acute respiratory distress syndrome (ARDS), circulatory shock, metabolic acidosis, and death occurs more frequently in older adults.16 The rapid clinical deterioration of the clinical condition of older patients has been reported by Wang et al.19 and Yang et al.20

Delirium is reportedly common among older people with COVID-19 and can be the only presenting feature. Beach et al.21 indicated that delirium could result from direct infection of the central nervous system and proposed the need to include delirium in COVID-19 screening programs. In a comparative study, Benussi et al.22 reported a 26.8% rate of incident delirium among older patients with COVID-19 compared with 7% among test-negative individuals. A study in Switzerland indicated that typical symptoms such as fever and cough were uncommon and that atypical features such as falls, delirium, and unusual fatigue were more frequent among older patients with COVID-19.23

**EFFECTS OF SOCIAL DISTANCING AND ISOLATION ON OLDER PEOPLE**

Although social distancing could save the lives of older people, it also adds to their loneliness. Social constraints subsequent to social distancing and isolation lead to significant limitations of daily activities, inaccessibility to health workers on whom the older people are reliant, financial constraints, and difficulty in adjusting to new social barriers created in activities such as online shopping.24

Social distancing and isolation have significant health and psychological effects on older adults. Unlike younger adults, older people are often unable to use technology to mitigate isolation and its psychological effects.25 Older adults who engage in frequent social interactions such as social groups, societies, and frequent visits to relatives have far lower morbidity rates than individuals in isolation.26 The ability to engage in these social activities is severely reduced during social distancing. Older people often make less use of technology, especially virtual technology, and they are less driven to learn new technology-related skills.27 Furthermore, older people are less likely to use technology even if specifically tailored for them. The main reason for the poor use of technology among older adults is not a lack of access to technology or connectivity but rather the lower expectations that are put on older people with regard to technology use and the assumption of risk owing to the knowledge gap.27 Technology is essential in long-term social distancing to satisfy psychological needs and access services.

Social isolation in older people can lead to psychological morbidities such as depression, poor sleep quality, impaired executive

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function, accelerated cognitive decline, and physiological disturbances such as poor cardiovascular function and impaired immunity. Depression rates are also higher among older people in isolation and more so in males and those with medical morbidities. The quality of living of older adults is also reduced following social isolation. A cohort study of 800 senior citizens in Chicago reported an increased risk of Alzheimer disease among adults in isolation. In contrast, a study of over 1,000 subjects in Stockholm reported social isolation to be a protective factor for dementia. A study including more than 5,000 men and women aged > 50 years found that loneliness was associated with an increased risk of cardiovascular disease (odds ratio = 1.27; 95% confidence interval, 1.01–1.57). Plagg et al. suggested that decisions regarding the prolonged social isolation of older people should be made after considering short-term advantages and short- and long-term disadvantages. The disadvantages highlighted in this review include vascular and neurological diseases, premature mortality, cognitive impairment, risk of Alzheimer disease, emotional distress, anxiety, and acceleration of existing conditions.

MARGINALIZATION OF OLDER ADULTS IN THE COVID–19 PANDEMIC

Some reports have indicated the marginalization of the health of older adults during the current COVID-19 pandemic, especially in countries with mitigation strategies. This is probably an attempt to bring about herd immunity. A crisis management document produced in Turin by the Piedmont authorities during the peak of the COVID-19 epidemic in Italy proposed to exclude patients aged > 80 years and older people with comorbidities as determined by the Charlson Comorbidity Index from treatment. Following the rapid increase in cases in Spain, instances have been reported wherein staff departed from care homes, leaving the occupants to their fates. Anomalous reporting of COVID-19-related deaths in care homes has been a major concern as it underestimates the threat of the current pandemic on older adults in those countries. While thousands of deaths in care home facilities in the UK may not have been counted, similar observations have been made in Italy. Furthermore, the global approach for COVID-19 screening is not uniform. While countries such as South Korea launched extensive searches for infected individuals, other countries limited testing to symptomatic individuals. Restricted testing fails to estimate the extent of the infection and in turn facilitates the spread of the disease in the community. Many countries have realized the importance of testing critical masses such as health care workers and older adults. A report from Scotland indicated that contact tracing in care homes was limited to those with COVID-19-positive patients, with only sporadic testing in care facilities without confirmed patients.

Besides comorbidities, frailty has become a decisive factor in selecting older people for specialized care during the COVID-19 pandemic. The National Institute for Care and Excellence (NICE) in the UK proposed using the Clinical Frailty Scale (CFS) as a guide in providing specialized care for this age group. The CFS, which is scored from 1 to 7, is a judgment-based tool used to assess the overall health of people aged 65 years and above. The NICE set an arbitrary cut-off point of 5 to determine the benefit of intensive care in older COVID-19 patients. Similar to frailty, patients with dementia may also encounter difficulties in the current pandemic. They are less likely to access health information and comply with safeguard and sanitary measures. Furthermore, patients with dementia may have limitations in telecommunications. According to the NICE, the CFS is also suitable for application in dementia patients.

The use of the strategy of building herd immunity over that of isolation increases the risk in older adults. Herd immunity requires more than 60% of the population to gain active immunity, which further enhances the risk of infection in older adults already at an increased risk. This strategy is considered to be more economically savvy as it allows for normal economic function. The COVID-19 crisis has showcased how older people are marginalized in countries with high disease burdens owing to a lack of resources and in countries with low to medium disease burden at the value of economic development.

MEASURES TO SAFEGUARD OLDER PEOPLE DURING A PANDEMIC

Prior preparedness is critical for successfully facing a pandemic. Preparedness requires attention to the needs of marginalized populations such as older adults. A comprehensive assessment of their immediate, short-term, and long-term needs will help in planning their health and other services. These can be broadly divided as follows.

1. Preventive measures: The special needs of older adults should be considered when implementing preventive measures. This population may require more supervision during isolation. While adequate ventilation may reduce the risk of cross-infection, the safety of the living environment should be ensured to prevent falls. Adequate facilities should be provided for frequent hand-washing.

2. Health: Proper control of comorbid conditions is para-
mount to preserve immunity, prevent unnecessary hospitalizations, and thereby reduce the infection risk. Facilities should be provided for home monitoring of temperature, blood pressure, and blood sugar. More supervision is required to identify early and atypical symptoms of infections, and the screening criteria should be flexible in older people. Age should not be the sole criterion for prioritizing healthcare, and more holistic approaches should be adopted. Early and aggressive screening and treatment of older patients may avoid the need for intensive care and life support measures.

(3) Nutrition: The maintenance of proper nutrition is important during pandemics. Older adults are prone to acute malnutrition, which can compromise immunity; thus, this population should be given priority in food supply programs. Furthermore, older adults should not be allowed to wait in long queues to collect their supplies.

(4) Physical activity: Although movement restrictions can hinder outdoor physical activities such as walking, older adults should be encouraged to engage in indoor physical activities, including simple yoga exercises, guided by TV sessions if necessary, or Tai chi, a popular form of slow rhythmic exercise among older people in some countries.

(5) Social activities: Older adults should be encouraged to keep communicating with family members and friends and should be provided free or discounted packages to do so. Electronic media should include regular programs to motivate and encourage older adults to face the pandemic.

(6) Religious and other activities: Pandemics provide an ideal opportunity to focus on one's inner self, namely the mind, soul, and nature. Meditation may reduce anxiety and allow individuals to maintain positivity and calm during a pandemic.

(7) Future directions: Natural disasters are unpredictable and unavoidable. Measures should be taken to prepare older adults to safely and effectively face such disasters. Older adults should be introduced to new communication methods and applications to stay connected with others during lockdowns. Attempts must be made to improve health literacy and especially increase computer and information literacy so that older adults can access and comply with health information.

CONCLUSIONS

Older adults are a group with special needs that require consideration during disaster planning and implementation of measures to curb the effects of pandemics. This population should not be marginalized or made to feel marginalized regarding health and other social requirements. Management protocols should allow the necessary flexibility in treating older people during pandemics because they have higher risks of acquiring the infection, more aggressive clinical courses, and worse outcomes.

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CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, RL, SL; Data curation, RL, SL; Investigation, RL, SL; Methodology, RL, SL; Project administration, RL, SL; Writing–original draft, RL, SL; Writing–review & editing, RL, SL.

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Special Issue on Long-Term Care for Older Adults in East Asian Countries

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East Asian countries are the most rapidly aging regions in the world, as the life expectancies of their populations are relatively high. As long as longevity increases without a meaningful increase in health-adjusted life expectancy, the proportion of life spent in poor health and the number of older people living with disease and functional impairment is bound to increase. This is a critical issue that threatens the sustainability of each society. Thus, it has been a high policy priority to develop long-term care systems separately from or integrated with the healthcare systems beyond medical care, including disease treatment and prevention. A long-term care system is defined as a system that enables older people experiencing significant declines in capacity to receive the care and support of others, consistent with their basic rights, fundamental freedoms, and human dignity. Several countries have separate long-term care systems. In Japan, the most aged country in the world, the long-term care insurance system was initiated and established in 2000. It has been 12 years since the Korean government implemented a long-term care system incorporated with the National Health Insurance in 2008. In Taiwan, a variety of long-term care services have been provided to the public by the tax-funded system. I am pleased to announce the release of a special issue in *Annals of Geriatric Medicine and Research* on the current status of long-term care services in East Asian countries. The purpose of this special issue is to provide an overview of long-term care services among neighboring countries with cultural similarities and similar population pyramids and to raise global interest in the role of long-term care systems. Representative geriatric and gerontologic experts from Korea, Japan, and Taiwan have contributed to describing the past, present, and future of long-term care systems. This special issue provides a glimpse into the legal considerations, institutional frameworks, financial resources, service content, limitations, and challenges of these systems. The circumstances faced by these countries may not be different from those of many other countries in the 21st century. This issue would be informative for those coping with ongoing problems threatening the health and welfare of older adults.

In the future, our journal will serve as a venue for sharing and introducing each other’s experiences not only from these three countries, but also from other Asian countries expecting uprise of population aging. I hope that this initiative will help promote the building of a special interest group in the long-term care field and help keep this issue on the table.

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CONFLICT OF INTEREST
The author claims no conflicts of interest.

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Long-Term Care System in Japan

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The long-term care insurance (LTCI) system was introduced in Japan in 2000 to address the demands of older persons with disabilities based on the concept of a user-oriented social insurance system with support for independence. Older people with a certification for LTCI service needs can utilize facility services, in-home services, and community-based services depending on their physical and cognitive impairments. After the implementation of the LTCI system, there was a rapid increase in persons certified for LTCI service needs, with a corresponding increase in the financial burden on the government. Therefore, the Japanese government started a disability prevention program in which older people were screened for frailty by the Kihon checklist in addition to a high-risk approach with appropriate prevention programs in each community. After unsatisfactory outcomes of the high-risk approach for disability prevention, the government changed the primary strategy to a community-based population strategy to build a community to seamlessly provide preventive, medical, and long-term care and welfare and housing services to all individuals. Further improvement of the community-based integrated care system is needed for healthy aging in a superaged society.

Key Words: Long-term care insurance, Disability, Integrated health care systems

INTRODUCTION

Origin of Welfare in Japan
Hidenin (悲田院 in Japanese) appears to be the first precursor of today’s welfare institutions for older people in Japan. Hidenin is a Buddhist temple built in the 6th century in Kyoto that aimed to care for the poor and children, as well as older people, who could not look after themselves and who could not be cared for by their community or family. It is one of the oldest welfare facilities for older people in the world. As in other Asian countries, Buddhism was an influential factor behind early welfare activities in Japan.

Before the Introduction of the LTCI System
The proportion of older people aged 65 years or over in Japan was less than 5.0% in 1950. After the first and second baby booms following World War II, Japan has experienced unprecedented aging of its population. Owing to the low birth rate and an increasing trend in the number of nuclear families in addition to population aging, in the late 20th century, many older people were admitted to and remained in hospitals because their families were unable or unwilling to look after them. The associated increase in medical expenditure for this so-called “social admission” became a serious issue for society. Although the Japanese government implemented a 10-year strategy for the health and welfare of older people (the “Gold Plan”) in 1989, the system encountered financial issues owing to its reliance on tax revenue and its increasing expenditure. This is a major reason for the implementation of the long-term care insurance (LTCI) system.

Changing Japanese Demographics
Japan is the most aged country in the world. People aged 65 years or older accounted for 28.4% of the total population in 2019 and
that proportion is expected to reach a plateau of approximately 40% in 2040–2050 (Fig. 1). In 2018, the average life expectancy was 81.25 years for men and 87.32 years for women. There are approximately 6 million people aged 85 years or older, and this number will reach 10 million in 2040 when the total population in Japan will be approximately 100 million (currently 120 million). In contrast, the population aged 40–64 years will start to decrease after 2021. Thus, we will live in a society where approximately 1 in 10 people will be 85 years or older. In addition, the numbers of older adults with disabilities and those living alone were 4.71 million in 2019 and 5.93 million, respectively, in 2015 and will increase dramatically, which is expected to result in a further financial burden on society.

IMPLEMENTATION OF THE LTCI SYSTEM IN JAPAN

As the country’s demographics change so does the disease structure. The demand for medical and welfare systems needs to be changed if the increasing number of older people require long-term care for longer periods along with the trend toward nuclear families and the aging of caregivers in families. The Japanese government launched the LTCI system in 2000 considering future demographics and national finances concerning population aging and related healthcare needs. The LTCI system in Japan was based on three basic concepts: support for independence, social insurance, and a user-oriented system. The aims of establishing the LTCI system were to shift the burden of family caregiving to social solidarity, shift cost-sharing with insurance premiums, and integrate long-term medical care and welfare services.

Outline of the LTCI System

The LTCI budget in Japan consists of premiums (50%) and taxes (50%). In this system, every citizen aged 40 years or over pays premiums, whereas the taxes are derived from the national government (25%), prefecture (12.5%), and municipality (12.5%) (Fig. 2). In Japan’s LTCI system, older adults who are certified for the LTCI service pay a 10% copayment for services; the remaining 90% is covered by the LTCI budget.

The municipal governments formulate an LTCI service plan that is updated every 3 years. Insurance premiums and copayments are revised according to this plan. As aging proceeds, long-term care expenses have increased from ¥3.6 trillion (US $32.7 billion) in 2000 when the LTCI system was introduced to ¥11.7 trillion (US $106.4 billion) in 2019. This amount is projected to exceed ¥15 trillion (US $136.4 billion) by 2025 (Fig. 3). The change affected the financial burden on individuals; premiums from ¥2,911 in 2000 to ¥5,514 in 2015 and the copayment rate was increased to 20% or 30% for dependent older adults with moderate income (¥2.8–3.4 million) and high income (¥3.4 million or more). Based on the estimated future Japanese demographic changes, both long-term care costs and premiums are expected to increase; therefore, these revisions aim to maintain the equality and promote the sustainability of the LTCI system. However, it is becoming increasingly difficult
services are provided when persons with category 1 require care or support for any reason and when persons with category 2 develop a specified disease and therefore require care or support.

Procedure for the Use of the LTCI

In Japan’s LTCI system, every person aged 65 years or older and middle-aged persons (aged 40–64 years) with specified diseases are eligible for benefits based strictly on physical and cognitive disability. We use category 1 for insured persons aged 65 years or older and category 2 for insured persons aged 40–64 years. LTCI services are provided to insured persons who are certified for support or care requirements according to their care needs and certification assessment. The insurance benefits include in-home services (e.g., home visits/day services and short-stay services/care) and services at facilities, including long-term care welfare facilities (also called special nursing homes), long-term care health facilities (also called geriatric health services facilities), and long-term care medical facilities (medical long-term care sanatoriums) without cash benefits or other direct benefits for family caregivers. Dependent older adults can select and use provided facility, in-home, or community-based services according to their care needs and care managers are actively involved in care plans and service arrangements (Fig. 4). Individuals who are not eligible for long-term or support care may utilize preventive care services.

Fig. 2. Japan’s long-term care insurance system in 2018. Adapted from the Japan Ministry of Internal Affairs and Communications.

Fig. 3. Trends of long-term care total cost and premiums. Adapted from the Japan Ministry of Internal Affairs and Communications.
COMMUNITY-BASED INTEGRATED CARE SYSTEM

In Japan, future demands for medical care will accelerate the transition to healthcare and nursing care services for dementia, frailty, sarcopenia, and other geriatric syndromes. In addition to acute medical care, the provision of healthcare and nursing care should be considered for the convalescent and chronic stages of conditions, which are provided in convalescent rehabilitation facilities and several types of nursing homes. In this environment, it is not sufficient to provide medical care that merely addresses each disease in a fragmented manner for older people. A broad perspective that considers the function of all organs, activities of daily living, frailty, and environmental factors is required. With this in mind, the Japanese government has proposed the establishment of a “Community-based Integrated Care System” by 2025, when baby boomers will be 75 years or older. The purpose of this system is to comprehensively ensure the provision of healthcare, nursing care, preventive care, housing, and livelihood support in each community.

Home medical care is the cornerstone of healthcare in a community-based integrated care system; the promotion of this field is undoubtedly important in promoting community-based integrated care. Various home-based services, such as home-visit services and nursing care, play a very important role in community-based integrated care along with home medical care. However, home medical care requires further development by considering future demand. Constructing a comprehensive home medical care system in Japan is a huge challenge and an indispensable milestone for aging.

Disability Prevention Program: High-Risk Strategy

In 2006, the government implemented measures aimed to identify frail or prefrail older adults, provide early preventive care programs for the prevention of functional decline, and delay dependence on long-term care. Because frail or prefrail older adults have a high risk of disability, it is important to screen this population early and provide interventions to prevent incident disability. The measure consists of identifying older people with disability risks by screening them using a validated questionnaire, Kihon checklist (Table 1).

Identified frail or prefrail older persons are subsequently referred to no-cost community prevention programs. This prevention program is effective in preventing the progression of frailty and further disability in community-dwelling older adults.

However, the utilization of the Kihon checklist was not sufficient to identify individuals at a high risk for disability; additionally, participation in the local intervention programs was quite low. Based on available evidence, the government estimated that approximately 5% of the total older population was at risk and therefore should be the target of preventive care. However, in 2014, by the 9th year of strategy implementation, only 0.8% of older adults had joined the community prevention program, which was unexpectedly low. This result was because of the low participation in the screening process for functional difficulties, which was only 34.8% of older people. We speculate that physical and environmental barriers and the lack of support to overcome these barriers, such as incentives and transportation, may explain the low participation. In addition, low awareness of disability prevention among general practitioners and the general public might have affected the outcome. The low participation in community prevention programs resulted in limited attributable effect unless researchers committed to the prevention program. The government recognized the difficulties in maintaining participants’ motivation and changed its policies for population-based preventive service provisions.

Community-based Population Strategies

With extensive efforts for disability prevention after the implemen-
tation of the LTCI system, public long-term disability prevention plans now focus on promoting social participation and preventing the isolation of older people as isolation is a strong risk factor for disability and mortality. In 2015, the government reformed the Long-term Care Insurance Act by changing its primary strategy for long-term disability prevention from a high-risk strategy to a community-based population strategy. The new strategy aims to build a community that can seamlessly provide preventive, medical, and long-term care and welfare and housing services to all individuals. Based on the population strategy for long-term disability prevention, central and local governments have promoted community activities, such as salons, to facilitate group participation and encourage social activities among older adults. These group activities lead to reduced disability incidence and further long-term care costs in older adults.\(^{13,14}\) Therefore, both the Japanese central and local governments have been promoting community group activities in each community. As a result, the number of groups increased from 43,154 in 2013 to 91,059 in 2017 (Fig. 5).\(^{15}\) Shifting from a high-risk to a population strategy involving multidisciplinary community collaborations has been successful in Japan. For community-based integrated care systems to succeed, collaborations be-

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**Table 1. Kihon checklist**

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<tbody>
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<td>Do you go out by bus or train by yourself?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Do you go shopping to buy daily necessities by yourself?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Do you manage your own deposits and savings at the bank?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>Do you sometimes visit your friends?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Do you turn to your family or friends for advice?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>Do you normally climb stairs without using a handrail or wall for support?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>Do you normally stand up from a chair without any aids?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>Do you normally walk continuously for 15 minutes?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>Have you experienced a fall in the past year?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Do you have a fear of falling while walking?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>Have you lost 2 kg or more in the past 6 months?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>If BMI is less than 18.5, this item is scored.</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>Do you have any difficulties eating tough foods compared to 6 months ago?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>Have you choked on your tea or soup recently?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>Do you often experience having a dry mouth?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>Do you go out at least once a week?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>17</td>
<td>Do you go out less frequently compared to last year?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>Do your family or your friends point out your memory loss?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>19</td>
<td>Do you make calls by looking up phone numbers?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>20</td>
<td>Do you find yourself not knowing today’s date?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>21</td>
<td>In the last 2 weeks, have you felt a lack of fulfillment in your daily life?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>22</td>
<td>In the last 2 weeks, have you felt a lack of joy when doing the things you used to enjoy?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>23</td>
<td>In the last 2 weeks, have you felt difficulty in doing what you could do easily before?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>In the last 2 weeks, have you felt helpless?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>25</td>
<td>In the last 2 weeks, have you felt tired without a reason?</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

BMI, body mass index.

Adapted from Arai H, Satake S. English translation of the Kihon Checklist. Geriatr Gerontol Int 2015;15(4):518-9, with the permission of John Wiley & Sons.\(^9\)

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![Fig. 5. Trends of number of community groups and participation rate. Adapted from the Japan Ministry of Internal Affairs and Communications.\(^{15}\)](www.e-agmr.org)
between community members and diverse service providers are mandatory. These collaborations allow community members to create or modify their community welfare services in line with their needs and local situations. Quantitative health equity assessments and visualization of results in an easily understandable manner are also useful for identifying and prioritizing problems and sharing community goals of local actions and policies with service providers and community members.

Experience and Future Perspective of Disability Prevention Strategies

In 2017, the World Health Organization published the Guidelines on Integrated Care for Older People (ICOPE) to provide guidance regarding preventing, slowing, or reversing the decline of intrinsic capabilities and maximizing functional abilities of older individuals. The guidelines make evidence-based recommendations for the comprehensive assessment of the health status of older people and the delivery of integrated healthcare. Most of the guideline recommendations involve secondary prevention measures, i.e., identifying frail older people and providing them with preventive care. However, as supported by Japan’s experience, secondary prevention measures or screening of frail individuals requires effective screening measures to identify frail individuals, effective interventions to mitigate possible risks, and effective means to deliver interventions to frail individuals. Integrated care for long-term disability prevention should include more community-based interventions. Healthcare professionals and organizations should be actively involved in building local organizational networks to provide such care.

Our approach for disability prevention in our LTCI system remains incomplete and requires further revision. We do not have enough geriatricians and physicians with geriatric practice and need to increase the number of physicians who are interested in frailty prevention for their daily practice. Most of the physicians still take a disease-oriented approach rather than a function-oriented approach for older adults. A gap between healthcare professionals and care workers is another significant issue that needs to be addressed. The Japanese government has introduced 15 questionnaires for the health checkup for older adults aged 75 years or over from April 2020 to identify frail older adults and provide appropriate disability prevention programs in collaboration with public health nurses and primary healthcare physicians. Our approach for disability prevention is still underway; however, we believe that we can increase the awareness of frailty and its prevention in physicians and the general public and change the approach for frailty prevention.

CONCLUSIONS

Japan is the most aged country worldwide, and the burden of long-term care is continuously increasing. To minimize the negative effect and maximize the positive effect of aging and to achieve healthy longevity, it is pivotal to increase the quality of a community-based integrated healthcare system and accumulate further evidence on disability prevention in Japan.

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CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, HA; Writing original draft, HA, MY; Writing review & editing, HA.

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INTRODUCTION

Fast-Aging Korea

Since the early 1960s with the rapid socioeconomic development and implementation of family planning, a remarkable demographic transition kicked off in Korea, with subsequent unprecedented growth in the aging population. As of April 2020, 15.9% of the Korean population is aged 65 years or older, a proportion that is expected to reach 37.0% by 2050, the second-highest proportion among the Organisation for Economic Cooperation and Development countries after Japan.

Traditional Welfare for Older Adults in Korea

“Respect for seniors” has been one of the core principles of Confucian philosophy that originated in the Chosun dynasty. This idea considered caring for parents to be a family duty; thus, institutionalized care was regarded as inappropriate until recent decades when long-term care facilities (LTCFs) became necessary. In 1885, a French Catholic missionary priest, Jean Marie Gustave Blanc, established a care home and cared for 40 people in Seoul, which was the first documented facility for older people in Korea.

Modernization Transformed Living Arrangements

With industrialization, urbanization, and overall economic development, the household structure generally shifts from an extended to a nuclear form. The rate of family support for older parents began to decrease from 18.8% in 1970 to 9.1% in 1995 and 5.3% in 2015, consistent with the modernization of the Korean society. Accordingly, home is no longer a common place of care for older adults and its role has been replaced by various care facilities.

Facilities for Independent Seniors

A senior center, a place where older adults build friendships and engage in hobbies, is one of the most typical and popular leisure and welfare facilities for Korean seniors. Senior centers originated from places for rest and leisure for neighborhood older adults in rural areas and have now expanded to cities. However, they do not receive sufficient government funds to operate programs specific to older adults.

In contrast, senior welfare centers are operated by local governments and offer a wide variety of leisure and social activities, as well as programs and services that promote health and prevent diseases at no to low costs and are usually located in urban areas. A total of 66,286 senior centers and 385 senior welfare centers were reported in 2018.
IMPLEMENTATION OF THE LTCI SYSTEM IN KOREA

The Japanese long-term care insurance (LTCI) system, which began in 2000, is the role model for the Korean LTCI. The “Promotion Board of the long-term care (LTC) system for the Elderly” was established in 2000, the same year in which Korea first became an “aging society”, with a proportion of older adults exceeding 7% of the whole population.\(^\text{[1]}\) The law regarding LTCI for older adults was passed in the National Assembly’s plenary session in 2007, and the program began in July 2008.\(^\text{[2]}\) According to the Act on LTCI for the Aged,\(^\text{[3]}\) LTCI aims to provide assistance in physical or housekeeping activities for older people and eventually improve citizens’ quality of life.

THE LTCI SYSTEM

Older adults aged 65 years or older or citizens younger than 65 years but with chronic illnesses or disabilities are eligible for LTCI. Among these, people with difficulties in activities of daily living for at least 6 months are eligible for LTCI. LTCI benefits include both in-kind and cash benefits. In-kind benefits include home care and institutional care services. The seven types of home care services are (1) day/night care center services, (2) home-visit care services by LTC assistants, (3) home-visit services to promote cognition activities, (4) home-visit nursing services by nurses, dental hygienists, or nursing assistants, (5) home-visit bathing services, (6) short-term institutionalized care, and (7) provision of welfare devices.\(^\text{[4]}\)

The LTCI program, unlike the National Health Insurance (NHI) program, operates the eligibility selection process. The LTCI benefits are granted only following application and approval.\(^\text{[5]}\) After application documents are received, LTCI agents visit the applicants and assess their eligibility using a 90-item LTCI checklist categorized into 11 sections, namely activities of daily living (ADL), instrumental ADL (IADL), cognition level, behavioral changes, need for nursing care, need for rehabilitation, need for welfare medical devices, state of care, environmental evaluation, visual/hearing ability, and diseases or symptoms. Currently, only 52 of the 90 items are evaluated and used to calculate final scores. Initially, LTCI recipients were classified into three categories, with those in level 1 having the most severe disabilities; with the addition of a new category, “special level of dementia” and splitting level 3 into two in July 2014 and the recent addition of a “cognition supporting level” in January 2018, there are currently six levels (Table 1).\(^\text{[6,17]}\) To be admitted to nursing homes, the recipients should be levels 1 or 2; however, with the approval of the LTCI committee, people who are in levels 3–5 can also be admitted. The final decision is made by the eligibility committee managed under each local LTCI corporation. This committee comprises 15 people, including at least one physician or traditional doctor.\(^\text{[3,18]}\) The monthly expenses for staying in nursing homes are approximately ₩ 900,000 ~1,300,000 (US$ 800 -1,100) and LTCI covers 80%–100% according to the beneficiaries’ economic status, while 85%–100% of expenses for in-home services are covered. Fig. 1 depicts the process of determining the care level from application to final results.

By regulation, contracted physicians must visit the facilities twice monthly to clinically examine the residents, order nursing treatments, or provide hospital referrals. However, these physicians are not allowed to provide any direct medical services to the residents except for prescriptions, as these places are not designated as medical care facilities by law.\(^\text{[9]}\) The quality of nursing homes is assessed every 3 years by the NHI corporation, with the results announced on the LTCI website.

Based on a recent survey, 90.9% of the respondents expressed satisfaction with the LTCI system; however, the number of LTCI recipients has increased approximately three-fold, from 214,000 in 2008 to 671,000 in 2019, and long-term financial shortage and financial problems are the main issues in the Korean LTC system.\(^\text{[20]}\)

The Ministry of Health and Welfare (MOHW) announced a plan to minimize financial loss by (1) expanding spot surveys to identify unjustified financial claims, (2) reducing pay for day-care centers, (3) strictly selecting recipients who benefit financially, and (4) tightening the qualification for the opening of LTC facilities.\(^\text{[21]}\)

LTC HOSPITALS

LTC hospitals (LTCHs) provide another distinct form of LTC in Korea. They deliver various medical services, including subacute to LTC, palliative care, and rehabilitation services. As of June 2020, there were 1,481 LTCHs in Korea. LTCHs have become widespread across the country because all citizens are eligible for coverage under the NHI Program, in which out-of-pocket payment is 10%–20% of the total medical fees.\(^\text{[22-24]}\) The major priorities of LTCHs center around medical care and functional rehabilitation so that a patient may return home.\(^\text{[25]}\) Table 2 demonstrates the differences between LTCHs and nursing homes. However, some studies have found few differences in functions between LTCHs and nursing homes.\(^\text{[26]}\) The Health Insurance Review & Assessment Service (HIRA) instituted a unique medical insurance fee system for LTCHs in 2008 by requiring LTCHs to classify inpatients into one of 15 Resource Utilization Groups (RUGs) in seven categories based on assessment data from an Inpatients’ Data Set (IDS). An IDS is a tool used for the standardized assessment of

www.e-agmr.org
inpatients in LTCHs and is similar to the Minimum Data Set (MDS) for nursing home residents in the United States. It comprises 11 sections (A to K): general characteristics (A), mental state (B), cognition and behavioral problems (C), functional status (D), incontinence (E), diseases (F), general health problems (G), oral and nutritional status (H), skin problems (I), medications (J), and special management and rehabilitation (K).\(^27,28\) In this new payment system, LTCHs are reimbursed according to their patients’ functional status and requirements for medical services. LTCHs must electronically submit an IDS with various indices to the HIRA every month.\(^29\) In November 2019, the seven categories were simplified to five.

Since 2008, the HIRA has evaluated LTCH quality every one or two years. In 2013, a new accreditation system that covers 3 domains was introduced for LTCHs: basic values, patient management, and supporting structure. These domains are subdivided into 11 chapters—safety, quality improvement, medical delivery system and evaluation, medical examination, drug management, patient rights, hospital management, manpower management, infection control, safe facilities and environment, and medical record management.\(^30\) This is an obligatory evaluation performed by the Korea Institute for Healthcare Accreditation; LTCHs must pass this accreditation survey every 4 years to avoid a monetary penalty.

### PLANNING FOR THE NEW COMMUNITY CARE SYSTEM

In November 2018, the MOHW announced a plan to launch so-

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**Table 1.** Long-term care eligibility levels

<table>
<thead>
<tr>
<th>Level</th>
<th>Mental and physical status</th>
<th>Long-term care approval score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Requires help in all aspects of daily life</td>
<td>≥ 95</td>
</tr>
<tr>
<td>2</td>
<td>Requires help in most parts of daily life</td>
<td>≥ 75 and &lt; 95</td>
</tr>
<tr>
<td>3</td>
<td>Requires help in part of daily life</td>
<td>≥ 60 and &lt; 75</td>
</tr>
<tr>
<td>4</td>
<td>Requires some help for daily living because of functional disability</td>
<td>≥ 51 and &lt; 60</td>
</tr>
<tr>
<td>5 (Special level of dementia)</td>
<td>Dementia with limited functional decline</td>
<td>≥ 45 and &lt; 51, dementia</td>
</tr>
<tr>
<td>6 (Cognition-supporting level)</td>
<td>Dementia with intact physical function</td>
<td>&lt; 45, dementia</td>
</tr>
</tbody>
</table>

---

**Fig. 1.** Process of determining the care level from application to final results. LTCI, long-term care insurance; ADL, activities of daily living; IADL, instrumental ADL.
Table 2. Comparisons of two types of long-term care facilities

<table>
<thead>
<tr>
<th>Facility type</th>
<th>Nursing home</th>
<th>Long-term care hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related law</td>
<td>Long-term care insurance law</td>
<td>Medical law</td>
</tr>
<tr>
<td>National insurance</td>
<td>Long-term care insurance</td>
<td>National health insurance</td>
</tr>
<tr>
<td>Services mainly provided</td>
<td>Assistance with daily living</td>
<td>Treatment and prevention of geriatric diseases and geriatric syndromes</td>
</tr>
<tr>
<td>Indication for admission</td>
<td>Long-term care insurance level 1 or 2</td>
<td>Physician decision</td>
</tr>
<tr>
<td>Manpower required</td>
<td>Social worker (1 per 100 residents), nurses or nursing assistants (1/25), physiotherapist or occupational therapist (1 per 100 residents)</td>
<td>Medical or traditional doctor (1 per 40 residents), nurses (1 per 6 residents); 2/3 of nurses can be replaced by nursing assistants, physiotherapist (1 per 100 residents), social workers (1 per hospital)</td>
</tr>
</tbody>
</table>

The current and future Korean long-term care (LTC) system is overviewed in Fig. 2. The MOHW has proposed various models such as comprehensive patient assessment and care planning in LTCHs, in-home services for discharged patients, home medical care, primary care for chronic diseases, home hospice care, and support for care houses and families. However, this remains a challenge as institutionalized care is already too familiar to leave for Korean citizens and the implementation of home medical care requires obtaining physician agreement and legal evidence.

The current and future Korean LTC system is overviewed in Fig. 2.
CONCLUSION

Korea is one of the fastest-aging countries worldwide. The LTC of older adults imposes social burdens on their families and the government. While nursing homes and LTCHs are currently the common solutions for older adults requiring LTC, the Korean government is planning to implement integrated community care services by 2025.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

The researcher claims no conflicts of interest.

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34. Lee JH. Little evidence of home visiting medicine...there is long way to go in community care [Internet]. Seoul, Korea: Doctor’s News; 2019 [cited 2020 Jun 7]. Available from: http://www.doctorsnews.co.kr/news/articleView.html?idxno=127178&sc_word=&sc_word2=
INTRODUCTION

Background in Taiwan

Taiwan, like many other countries, is under pressure to develop effective policies in response to population aging. Trends of declining fertility rates and expanding lifespan together have contributed to the growth of the “gray population”. The proportion of the population aged 65 years and over has doubled from 7% in 1993 to 14% in 2018. Life expectancy has increased over the last 50 years to 77.5 and 84.0 years for men and women, respectively.

Although nearly 55.5% of Taiwan's older people live with their adult children, the increasing proportion of women in the labor market and the declining ratio of those needing care to potential caregivers have raised questions regarding families' ability to care for the disabled older population.

Official projections show that the number of people in need of long-term care will increase from 577,457 in 2017 to 771,431 in 2026. To respond to the rapidly growing need for care in these population, Taiwan is seeking a clear direction in which to adjust the development of long-term care.

Small-scale long-term care plans run by local governments first emerged in the 1990s. The central government initiated a major nationwide plan for long-term care in 2007, began planning for universal long-term care insurance in 2009, and finalized the policy plan in 2015. However, the 2016 presidential election resulted in a shift in political power, and the newly elected government abandoned the proposal for a universal long-term care system and instead launched a tax-funded universal long-term care system. The new plan has been successful in terms of expanding service coverage. The number of people receiving long-term care services increased from 9,148 in 2008 to 258,351 in 2019, accounting for 41.47% of those in need.

This document uses Taiwan as an example to discuss strategies for developing long-term care. Taiwan has successfully expanded its long-term care coverage within a short-time period and its experiences may serve as a good example for other countries facing rapid population aging and under pressure to expand such services.

This document comprises three parts. The first briefly reviews the development of long-term care policies since the 1990s and introduces several policy reforms for long-term care services. The second part introduces strategies for expanding long-term care, especially focusing on Long-Term Care 2.0 (LTC 2.0). The final
part, the discussion, includes policy suggestions, implications for providers, and influences on users and families.

**EARLY DEVELOPMENT OF TAIWAN’S LONG-TERM CARE POLICY**

While population aging has been an important policy issue since the early 1990s, the focus of political debates on aging policy was primarily income maintenance. Long-term care was ignored. There are two reasons for this. First, under Taiwan’s divided pension system, only those who worked in special occupational groups could receive adequate pensions after retirement. Most of the population faced the risk of old-age poverty. Therefore, the government was under pressure to enhance the income support system for older people. Second, it was reasonable for the government to prioritize cash benefits over care services under the pressures of rapid population aging and political competition, as this could increase the number of beneficiaries in a short time. Once the government had secured financial resources, the social administration system could deliver cash benefits to eligible individuals without delay. In contrast, it would have been more challenging to quickly expand the care services system as that would have required not only financial resources but also extra manpower and service providers. The latter cannot easily be quickly implemented. In the 1990s in Taiwan, the issue of establishing a comprehensive old age income maintenance system was at the core of policy debates in all major political elections.

However, the issue of developing a comprehensive long-term care system received less attention in the political arena before the 2010s. The government had implemented several programs regarding care for older people between the 1990s and early 2000s. The Kuomintang (KMT) government put two programs into practice in 1998, namely, the Improving Care Services for Older People Program and the Three-Year Plan on Long-term Care for Older People. This was the first time that the Taiwanese government addressed long-term care as a policy issue and developed related programs. However, these programs were limited. The government lacked funds for these schemes. Related ministries were required to implement services with existing financial resources. These schemes were considered insignificant, and no academic studies or governmental reports have evaluated their performance. However, they demonstrated that the government had noticed the importance of developing a care system for older people.

In 2000, the Democratic Progress Party (DPP) replaced the KMT as the ruling party. It was the first time in Taiwanese history. The DPP government implemented two phases of the 3-year Care Service and Care Industry Development Plan, from 2002 to 2007, that focused on the development of community and home care services. Although those programs were extended to cover those not categorized as low income in 2002, these schemes benefited only a small portion of the population. For instance, when the first stage of the Plan was completed in 2004, only 12,000 people received domiciliary services.

In 2007, a 10-Year Long-Term Care Project, LTC 1.0, was implemented. The LTC 1.0 plan required that local governments set up care management systems and develop in-kind services such as various home care and community care services. They were also expected to provide subsidies for these services.

The 10-year plan is important as it orientated the directions and strategies for Taiwan’s long-term care development. However, LTC 1.0 faced three main challenges. First, from the administrative aspect, funding for the plan remained insufficient. According to central government regulations, local governments, had to share fixed copayment ratios for services and thus they, especially poorer local governments, lacked funds to support services. Second, from the service provision aspect, institutional care was not included and only non-profit organizations (NPOs) could provide services. Moreover, NPOs had to wait a long time for benefits, usually over half a year. In addition, people were unfamiliar with the application procedure and regulations. Even when they decided to apply for services, the process usually took over a month, and support for families was insufficient.

Because funding was inadequate, in addition to issues with service supply and application procedures, the KMT sought to build a single-payer universal social insurance system to solve those problems. The newly elected president, Ma Ying-jeou, pledged, during his campaign, to introduce long-term care insurance, and the Task Force for Long-term Care Insurance Planning was formed in July 2009. The name of the task force demonstrated the government’s policy direction to establish long-term care insurance. It soon finalized its planning and published the Report on Long-term Care Insurance Planning in December 2009 as a policy guideline that proposed adopting compulsory social insurance to fund long-term care services.

The KMT’s introduction of the concept of long-term care insurance was driven mainly by two forces. The first was its political competition with the DPP. Its political appeal was that a social insurance-style long-term care system is better than a tax-funded one in terms of financial sustainability. The second was the pressure for Taiwan to catch up with its neighboring countries as Japan and South Korea implementing long-term care insurance in 2000 and 2008, respectively. Many Taiwanese politicians saw that as a progressive system to follow. A government document stated that “our neighbor countries Japan and Korea implemented long-term care
insurance when the proportions of people aged 65 or over exceeded 15.7% and 9.9%, respectively. Therefore, based on their experience, we should soon establish long-term care insurance in response to trends of population aging.

The KMT’s planning for long-term care continued after the report was published in 2009. The timetable set by the report put the proposed long-term care insurance into force by 2016. The Executive Yuan passed a long-term care insurance bill in July 2015. However, it did not take further action for immediate enactment and the KMT lost the presidential election in January 2016. Debate during the long-term care insurance design process focused on four issues. First, they looked to Germany for guidance on designing population coverage for the total population, meanwhile, Japan’s model including only those over 40 years of age. Second, in terms of benefits, the committee members had to decide whether both in-kind and in-cash services would be provided, as in Germany, or only in-kind services would be provided, as is the case in Japan. Moreover, regarding the administration system, it was unknown whether the insurance could solve issues such as worker shortages and whether the service supply was sufficient. Finally, if and when the single-payer social insurance institution was established, policymakers would have to determine the role and function of local governments. The KMT spent 8 years designing and working to overcome these challenges. During this period, the Long-Term Care Service Act was passed in June 2015, which provided a legislative base for constructing the LTC service system. In 2016, however, the KMT lost power, and the plan for long-term care insurance was abandoned.

The result of the 2016 presidential election again changed the history of Taiwan’s long-term care. The DPP took over governing and had a different approach toward long-term care services. The new president, Tsai Ing-Wen, had published a policy platform on long-term care during her campaign. The platform pledged to implement a New 10-year Plan for Long-Term Care, or the 2.0 Plan of 10-year Plan for Long-Term Care, now known as Long-Term Care 2.0 (LTC 2.0). The DPP government criticized the KMT’s plan for compulsory universal long-term care insurance. Instead, LTC 2.0 was to be financed by taxes. The DPP argued that it would be unfair and unjust to collect social insurance contributions for long-term care service, as the service system was not yet in place. The government instead would fund the long-term care system by increasing estate, gift, and tobacco taxes.

The important consideration is the shift in Taiwan’s politics. Between 2000 and 2016, Taiwan’s two major political parties traded leadership, which meant several sudden changes in how the central government envisioned long-term care policy. For example, the DPP implemented the 10-year Plan for Long-Term Care in 2007. When the KMT replaced the DPP in 2008, they planned universal long-term care insurance starting in 2009. Additionally, the most recent change, in 2016, which saw a complete handover in both presidential and legislative control, led to a major shift in long-term care policy, moving from a policy based on social insurance to one based on welfare. It is important to note that the long-term care system in Taiwan is still in the early stages of expansion. As Fig. 1 indicates, it was not until 2016 that the government significantly increased its investment of financial resources into long-term care.

**LTC 2.0 AND EXPANSION OF SERVICES**

In 2017, the DPP implemented the LTC 2.0, which included the following aims: first, to construct a high-quality, fair-priced, and universal LTC care system; second, to put aging-in-place values into practice and provide support for families via multiple and continuous home- and community-based institutional types of care; third, to extend care to include preventive care; and fourth, to integrate multipurpose supportive community services and link dis-
charge preparation services to home-based medical care. Moreover, the eligible population included not only older people aged 65 years and over with functional limitations in activities of daily living (ADL) but was also expanded to include people with dementia aged 50 years and over and older people aged 65 years and over with frailty.\textsuperscript{11}

LTC 2.0 covers 17 types of services. The following items were added: dementia care, aboriginal community-integrated services, small-size multiple-function centers (linking adult daycare, respite care, and others), multiple support services for family caregiver centers, a community-based integration care system (ABC system), community health preventive care, preventive and delaying disability programs, links to discharge plans from hospitals, and links to home-based medical care. The delivery flow for accessing long-term care in the LTC 2.0 system begins with a long-term care management center, which is a department of local governments. Users can access long-term care management center services by themselves or may be transferred to the center from hospitals or clinics. Then care managers at the management centers assess care needs; formulate a care plan; collaborate with the ABC network to communicate and negotiate with users, families, and providers; and implement the care plan. Eligibility determination uses a long-term care case-mix system checklist categorized into 11 parts, including ADL, instrumental ADL (IADL), cognition level, behavioral changes, rehabilitation, home environment, and caregiver stress. Initially, recipients were classified into eight categories, with those in level 8 having the most severe disabilities.\textsuperscript{11,12}

The community-integrated care system, a three-layered service network termed the ABC network, is the core innovation in the LTC 2.0 reform. Users requiring long-term care, regardless of whether they stay in the hospital or live in the community, can connect with the local government’s care manager, whose role is to approve the disability level and benefit amounts. Then, service provider A’s function is to develop a care plan and connect the service providers. The missions of B and C, respectively, are to provide long-term care services and promote community care stations, as well as to help people find opportunities to participate in social activities and promote health and temporary care (Fig. 2).

The payment system was also modified in 2018, during the LTC 2.0 reform. Previously, fees for home-based care were based on service hours. In the new system, payment is categorized into four parts: personal (home and day care services, etc.) and professional care (home nursing, rehabilitation, nutrition service, etc.; NT $334–$1,206/month), transportation (NT $56–$80/month), assistive devices and home modifications (NT $1,333/month), and respite care for family caregivers (NT $1,078–$1,617/month). According to the disability level, each case has an upper limit and each type of service delivery is paid by fee-for-service. Users and family choose what they prefer to use from a menu of professional and personal care services. Co-payments are waived for low-income users. Users are responsible for charges for service usage exceeding the upper limit.\textsuperscript{13}

The LTC 2.0 reform has seven successes. First, population coverage has increased. Compared to 29% in 2018, the growth rate of new applications in 2019 was almost 52%. This rapid expansion of service is a remarkable achievement of Taiwan’s long-term care system. The reduction of co-payments was the key factor because service users had to share 30% of fees as co-payments for long-term care before LTC 2.0 was implemented. The copayment rate was reduced to 16% under LTC 2.0. This reduction generated motivation for eligible users to take up the service.

Second, the contract system for service providers has been radi-

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**Fig. 2.** The service delivery system design (source: the Ministry of Health and Welfare, https://1966.gov.tw/LTC/cp-3636-42415-201.html)
cally changed. In the early stage of LTC 2.0, long-term care organizations were required to go through a complex and long process to compete for a limited number of positions as contracted service organizations. Moreover, only NPOs could join the service system. The Long-Term Care Service Act enacted in 2017 allows all long-term care organizations, both for- and non-profit, to join the system. This resulted in a boom in the number of service organizations immediately after its implementation, which has helped increase the availability of long-term care services. Fig. 3 shows the increased rates for each of the services. Compared to the previous outcome, the LTC 2.0 policy reform seeks to provide incentives to grow or expand the long-term care industry.

Third, the for service fees has been modified. The new and generous payment system not only encourages for-profit organizations to join but also attracts “local” manpower. For instance, home care services were previously paid according to the hours of service provided. This payment method put a limit on care workers’ salaries, as there was a maximum number of work hours for a job. The new fee-for-service system permits care workers now to increase their salaries by improving their service efficiency. The more service they provide, the higher the pay. This new payment method has resulted in substantial increases in care workers’ salaries. Therefore, more manpower has participated in the service system, which underpins the expansion of the LTC 2.0 service system.

Fourth, additional incentives are provided for long-term care organizations to expand to rural areas with insufficient service. These include more subsidies from the government and higher payment for services. For instance, governmental financial subsidies allow long-term care institutions to buy more vehicles to provide transportation services in rural areas. Additionally, service providers can receive up to 20% extra payment for each service they provide in rural areas.

Fifth, LTC 2.0 not only focuses on the needs of care recipients but also considers the care burdens of family caregivers. Every city already has family caregiver support centers and each local service center is supposed to provide all of the following 8 types of services: case management, individual and group home care skills training, respite service, psychological counseling, support groups, relaxation and stress-management courses or activities, and telephone support.

Sixth, the number of dementia service centers has increased. These centers help clients receive rapid diagnoses and access necessary resources. Seventh, the reform is allowing employers of migrant care workers to apply for respite and professional care services. Fig. 4 clearly shows the significance in terms of increases in service usage since 2018.

The final success is the expansion of community health preventive and delaying disability programs. The government cites Japan as a reference for its long-term care system. From late August to early September, 2016, a team comprising Taiwan’s Deputy Minister of the Department of Health and Welfare and several high-level officers visited Japan to learn about its community care system. The report submitted by the visiting group suggested that Japan’s “comprehensive community social care model” should be a model for Taiwan’s long-term care development. This visitation report and frequent communication visits between Taiwan’s and Japan’s NPOs have not only become the ideal for the ABC framework but have also led to the expansion of Taiwan’s long-term care system into preventive healthcare. Community care stations and health centers provide health training programs as well as hope for older

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**Fig. 3.** Outcomes of Long-Term Care 2.0: service supply.
people by helping users form exercise habits and perform health self-management to postpone or avoid disability.

Despite its many successes, LTC 2.0 still has room for improvement. From the administrative viewpoint, the long-term care service was managed by two separate departments before 2017. To address this problem, the central government established a new department, the Long-term Care Bureau. However, at the local government level, long-term care services are managed by two separate departments: the social department controls the majority of service supply, whereas care management centers belong to the health department. This results in unbalanced services development, an issue that is prevalent in different counties.

On the supply side, LTC 2.0 payment is only for community/home services. Thus, these generous payments have attracted both providers and manpower for the community and home care sectors. However, neither resources nor payment is provided for institutional care, which has resulted in a significant disadvantage for institutional care. Therefore, the number of care institutions has not grown with the rise in the aging population. Fortunately, in September of 2019, the central government announced that it would provide subsidies for users of institutional care. However, it will be some time before we see any effects in terms of institutional growth.

One characteristic of LTC 2.0 was an attempt to establish a community-integrated service network with the ABC network functioning as a team and community care station, or C, comprising the largest in number. According to the original design, each township set an A, with a role requiring both day and home care services. Each junior school district set a B, and every three villages set at least a C. The ideal numbers of ABCs are shown in Fig. 5. Notwithstanding, service providers prefer to take the A role, meaning they can take control of care packages. Some service providers have persuaded the government to waive the requirements of A. The new payment system allows no incentives for service providers to build community integration networks. This has resulted in continued insufficiently effective basic community care station numbers and functions; moreover, the cooperative relationships between service providers also require improvement. The original plan intended that the ABC network work like a pyramid, with C (community care stations) comprising the largest number and serving as a foundation for the network as a whole. But in reality, what we have seen is shaped more like a diamond, with the majority being B, service providers and A, coordinators, with community care stations, C, still lacking (Fig. 5).

From the user and family viewpoints, the policy so fervently encourages people to use LTC 2.0 that the labor department has continually loosened regulations regarding hiring family migrant care workers. For example, people age 85 years or older with only one item of disability can now hire a live-in migrant care worker. Because family migrant care workers are cheaper and more flexible than formal services, the number of family migrant care workers continues to increase. The main care model in Taiwan includes

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**Fig. 4.** Outcomes of Long-Term Care 2.0: actual service usage.

**Fig. 5.** The shape of the ABC network (A indicates coordinators; B, service providers; C, community care stations).
four choices: institutional care (11%), family migrant care workers (26%), care responsibility provided only by family members (40%), or using LTC 2.0 services (23%).

**DISCUSSION AND CONCLUSION**

It has been almost two decades since a World Health Organization-sponsored study encouraged governments to provide universal long-term care services rather than small-scale, selective services. One of its most important recommendations was to view long-term care as a “normal life” risk. The risk is that many families may become impoverished by paying for long-term care services. Therefore, governments should, at least partly, shoulder the responsibility for developing public long-term care services. Taiwan’s experience has shown that, with effective strategies, the government can rapidly expand long-term care.

However, Taiwan’s experience also demonstrates the substantial impacts of political factors on the development of long-term care. A universal long-term care insurance plan based on years of study was abandoned overnight because of a shift in political power. The DPP government has stated repeatedly that the current tax-funded system is sustainable. However, scholars remain suspicious of this claim. Campaigns for universal long-term care insurance have never faded. With coverage expanding rapidly, the government is facing growing pressure to secure adequate funding for long-term care. The next important policy task is to build a consensus regarding a sustainable financial plan.

At the administrative level, the Ministry of Health and Welfare has established the LTC Division to integrate resources in the health and social sectors. Further cooperation with the labor division is needed for manpower training and providing information to employers of migrant care workers regarding the use of long-term care services. In addition, as local governments are responsible for supervising long-term care services, the central government must provide them more resources and professional support to improve the quality of services.

In terms of service, institutional care remains a missing piece for long-term care in Taiwan. The Taiwanese government’s policy orientation for long-term care is to encourage aging in place. Under such a policy direction, most resources have been allocated to in-home care and community care. The government is reluctant to invest resources in institutional care. However, institutional care is an important part of long-term care and should be included in the long-term care system so that people in need can get better service.

The implication in Taiwan’s case is that establishing an accessible, affordable, universal long-term care service system with good-quality, upstream prevention to delay disability and provide support services for family caregivers is a step in the right direction. These strategies allow families more time and energy to care for their older family members and fulfill the policy goal of “aging in place”.

**ACKNOWLEDGMENTS**

**CONFLICT OF INTEREST**

The researchers claim no conflicts of interest.

**AUTHOR CONTRIBUTIONS**

Conceptualization, CC, TF; Writing-original draft, CC; Writing-review & editing, TF.

**REFERENCES**


Trajectories of Body Mass Index and Their Associations with Mortality among Older Adults in Korea: Analysis of the Korean Longitudinal Study of Aging

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Background: Weight change is a known risk factor for mortality. Previous Korean studies only considered mortality consequences of weight change between two time points over relatively short periods. This study investigated whether body mass index (BMI) trajectory patterns were associated with all-cause mortality based on continuous BMI observations during a 10-year follow-up period among Korean older adults. 

Method: This study analyzed data from the 2006–2016 Korean Longitudinal Study of Aging database. The participants included in this study were 3,478 people aged 65 years or older who have measured BMI more than once. A trajectory model was developed to classify different homogeneous trajectory subgroups according to BMI, and Cox proportional hazards models were used to investigate the association of BMI trajectory with all-cause mortality.

Result: We identified four trajectory groups: obese (OG); overweight (OWG); high normal weight (HNWG); and low normal weight (LNWG). The LNWG and HNWG experienced continuous weight loss during the study period. Trajectories with higher BMI were associated with lower mortality. The adjusted hazard ratios (95% confidence intervals) for all-cause mortality in the LNWG, HNWG, and OWG were 2.40 (1.69–3.40), 1.75 (1.26–2.45), and 1.38 (0.99–1.96), respectively, compared with those in the OG.

Conclusion: We found that the lower the BMI of the weight trajectory group, the higher the mortality over 10 years in Korean older adults. This result suggested that baseline obesity status and degree of weight loss during follow-up contributed to mortality in later life.

Key Words: Body mass index, Body-weight trajectory, Mortality, Aged, Korean

INTRODUCTION

Weight change is an important risk factor for mortality. The association of weight change with mortality is frequently shown as a reverse J-shaped curve. Weight loss in overweight or obese people and weight gain in underweight people have beneficial effects on health. However, studies have reported conflicting results depending on ethnicity and age groups. While some studies reported that weight loss and weight gain increased mortality, others found no associations.

Instead of using baseline body mass index (BMI) as in previous studies, some studies used body weight change as a predictor of mortality in Korea. Thus, weight status changes throughout a lifetime should be considered. However, most studies have focused only on the mortality consequences of weight (or BMI) changes between two time points during the study period. Because there is a limit to defining an individual's subgroup based on short-term weight or BMI changes, this approach obscures heterogeneity in weight changes that occur after the second time point, as well as weight fluctuations. In particular, the dynamic measures of BMI may better predict mortality in older adults.

Several studies have performed repeated observations of weight...
at regular intervals over a period longer than 10 years to evaluate
the associations between weight changes and mortality in older
adults. However, the study using data from the Health and Retire-
ment Study by Zheng et al. \(^{11}\) included a relatively young popula-

tion with mostly white ethnicity. Many non-western societies have
varying distributions of body weight from the United States; \(^{33}\)
thus, studies of older Asian adults are needed.

Therefore, this study followed up BMI changes over 10 years
among community-dwelling Korean adults aged 65 years or older
and investigated the effects of these changes on mortality using
data from the Korean Longitudinal Study of Aging (KLoSA). A
trajectory model was developed to classify different subgroups ac-
cording to BMI.

**MATERIALS AND METHODS**

**Data and Study Sample**

The KLoSA is a nationwide longitudinal panel survey of 10,254
randomly sampled Koreans aged 45 years or older (born before
1961), excluding residents of Jeju Island. Since 2006, a biennial ba-
sic survey has been conducted, with a total of six follow-up surveys
completed by the time of the present study. The sample retention
rate of the existing panel showed a stable trend of 78% as of the 6th
follow-up survey, with a total of 6,618 valid samples available for
analysis.

The questionnaire used in this study was conducted using com-
puter-assisted personal interviewing, a computer-based interper-
sonal interview method. The survey comprised a wide range of
questions, including those on household background, human attrib-
utes, family, health, employment, income and consumption, as-
sets, subjective expectations, and quality of life. The KLoSA also
includes data on deaths. Since 2008, deaths have been reported at
2-year intervals, with data collected on the date, cause, and place of
death and the medical history of the dead. The information related
to the death was obtained by asking family members about their
pre-death situation. All participants provided written informed
consent, and the survey protocol was approved by the Institudial
Review Board of Wonkwang University Sanbon Medical Center
(No. WMCSB 202006-42).

After excluding individuals aged under 65 years, a total of 4,164
individuals remained. We further excluded individuals with only
one BMI measurement during follow-up \((n=663)\) and those with
errors in the dataset \((n=23)\). Finally, 3,478 participants aged 65
years or older, comprising 1,467 men \((42.2\%)\) and 2,011 women
\((57.8\%)\), were included in the analysis of the association between
BMI and all-cause mortality (Fig. 1).

**Measurements**

The covariates in this study can be broadly divided into sociodeque-

graphic factors, behavioral factors, and factors related to the
current health status of the participants. The sociodemographic
and behavioral factors included age, sex, marital status, educational
level, smoking and drinking history, and regular exercise. Regular
exercise was defined as at least one exercise per week, while others
classified as “non-exercise”. Smokers were classified into non-smok-
ers, former smokers, and current smokers. Former smokers were
defined as people who had not smoking at present but had experi-
enced smoking more than five packs \((100 \text{ cigarettes})\) in total. Par-
ticipants who had smoked less or had not smoked in the past were
considered “non- smokers”. Drinkers were divided into non-drink-
ers and current drinkers, with those who drink sometimes or fre-
quently or those who had drunk recently classified as “current
drinkers”. Others, including former drinkers, were classified as
“non-drinkers”.

Health status was assessed based on chronic disease status,
self-rated health, and functional status. The six chronic diseases in-
cluded in this study were hypertension \((\text{HTN})\), diabetes mellitus
\((\text{DM})\), chronic lung disease, chronic liver disease, heart disease,
and stroke. Self-rated health was classified into five categories—
namely, 1 (very good), 2 (good), 3 (normal), 4 (bad), and 5 (very
bad)—as described in the Survey of Health, Ageing and Retire-
ment in Europe (SHARE) study, and they were reclassified into

![Fig. 1. Flow chart of study population selection. BMI, body mass index.](www.e-agmr.org)
good, moderate, and bad in the present study. The functional status of the participants was assessed based on activities of daily living (ADL) values. ADL was scored based on whether a person requires assistance to perform activities, including dressing, washing/brushing, bathing/showering, eating, leaving the room, using the toilet, and controlling the stool. The value was “1” for participants requiring partial or full help with the activity and “0” if they did not require help. All values were summed and indexed.

Handgrip strength was measured as part of the physical function measurement. The grip strength of both hands was measured twice using a dynamometer (Hand Grip Meter Blue 6103; Tanita Co., Tokyo, Japan) and expressed as the total mean value of the grip strength values for the left and right hands. The 10-item Center for Epidemiological Studies Depression Scale (CES-D10) and Korean version of Mini-Mental State Examination (K-MMSE) were used to assess the mental and cognitive status of the participants. In the depression scale, the questionnaire was assigned a value of “1” or “0”, and all values were summed.

This study analyzed four BMI trajectory subgroups. BMI is expressed as the ratio of the weight in kilograms to the square of height in meters. We used the classifications from the 2018 guidelines of the Korean Society for the Study of Obesity, in which BMI of 25 kg/m$^2$ or higher is categorized as obesity, 23–24.9 kg/m$^2$ as pre-obesity (overweight or risk weight), 18.5–22.9 kg/m$^2$ as normal weight, and less than 18.5 kg/m$^2$ as underweight.

Statistical Analysis
Analysis of covariance and $\chi^2$ tests were used to assess baseline characteristics of each trajectory group for continuous and categorical variables, respectively. Values are expressed as mean ± standard deviation or as percentages. All participants were divided into trajectory subgroups using the Traj command in STATA, which is based on the group-based trajectory modeling method proposed by Nagin and employs a two-stage model selection process. The number of trajectory groups was determined in the first stage, while the best trajectory group (HNWG: baseline BMI, 22.0 ± 1.64 kg/m$^2$; linear slope, -0.05; 95% CI, -0.12 to -0.08); overweight, stable trajectory group (OWG: baseline BMI, 24.5 ± 1.72 kg/m$^2$; linear slope, -0.01; 95% CI, -0.19 to -0.12); high normal weight, decreasing trajectory group (LNWG: baseline BMI, 19.4 ± 1.92 kg/m$^2$; linear slope, -0.01; 95% CI, -0.03 to 0.02); and obesity, stable trajectory group (OG: baseline BMI, 28.1 ± 2.16 kg/m$^2$; linear slope, -0.01; 95% CI, -0.12 to -0.08) were selected.

RESULTS
Trajectory Model Development
The participants were divided into four trajectory groups according to the degree of BMI. The four-group model was refined to achieve the lowest absolute BIC value. While the five-group model had the lowest BIC value, the sample sizes in each group were small (< 5%). Subject-specific judgment combined with BIC has been suggested to determine the number of groups. Together with other criteria such as reasonable sample size for each group membership (e.g., reasonably large group size > 5%), we identified four distinct trajectories, namely the low normal weight, decreasing trajectory group (LNWG: baseline BMI, 19.4 ± 1.92 kg/m$^2$; linear slope, -0.15; 95% CI, -0.19 to -0.12); high normal weight, decreasing trajectory group (HNWG: baseline BMI, 22.0 ± 1.64 kg/m$^2$; linear slope, -0.01; 95% CI, -0.12 to -0.08); overweight, stable trajectory group (OWG: baseline BMI, 24.5 ± 1.72 kg/m$^2$; linear slope, -0.05; 95% CI, -0.03 to 0.02); and obesity, stable trajectory group (OG: baseline BMI, 28.1 ± 2.16 kg/m$^2$; linear slope, -0.05; 95% CI, -0.10 to 0.01). BMI decreased over time in the LNWG and HNWG but did not change in the OWG and OG. The BIC value for this model was -36552.88 and had the best fit among all other four-group models (Supplementary Table S1). BMI was measured as a mean of 4.78 times among participants during the six survey waves. The

Handgrip strength was measured as part of the physical function measurement. The grip strength of both hands was measured twice using a dynamometer (Hand Grip Meter Blue 6103; Tanita Co., Tokyo, Japan) and expressed as the total mean value of the grip strength values for the left and right hands. The 10-item Centre for Epidemiological Studies Depression Scale (CES-D10) and Korean version of Mini-Mental State Examination (K-MMSE) were used to assess the mental and cognitive status of the participants. In the depression scale, the questionnaire was assigned a value of “1” or “0”, and all values were summed.

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Analysis of covariance and $\chi^2$ tests were used to assess baseline characteristics of each trajectory group for continuous and categorical variables, respectively. Values are expressed as mean ± standard deviation or as percentages. All participants were divided into trajectory subgroups using the Traj command in STATA, which is based on the group-based trajectory modeling method proposed by Nagin and employs a two-stage model selection process. The number of trajectory groups was determined in the first stage, while the best polynomial trajectory function was determined and the Bayesian Information Criteria (BIC) value was calculated in the second stage. As recommended, the best-fitting model was chosen based on BIC scores and an examination of 95% confidence interval (CI).

Results were expressed as hazard ratio (HR) with 95% CI. All analyses were conducted using STATA (Stata/MP 13.1 for Windows). p-values less than 0.05 were considered statistically significant.
response rates of BMI at baseline and 2nd waves were 96.6%, and 95.2%, respectively, and they deceased in the following waves at 89.7% (3rd wave), 87.1% (4th wave), 87.9% (5th wave), and 87.4% (6th wave).

**Evaluation of the Model Fit**

The model fit was evaluated using several diagnostics as suggested by Nagin. For all four trajectory groups, the lowest average posterior probability was 0.91, far greater than the recommended value of 0.7. This means that the model assigned participants to different trajectory groups with little ambiguity. Furthermore, the lowest OCC value was 13.4, which is also greater than the recommendation of 5 as a general guideline. In addition, the probability of group membership (π) and the proportion assigned to each group using the maximum probability rule (P) were almost identical for each group. This indicates that the model assigned participants to different trajectory groups with high certainty (Supplementary Table S2).

**Demographic and Comorbidity Characteristics of the Trajectory Groups**

The baseline characteristics of the four trajectory subgroups are shown in Table 1. The proportions of participants in the four trajectory groups were 19.0%, 41.5%, 31.0%, and 8.5% in the LNWG, HNWG, OWG, and OG, respectively. The higher the group’s mean BMI, the lower the mean age (p < 0.001) and the higher the proportion of women (p < 0.001). Participants in groups with a higher mean BMI tended to exercise more regularly and were less likely to be current smokers (p < 0.001), and their prevalence of DM and HTN was higher (p < 0.001). In addition, the MMSE score was significantly higher with increasing mean BMI.

Fig. 2 shows the changes in BMI with age for each trajectory group. Almost 60% of the participants were within the normal weight range at baseline. The LNWG lost weight to almost underweight levels during the 10-year follow-up period, while the other groups showed weight changes within their original category. The overweight and obesity groups remained within the same BMI categories.

**Cox Proportional Hazard Ratio of All-Cause Mortality according to BMI Trajectories in Participants**

Table 2 shows the Cox proportional hazard ratios of all-cause mortalities among groups, with the trajectory of the OG set as the reference. The participants were adjusted for confounding variables (age, sex, chronic disease, self-rated health, level of education, marital state, smoking, alcohol, regular exercise, handgrip strength, ADL, MMSE, and depression). As shown in Table 2, the other three trajectories are associated with an excess risk of death compared to the OG. The crude HRs (95% CI) of the LNWG and HNWG compared with those of the OG were 2.61 (1.92–3.57) and 1.96 (1.46–2.66), respectively, while the adjusted ratios were 2.40 (1.69–3.40) and 1.75 (1.26–2.45), respectively. Among the confounding variables analyzed in Model 2, the variables related to mortality were age, sex (male), DM, chronic lung disease, stroke, and smoking. In addition, the results confirmed that the lower the individual’s MMSE score, the lower the cognitive function and the higher the probability of death.

The Kaplan–Meier survival curves presented in Fig. 3 show a better overall survival probability in the group with higher BMI. While the obesity and overweight group initially showed similar survival rates, the gap gradually increased over time.

**Subgroup and Sensitivity Analyses**

After stratifying participants with respect to sex, we selected separate four-group trajectory models in men and women using the same method described above (Supplementary Fig. S1). After adjusting for confounding variables, the HRs (95% CI) of mortality in the LNWG, HNWG, and OWG compared with those in the OG were 1.91 (1.01–3.98), 1.60 (0.90–2.87) and 1.35 (0.79–2.32), respectively, in men and 2.99 (1.44–6.24), 1.92 (1.04–3.54) and 1.40 (0.81–2.42), respectively, in women (Supplementary Tables S3, S4, and Fig. S2). Compared with participants included in the analysis, those excluded during enrollment or who dropped out during the study period were older, less obese, likely to be living alone, more depressed, showed more cognitive decline, had more chronic diseases, and had lower handgrip strength (Supplementary Table S5).

Participants who died or were censored during the study period tended to be older and current smokers and have more morbidity (more chronic diseases, more depressed, lower ADL, MMSE, and handgrip strength) compared with those who survived (Supplementary Table S5).

To reduce potential confounding bias between weight loss and mortality such as smoking, cancer, and cardiovascular disease (CVD), we performed sensitivity analyses, excluding smokers and those with cancer and CVD. The weight loss patterns and HRs of each weight group in the sensitivity analyses were similar to the main results. The respective adjusted HRs (95% CI) of mortality in the LNWG, HNWG, and OWG compared with those in the OG were 2.39 (1.57–3.64), 1.86 (1.26–3.64), and 1.32 (0.88–1.98), respectively, in non-smokers; 2.41 (1.69–3.43), 1.71 (1.23–2.40), and 1.32 (0.93–1.87), respectively, in the no-cancer group; and 2.14 (1.49–3.08), 1.63 (1.15–2.29), and 1.26 (0.88–1.81), respectively, in the no-CVD group (Supplementary Table S6).
### Table 1. Participant characteristics of according to BMI trajectory

|                        | LNWG (n = 652) | HNWG (n = 1,458) | OWG (n = 1,074) | OG (n = 294) | p-value
|------------------------|----------------|------------------|----------------|-------------|---------
| Age (y)                | 73.1 ± 5.96    | 73.0 ± 6.24      | 71.9 ± 5.74    | 71.7 ± 5.49 | <0.001
| Sex, female            | 352 (54.0)     | 807 (55.4)       | 648 (60.3)     | 204 (69.4)  | <0.001
| Baseline BMI (kg/m²)   | 19.40 ± 1.92   | 22.00 ± 1.64     | 24.50 ± 1.72   | 28.10 ± 2.16 | <0.001
| Chronic diseases       |                |                  |                |             |         
| HTN                    | 159 (24.4)     | 535 (36.7)       | 504 (47.0)     | 185 (62.9)  | <0.001
| DM                     | 73 (11.2)      | 230 (15.8)       | 182 (17.0)     | 71 (24.2)   | <0.001
| Cancer                 | 19 (2.9)       | 33 (2.3)         | 29 (2.7)       | 8 (2.7)     | 0.810
| Chronic lung disease   | 36 (5.5)       | 443 (3.0)        | 26 (2.4)       | 11 (3.7)    | 0.005
| Chronic liver disease  | 8 (1.2)        | 23 (1.6)         | 14 (1.3)       | 6 (2.0)     | 0.740
| Heart disease          | 42 (6.4)       | 85 (5.8)         | 101 (9.4)      | 28 (9.5)    | 0.002
| Stroke                 | 27 (4.1)       | 59 (4.1)         | 52 (4.8)       | 16 (5.4)    | 0.725
| Number of chronic diseases | 0.80 ± 0.93 | 1.00 ± 0.98      | 1.20 ± 1.03    | 1.60 ± 1.17 | <0.001
| Education              |                |                  |                |             |         
| Elementary school or less | 508 (77.9) | 1,055 (72.5)     | 747 (69.6)     | 202 (68.7)  | 0.020
| Middle school          | 55 (8.4)       | 145 (10.0)       | 110 (10.3)     | 34 (11.6)   |         
| High school            | 56 (8.6)       | 186 (12.8)       | 147 (13.7)     | 40 (13.6)   |         
| University or above    | 33 (5.1)       | 707 (48.4)       | 69 (6.4)       | 18 (6.1)    |         
| Marital state          |                |                  |                |             | 0.040   
| Living with spouse     | 425 (65.2)     | 961 (65.9)       | 678 (65.0)     | 168 (57.1)  |         
| Not living with spouse | 227 (34.8)     | 497 (34.1)       | 376 (35.0)     | 126 (42.9)  |         
| Self-rated heath       |                |                  |                |             |         
| Good                   | 114 (17.5)     | 296 (20.3)       | 235 (21.9)     | 57 (19.4)   | 0.020
| Moderate               | 201 (30.8)     | 514 (35.3)       | 361 (33.6)     | 86 (29.3)   |         
| Bad                    | 337 (51.7)     | 648 (44.4)       | 478 (44.5)     | 151 (51.3)  |         
| Smoking                |                |                  |                |             | <0.001  
| Non-smoker             | 421 (64.5)     | 1,049 (72.0)     | 836 (77.8)     | 238 (81.0)  |         
| Former smoker          | 82 (12.6)      | 178 (12.2)       | 110 (10.9)     | 25 (8.5)    |         
| Current smoker         | 149 (22.9)     | 231 (15.8)       | 121 (11.3)     | 31 (10.5)   |         
| Alcohol                |                |                  |                |             | 0.020   
| No                     | 463 (71.0)     | 1,005 (68.9)     | 785 (73.1)     | 226 (76.8)  |         
| Yes                    | 189 (29.0)     | 453 (31.1)       | 289 (26.9)     | 68 (23.2)   |         
| Regular exercise       |                |                  |                |             | <0.001  
| Yes                    | 165 (25.3)     | 484 (33.2)       | 359 (33.4)     | 108 (36.7)  |         
| No                     | 487 (74.7)     | 974 (66.8)       | 715 (66.6)     | 186 (63.3)  |         
| Depression (CES-D score) | 3.90 ± 2.92 | 3.60 ± 2.81      | 3.60 ± 2.80    | 3.70 ± 2.89 | 0.220
| ADL score              | 0.33 ± 1.27    | 0.24 ± 1.03      | 0.22 ± 1.03    | 0.20 ± 1.02 | 0.150
| MMSE score             | 22.50 ± 6.30   | 22.80 ± 6.05     | 23.30 ± 5.92   | 24.00 ± 5.37 | 0.001
| Hand grip strength (kg)| 21.00 ± 7.45   | 22.00 ± 7.62     | 22.40 ± 8.06   | 21.80 ± 7.71 | 0.008

Values are presented as mean±standard deviation or number (%).
BMI, body mass index; LNWG, low normal weight, decreasing group; HNWG, high normal weight, decreasing group; OWG, overweight, stable group; OG, obese, stable group; HTN, hypertension; DM, diabetes mellitus; CES-D, Center for Epidemiological Studies-Depression scale; ADL, activities of daily living; MMSE, Mini-Mental State Examination.

DISCUSSION

This is the first study to identify the heterogeneity of BMI trajectories and demonstrate its association with mortality in the older population in Korea. The participants were classified into obesity, overweight, high-normal, and low-normal groups, all of which showed a slight decrease in BMI over a 10-year period. BMI decreased with age in the LNWG and HNWG but was stable in the
Of the four trajectory groups, the group with high BMI was younger, had better cognition, and exercised regularly compared with the group with lower BMI. However, the group with a lower BMI had a relatively lower prevalence of HTN and DM and included more male and current smokers. As shown in Model 2 (Table 2), after adjusting for confounding variables, the group with lower BMI had a consistently higher risk of all-cause mortality.

A meta-analysis of prospective studies reported that weight loss was related to an increased risk of all-cause mortality in middle-aged populations. However, as the relationship between body weight and mortality appears to vary by age, it is important to investigate whether the association between weight change and mortality persists in older populations.

Many studies have reported the association between BMI and mortality in Korea. Several large cohort studies have been conducted based on baseline BMI in patients aged over 65 years receiving regular health checkups. These studies reported higher mortality risks in the group with lower baseline BMI. Park et al. investigated the association of BMI change with mortality in addition to baseline BMI. Their subgroup analysis showed that BMI change better predicted mortality than a single measure. Using the National Health Insurance System health checkup data, Kim et al. reported the association between weight change and subsequent mortality, demonstrating a reverse J-shaped all-cause mortality curve for weight change; furthermore, weight loss was associated with a higher risk of mortality than was weight gain. However, these studies measured BMI just twice (at baseline and later) in a short period and included a relatively young population. In contrast, the current study attempted to classify BMI subgroups by repetitive measurement of BMI through long-term follow-up and by using a trajectory model.

Several studies have explored the relationship between BMI trajectory and all-cause mortality. As shown in Fig. 2, body mass index (BMI) trajectories of the participants during study period. BMI decreased with age in the low normal weight and high normal weight groups, but it was stable in the overweight and obesity groups.

Table 2. Cox proportional hazard ratio of all-cause mortality according to BMI trajectories in participants

<table>
<thead>
<tr>
<th></th>
<th>Crude</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>LNWG</td>
<td>2.61 (1.91–3.57)</td>
<td>2.74 (1.99–3.77)</td>
<td>2.40 (1.69–3.40)</td>
</tr>
<tr>
<td>HNWG</td>
<td>1.96 (1.46–2.66)</td>
<td>1.91 (1.41–2.60)</td>
<td>1.75 (1.26–2.45)</td>
</tr>
<tr>
<td>OWG</td>
<td>1.42 (1.04–1.95)</td>
<td>1.60 (1.16–2.19)</td>
<td>1.38 (0.99–1.96)</td>
</tr>
<tr>
<td>OG</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Male</td>
<td>-</td>
<td>2.07 (1.76–2.42)</td>
<td>2.89 (2.25–3.71)</td>
</tr>
<tr>
<td>Age</td>
<td>-</td>
<td>1.12 (1.11–1.13)</td>
<td>1.11 (1.10–1.13)</td>
</tr>
<tr>
<td>HTN</td>
<td>-</td>
<td>0.94 (0.82–1.08)</td>
<td>1.04 (0.89–1.21)</td>
</tr>
<tr>
<td>DM</td>
<td>-</td>
<td>1.68 (1.43–1.99)</td>
<td>1.69 (1.41–2.04)</td>
</tr>
<tr>
<td>Cancer</td>
<td>-</td>
<td>1.18 (0.83–1.69)</td>
<td>1.29 (0.85–1.95)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>1.41 (1.04–1.90)</td>
<td>1.47 (1.05–2.06)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>-</td>
<td>2.06 (1.62–2.62)</td>
<td>1.75 (1.28–2.40)</td>
</tr>
<tr>
<td>Smoking</td>
<td>-</td>
<td>-</td>
<td>1.42 (1.15–1.74)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>-</td>
<td>-</td>
<td>0.89 (0.75–1.06)</td>
</tr>
<tr>
<td>MMSE</td>
<td>-</td>
<td>-</td>
<td>0.98 (0.96–0.99)</td>
</tr>
</tbody>
</table>

Values are presented as hazard ratio (95% confidence interval) and analyzed using Cox-proportional hazards regression models.

BMI, body mass index; LNWG, low normal weight, decreasing group; HNWG, high normal weight, decreasing group; OWG, overweight, stable group; OG, obese, stable group; HTN, hypertension; DM, diabetes mellitus; MMSE, Mini-Mental State Examination.

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Several studies have explored the relationship between BMI tra-
jectories and mortality. Using data from the Health and Retirement Study for older Americans, Zheng et al. defined six linear trajectories (overweight stable, normal weight downward, normal weight upward, overweight obesity, class I obese upward, and class II/III upward). The normal weight downward and class II/III obese upward group had high mortality risk, while the overweight stable group had the lowest mortality. In our study, the weight trajectories of the LNWG and HNWG showed a decreased pattern during the study period and those of the OWG and OG were relatively stable. The OG had the highest survival rate, while the LNWG showed a higher risk of mortality. Although Zheng et al. analyzed a younger population (51–61 years), the differences were more likely due to racial differences. Since racial/ethnic differences in obesity status, body composition, and weight management behaviors have been reported, weight change and its association with life span may vary across racial/ethnic groups.

However, our results are similar to those of one Japanese study by Murayama et al. They identified four distinct BMI trajectories in a 19-year follow-up of older Japanese adults and reported that adults who were overweight but stable had the highest survival rate. Thus, older East Asians may differ from older Americans in terms of weight distribution and patterns of weight change over time.

Compared with short-term (within 5 years) weight changes reported previously, weight changes in the four trajectory groups were small. However, body weight can fluctuate substantially over the adult lifetime; thus, weight changes measured at multiple points over an extended time (approximately 10 years) may provide additional information. Moreover, while previous studies categorized weight change groups using arbitrary criteria such as 5% gain or loss from baseline body weight, these approaches did not provide precise individual classifications into the various bodyweight groups. Our trajectory modeling method can more precisely define weight change groups of real older populations, even if the changes are small.

People with low BMI are more likely to have less muscle and bone mass and increased body fat. Reduced muscle and bone mass increase the likelihood of osteoporosis and fractures and decrease body function, which in severe cases, leads to frailty and disability. Low muscle mass in the low BMI population causes deterioration of lung function and makes it difficult to withstand catabolic stress in respiratory crisis situations. In some studies, underweight people were more susceptible to respiratory disease and showed higher mortality rates. In contrast, high BMI suggests that muscle and body fat, which serve as energy and nutrient reserves, are likely to be sufficient. Underweight people could be undernourished, which reduces immune cell function, increasing these individuals’ susceptibility to infection. Underweight people are reportedly susceptible to infectious diseases such as tuberculosis. Studies have also shown higher probabilities of complications and mortality among individuals with chronic diseases, including CVD, and among those with lower BMI Chronic disease can result in a catabolic state that, in turn, leads to wasting syndrome and metabolic stress situations with muscle, bone, and body fat loss. Accordingly, people who lack sufficient energy and nutrient reserves are intolerable. Moreover, insufficient nutrition prolongs hospitalization and increases mortality in hospitalized patients. Thus, high BMI may have a protective effect against various deteriorating conditions, which may improve survival.

Several limitations should be considered when interpreting our outcomes. In general, people overreport their height, and they (especially obese people) tend to underreport their weight, resulting in under-estimated BMI. The present study used subject-reported height and weight to calculate BMI, which could lead to biased results in BMI trajectory patterns. Second, there was the possibility of selection bias. The participants of the KLoSA study were residents enrolled nationwide to form a nationally representative database. Individuals in long-term care facilities were not included in this study. Moreover, 16.5% of participants were excluded from the analysis due to drop-out during the study period. Comparisons of the characteristics of the included and excluded participants are shown in Supplementary Table S4. In general, the excluded participants were older and had more morbidity than the participants included in the analysis. This difference means that more vulnerable participants were more likely to drop out during the study period. The sample admitted to long-term care facilities owing to chronic diseases during follow-up may have been excluded from the main panel data. The participants often have more functional limitations and comorbidity than those who live at home. Therefore, this analysis of the effect of BMI on mortality could have a limitation among people with high levels of frailty. Third, intentional and unintentional weight changes were not distinguished. As unintentional weight loss has a higher mortality risk than intentional weight loss, we adjusted for various underlying diseases and functional limitations that could lead to unintentional weight changes. Fourth, in determining the degree of obesity, BMI is not an optimal indicator. Since BMI is calculated based on total weight, it is not possible to directly measure the weight of body fat and muscle composition. Moreover, this calculation does not reflect the distribution of body weight. It is more advantageous to measure waist circumference when a person had central adiposity with high levels of fat in the abdomen; however, the present study did not adjust for waist circumference. Finally, only all-cause mortality was assessed. The associations with cause-specific mortality, such
as death from cardiovascular or other causes, should also be investigated in future studies.

Nevertheless, this study has some important strengths. Most previous studies adopted methods of classifying BMI change into predetermined intervals arbitrarily, as defined by researchers. In contrast, this study used a trajectory model to express BMI change more objectively as a result, we identified four homogenous trajectory groups. Moreover, the relationship between BMI subgroup and mortality could be more accurately demonstrated through continuous and repeated BMI measurement over 10 years of follow-up. This study of data of the older population extracted from the KLOSA database has the advantage of a relatively large sample size and a prospective design. Physical assessment was performed using validated measures, and variables related to lifestyle and health were considered. Since this study included healthy community-dwelling residents in Korea, the findings can be generalized to the Korean population. Moreover, we performed the analyses after adjusting for multiple sociodemographic and behavioral variables (age, sex, marital status, educational level, co-morbidity, smoking, drinking, and regular exercise).

In conclusion, the results of our study showed dynamic associations between BMI and mortality among older adults in Korea. We identified a slight downward trajectory of BMI in the LNWG and HNWG groups and a stable trajectory in theOWG and OG groups. These findings are contrary to those in western populations, in which weight gain in the obese group and weight loss in the normal weight group were observed, but the findings are similar to those in Japan, where weight loss was observed in all subgroups except for the OWG. The OG group had the highest survival rate, while the LNWG group had a higher risk of mortality. This research suggests that baseline obesity status and degree of weight loss during the follow-up period contributed to mortality in later life. Further studies are needed to determine the mechanism of these results in more detail.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST
The researchers claim no conflicts of interest.

FUNDING
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AUTHOR CONTRIBUTIONS
Conceptualization, JL; Data curation, JWK, JL; Investigation, JWK, JL; Methodology, TP, DRL; Project administration, JL; Supervision, JL; Writing-original draft, JWK; Writing-review & editing, TP, DRL, JL.

SUPPLEMENTARY MATERIALS
Supplement materials can be found via https://doi.org/10.4235/agmr.20.0030.

REFERENCES


Background: In older adults, the risk of frailty is higher among those who are unmarried than among those who are married. However, no study has reported about the relationship between cohabitation status and frailty.

Methods: This cross-sectional study included 2,128 community-dwelling adults aged between 70 and 84 years who underwent interviews and physical function assessments for the Korean Frailty and Aging Cohort Study. The definition of frailty was derived from the Fried frailty phenotype. Cohabitation was categorized as "living alone", "with spouse only", "with children only", and "with spouse and children".

Results: The mean age was 76 years, and 46.3% of the adults were men. After adjusting for age, education, income, nutritional status, alcohol, smoking history, Geriatric Depression Scale, Mini-Mental State Examination, Korean Activities of Daily Living, Korean Instrumental Activities of Daily Living, urinary incontinence, and polypharmacy, the odds ratios of frailty were 0.323 (95% confidence interval [CI], 0.137–0.763; p<0.001) and 1.089 (95% CI, 0.671–1.769; p=0.730) for men and women living with a spouse, respectively. The odds ratios of frailty were 0.329 (95% CI, 0.117–0.927; p=0.035) and 0.332 (95% CI, 0.123–0.891; p=0.029) for men and women living with spouse and children, respectively.

Conclusion: Men living with a spouse or with a spouse and children had a lowered prevalence of frailty, and women living with a spouse and children together had a lowered prevalence of frailty.

Key Words: Aged, Family, Frailty, Korean, Spouses

INTRODUCTION

Korea is the fastest aging country in the world. More than 14% of the Korean population in 2017 was above 65 years of age, making it an aged society. Frailty is a common health problem associated with aging. It is defined as a significant decline in functional reserve and homeostasis of multiple organ systems, with resultant vulnerability of individuals to stressors, thereby leading to a higher risk of accelerated functional decline and negative health-related outcomes. The most common index is the frailty phenotype by Fried et al., which defined frailty as the presence of three or more of the following five components: self-reported exhaustion, decreased grip strength, slow walking speed, low physical activity, and unintended weight loss.

It is important to define frailty based on physical and social determinants for the early detection of people at a high risk of frailty, as well as for prevention of frailty. Statistics Korea reported that 34.2% of individuals aged above 65 years were living in one-person households.
households in 2019. The proportions of older adults living only with a spouse or living with a spouse and children were 33.2% and 9.6%, respectively. Since living alone is considered a risk factor for frailty, cohabitation might influence the onset of frailty. A meta-analysis revealed a nearly two-fold higher risk of frailty in unmarried people than in married people. However, to date, no study has examined the relationship between cohabitation and frailty.

Several studies have shown that it is more beneficial for men than for women to get married. Although another meta-analysis did not observe such gender-based differences, gender-based differences did affect the relationship between marital status and mortality, i.e., marriage was more beneficial to men than to women. Hence, gender may affect the relationship between frailty and cohabitation. This study aimed to clarify the association between cohabitation and frailty and the existence of a gender effect.

**MATERIALS AND METHODS**

**Study Setting and Population**

The participants of the Korean Frailty and Aging Cohort Study (KFACS) were aged between 70 and 84 years. The KFACS is a multicenter longitudinal study with a baseline survey conducted in 2016–2017. The participants were drawn from communities living around 10 medical centers (8 hospitals and 2 public health centers). Thus, 3,014 community-dwelling older adults from urban and rural regions nationwide were recruited after stratifying them based on age and sex. This cross-sectional study analyzed the baseline data of the KFACS from 2016 to 2017. We excluded participants with cerebrovascular diseases, hemiplegia, or paraplegia and collected baseline demographic, medical, behavioral, biological, psychosocial, and socioeconomic data. Among the participants, 986 men and 1,142 women who completed all questionnaires on the frailty phenotype and related covariates were considered. The Institutional Review Board of the Clinical Trial Review Committee of the Kyung Hee University Medical Center approved the research plan of the present study (No. 2020-01-065). All subjects provided consent prior to or at registration.

**Measures**

Cohabitants were assessed using the following interview question: “Who are you living with?” with the following seven choices: (1) alone, (2) only with a spouse, (3) only with children, (4) with a spouse and children, (5) with other family, (6) others, and (7) unidentified. Participants who chose from among options 1 to 4 were included in the analysis.

Regarding the definition of frailty, we used the Fried phenotype that comprised five components: exhaustion, poor grip strength, slow walking speed, low physical activity level, and unintended weight loss. Each component was determined as follows, and participants with a total score of 3 or more were classified as frail.

1. Exhaustion: one point was given for exhaustion when the subject responded “yes” to either of the questions (“I felt that everything I did was an effort” or “I could not get going”) for 3 or more days in a week. (1)
2. Poor grip strength: the highest value for each hand was included in the analysis using a hand dynamometer (Takei TKK 5401; Takei Scientific Instruments, Tokyo, Japan). The cutoffs for poor grip strength were 26 kg for men and 18 kg for women. (2)
3. Slow walking speed: one point was given for a walking speed below 1 m/s after walking 4 m at a usual gait speed using an automatic timer (Gaitspeedometer; Dyphi, Daejeon, Korea). (3)
4. Low physical inactivity: a metabolic equivalent task in minutes per week (MET-min/week) was calculated to determine physical activity level, with one point given for values below 494.6 kcal in men and below 283.5 kcal in women, corresponding to the lowest 20% of sex-specific total energy consumed in a general population-based survey of older adults. (4)
5. Unintended weight loss: one point was given for unintentional weight loss of 4.5 kg or more in the last year.

**Covariates**

The covariates were age, education level (under elementary or above), economic status (basic livelihood security recipient), Mini Nutritional Assessment (MNA; decreasingly worse), alcohol consumption (three or more alcoholic drinks a week or not), smoking (lifetime consumption of 100 or more cigarettes), Geriatric Depression Scale (GDS; range 0–15, increasingly worse), Mini-Mental State Examination (MMSE; < 24, ≥ 24), Korean Activities of Daily Living (KADL; range 7–21, increasingly worse), Korean Instrumental Activities of Daily Living (KIADL; range 0–33, increasingly worse), urinary incontinency, and polypharmacy (ingestion of 5 or more prescribed medications). The covariates were selected based on previous studies on marital status and frailty.

**Statistical Analysis**

We analyzed continuous variables using independent t-tests and categorical variables using chi-square tests. Data are presented as mean ± standard deviation or number (percentage).

We assessed the associations between cohabitants and frailty using binomial logistic regression analysis. The models were adjusted as follows:

1. Model 1: Adjusted for age, education, and income.
2. Model 2: Adjusted for age, education, income, MNA, alcohol...
consumption, and smoking history.

(3) Model 3: Adjusted for age, education, income, MNA, alcohol consumption drinker, smoking history, GDS, MMSE, KADL, and KIADL.

(4) Model 4: Adjusted for age, education, income, MNA, alcohol consumption, smoking history, GDS, MMSE, KADL, KIADL, urinary incontinence, and polypharmacy.

Statistical analysis was performed using IBM SPSS Statistics version 23.0 for Windows (IBM Corp., Armonk, NY, USA), and significance was defined as a p-value < 0.05.

RESULTS

General Characteristics of the Study Population

Among 2,128 study population, the number of frail group was 211 (9.9%). By cohabitants, the number of people who live with each cohabitant was as follows: alone 508 (23.9%), living with spouse only 1,084 (50.9%), living with children only 225 (10.6%), living with both spouse and children 311 (14.6%).

Among people with frailty, 21.4% of men (table 1) and 46.8% of women (table 2) were living alone. Also, 50% of men with frailty (table 1) and 31.9% of women with frailty (table 2) were living only with spouse.

Association between Cohabitants and Frailty

Men who lived with a spouse only were less likely to be frail compared with those who lived alone after adjusting for age, education, and income (odds ratio [OR] = 0.410; 95% confidence interval [CI], 0.203–0.827; p = 0.013) (Table 3). In models 1–4, men who lived with a spouse only were less likely to be frail compared with those living alone. In models 3 and 4, living with a spouse and children also reduced the OR of frailty in

Table 1. General characteristics of participants (men, n=986)

<table>
<thead>
<tr>
<th></th>
<th>Non-frail (n=916)</th>
<th>Frail (n=70)</th>
<th>Total (n=986)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>76.3 ± 3.8</td>
<td>79.39 ± 3.1</td>
<td>76.5 ± 3.9</td>
<td>&lt; 0.001</td>
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<tr>
<td>Education ≤ 5 y</td>
<td>70 (7.6)</td>
<td>14 (20)</td>
<td>84 (8.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Occupation with income</td>
<td>647 (70.6)</td>
<td>51 (72.8)</td>
<td>698 (70.7)</td>
<td>0.693</td>
</tr>
<tr>
<td>Unmarried</td>
<td>91 (9.9)</td>
<td>18 (25.7)</td>
<td>109 (11.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Basic livelihood security recipient</td>
<td>44 (4.8)</td>
<td>6 (8.5)</td>
<td>50 (5.0)</td>
<td>0.166</td>
</tr>
<tr>
<td>Smoking (lifetime)</td>
<td>702 (76.6)</td>
<td>53 (75.7)</td>
<td>755 (76.5)</td>
<td>0.860</td>
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<tr>
<td>Alcohol drinker</td>
<td>293 (31.9)</td>
<td>17 (24.2)</td>
<td>310 (31.4)</td>
<td>0.181</td>
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<tr>
<td>Hypertension</td>
<td>585 (63.8)</td>
<td>44 (62.8)</td>
<td>629 (63.7)</td>
<td>0.866</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>255 (27.8)</td>
<td>21 (30)</td>
<td>276 (27.9)</td>
<td>0.698</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>137 (14.9)</td>
<td>15 (21.4)</td>
<td>152 (15.4)</td>
<td>0.148</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>8 (0.8)</td>
<td>0 (0)</td>
<td>8 (0.8)</td>
<td>0.432</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>32 (3.4)</td>
<td>6 (8.5)</td>
<td>38 (3.8)</td>
<td>0.033</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>10 (1.0)</td>
<td>3 (4.2)</td>
<td>13 (1.3)</td>
<td>0.024</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>366 (39.9)</td>
<td>40 (57.1)</td>
<td>406 (41.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>KADL score</td>
<td>7.0 ± 0.2</td>
<td>7.2 ± 0.7</td>
<td>7.0 ± 0.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>KIADL score</td>
<td>13.2 ± 3.5</td>
<td>14.1 ± 4.1</td>
<td>13.2 ± 3.5</td>
<td>0.035</td>
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<tr>
<td>GDS score</td>
<td>2.1 ± 2.8</td>
<td>5.9 ± 4.4</td>
<td>2.4 ± 3.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MMSE score &lt; 24</td>
<td>115 (12.5)</td>
<td>26 (37.1)</td>
<td>141 (14.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MNA score &lt; 12</td>
<td>106 (11.5)</td>
<td>28 (40)</td>
<td>134 (13.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Weekly physical activities (kcal)</td>
<td>4,269.0 ± 4,511.7</td>
<td>1,761.3 ± 2,909.5</td>
<td>4,091.0 ± 4,462.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cohabitants</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Alone</td>
<td>79 (8.6)</td>
<td>15 (21.4)</td>
<td>94 (9.5)</td>
<td></td>
</tr>
<tr>
<td>With spouse only</td>
<td>634 (69.2)</td>
<td>35 (50)</td>
<td>669 (67.8)</td>
<td></td>
</tr>
<tr>
<td>With children only</td>
<td>23 (2.5)</td>
<td>6 (8.5)</td>
<td>29 (2.9)</td>
<td></td>
</tr>
<tr>
<td>With spouse and children</td>
<td>180 (19.6)</td>
<td>14 (20)</td>
<td>194 (19.6)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%). Polypharmacy implied ingestion of five or more prescribed medications, alcohol consumption implied weekly three or more alcoholic drinks, and smoking (lifetime) implied lifetime consumption of 100 or more cigarettes. The Korean Activities of Daily Living (KADL; range 7 to 21, increasingly worse), Korean Instrumental Activities of Daily Living (KIADL; range 0 to 33, increasingly worse), Geriatric Depression Scale (GDS; range 0 to 15, increasingly worse). MMSE, Mini-Mental State Examination; MNA, Mini Nutritional Assessment.
men compared with living alone.

For women, living with a spouse did not decrease the OR of frailty, whereas living with a spouse and children together showed lower risks of frailty (model 4; OR = 0.332).

DISCUSSION

This study analyzed the relationship between cohabitation and frailty. Previous studies found that marital status was related to frailty but only a few studies have shown a gender-based effect. Moreover, no study has explored the additional effect of living with children on frailty. In our study, we analyzed gender separately and observed differences based on gender. In men, the prevalence of frailty decreased when living with a spouse or with a spouse and children, whereas in women, the prevalence of frailty was low only when living with a spouse and children together. Therefore, merely living with someone else did not necessarily lead to lower risks of frailty in men in this study, rather only when they lived with their spouse. This finding is consistent with the results of a study in Italy that concluded that unmarried men are at a higher risk of being frail than married men. Likewise, other studies have reported an association between being married and longevity or better health, especially in men. One study concluded that eating with others was an independent survival factor in older men. A previous meta-analysis study concluded that unmarried individuals were more likely to be frail than married individuals, irrespective of gender. However, in this study, no significant difference was observed in the prevalence of frailty in women with respect to living with a spouse. Although not statistically significant, women living with a spouse had a higher prevalence of frailty than those living alone. Therefore, for older women, living with a spouse may negatively affect frailty. A cohort study that analyzed marital status and frailty found that widowed women had a lower risk of frailty than married women. A sociological study reported

<table>
<thead>
<tr>
<th>Table 2. General characteristics of participants (women, n=1,142)</th>
<th>Non-frail (n = 1,001)</th>
<th>Frail (n = 141)</th>
<th>Total (n = 1,142)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>75.4 ± 3.7</td>
<td>78.2 ± 3.7</td>
<td>75.5 ± 3.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Education ≤ 5 y</td>
<td>262 (26.1)</td>
<td>86 (60.9)</td>
<td>348 (30.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Occupation with income</td>
<td>796 (79.5)</td>
<td>113 (80.1)</td>
<td>909 (79.6)</td>
<td>0.693</td>
</tr>
<tr>
<td>Unmarried</td>
<td>509 (50.8)</td>
<td>89 (63.1)</td>
<td>598 (52.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Basic livelihood security recipient</td>
<td>53 (5.2)</td>
<td>16 (11.3)</td>
<td>69 (6.0)</td>
<td>0.166</td>
</tr>
<tr>
<td>Smoking (lifetime)</td>
<td>23 (2.3)</td>
<td>9 (6.3)</td>
<td>32 (2.8)</td>
<td>0.860</td>
</tr>
<tr>
<td>Alcohol drinker</td>
<td>34 (3.4)</td>
<td>7 (4.9)</td>
<td>41 (3.5)</td>
<td>0.181</td>
</tr>
<tr>
<td>Hypertension</td>
<td>704 (70.3)</td>
<td>102 (72.3)</td>
<td>806 (70.5)</td>
<td>0.866</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>209 (20.8)</td>
<td>41 (29.0)</td>
<td>250 (21.8)</td>
<td>0.698</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>378 (37.7)</td>
<td>59 (41.8)</td>
<td>437 (38.2)</td>
<td>0.148</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>33 (3.3)</td>
<td>7 (4.9)</td>
<td>40 (3.5)</td>
<td>0.432</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>311 (31.0)</td>
<td>45 (31.9)</td>
<td>356 (31.1)</td>
<td>0.033</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>53 (5.2)</td>
<td>16 (11.3)</td>
<td>69 (6.0)</td>
<td>0.024</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>302 (30.1)</td>
<td>83 (58.8)</td>
<td>385 (33.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>KADL score</td>
<td>7.1 ± 0.3</td>
<td>7.3 ± 0.6</td>
<td>7.1 ± 0.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>KIADL score</td>
<td>10.4 ± 1.2</td>
<td>11.2 ± 2.5</td>
<td>10.5 ± 1.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GDS score</td>
<td>3.4 ± 3.6</td>
<td>7.0 ± 4.6</td>
<td>3.8 ± 3.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MMSE score &lt; 24</td>
<td>234 (23.3)</td>
<td>72 (51.0)</td>
<td>306 (26.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MNA score &lt; 12</td>
<td>130 (12.9)</td>
<td>43 (30.4)</td>
<td>173 (15.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Weekly physical activities (kcal)</td>
<td>2,629.7 ± 2,838.0</td>
<td>1,066.1 ± 1,739.1</td>
<td>2,436.6 ± 2,774.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cohabitants</td>
<td></td>
<td></td>
<td></td>
<td>0.010</td>
</tr>
<tr>
<td>Alone</td>
<td>348 (34.7)</td>
<td>66 (46.8)</td>
<td>414 (36.2)</td>
<td></td>
</tr>
<tr>
<td>With spouse only</td>
<td>370 (36.9)</td>
<td>45 (31.9)</td>
<td>415 (36.3)</td>
<td></td>
</tr>
<tr>
<td>With children only</td>
<td>172 (17.1)</td>
<td>24 (17.0)</td>
<td>196 (17.1)</td>
<td></td>
</tr>
<tr>
<td>With spouse and children</td>
<td>111 (11.0)</td>
<td>6 (4.2)</td>
<td>117 (10.2)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%). Polypharmacy implied ingestion of five or more prescribed medications, alcohol consumption implied weekly three or more alcoholic drinks, and smoking (lifetime) implied lifetime consumption of 100 or more cigarettes. The Korean Activities of Daily Living (KADL; range 7 to 21, increasingly worse), Korean Instrumental Activities of Daily Living (KIADL; range 0 to 33, increasingly worse), Geriatric Depression Scale (GDS; range 0 to 15, increasingly worse). MMSE, Mini-Mental State Examination; MNA, Mini Nutritional Assessment.
Table 3. Association between cohabitants and frailty

<table>
<thead>
<tr>
<th>Type of cohabitant</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With spouse</td>
<td>0.410</td>
<td>0.203–0.827</td>
</tr>
<tr>
<td>With children</td>
<td>1.264</td>
<td>0.408–3.919</td>
</tr>
<tr>
<td>With spouse and children</td>
<td>0.634</td>
<td>0.275–1.460</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With spouse</td>
<td>0.362</td>
<td>0.173–0.756</td>
</tr>
<tr>
<td>With children</td>
<td>1.284</td>
<td>0.393–4.197</td>
</tr>
<tr>
<td>With spouse and children</td>
<td>0.550</td>
<td>0.230–1.318</td>
</tr>
<tr>
<td>Model 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With spouse</td>
<td>0.329</td>
<td>0.141–0.765</td>
</tr>
<tr>
<td>With children</td>
<td>0.908</td>
<td>0.247–3.348</td>
</tr>
<tr>
<td>With spouse and children</td>
<td>0.337</td>
<td>0.122–0.934</td>
</tr>
<tr>
<td>Model 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With spouse</td>
<td>0.323</td>
<td>0.137–0.763</td>
</tr>
<tr>
<td>With children</td>
<td>0.869</td>
<td>0.236–3.205</td>
</tr>
<tr>
<td>With spouse and children</td>
<td>0.329</td>
<td>0.117–0.927</td>
</tr>
</tbody>
</table>

Reference category for types of cohabitants is the “living alone” group. Model 1, adjusted for age, education, income; Model 2, adjusted for age, education, income, MNA, alcohol drinker, smoking history; Model 3, adjusted for age, education, income, MNA, alcohol drinker, smoking history, GDS, MMSE, KADL, KIADL; Model 4, adjusted for age, education, income, MNA, alcohol drinker, smoking history, GDS, MMSE, KADL, KIADL, urinary incontinence, polypharmacy.

OR, odds ratio; CI, confidence interval; MNA, Mini Nutritional Assessment; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; KADL, Korean Activities of Daily Living; KIADL, Korean Instrumental Activities of Daily Living.

that an unmarried status is much more disadvantageous to men than to women. Spitze and Ward found that a higher percentage of men preferred receiving care from their spouse during illness than did women. This is consistent with the result that after the spouse’s death, mortality in men is higher than that in women.

A 1998 survey in Korea reported that most Korean women were exclusively responsible for housework, including cooking at home. The Korean tradition strictly defines women’s role in rearing children and maintaining the household. They were considered to be supportive of men rather than being proactive in workplaces and houses. This finding is closely related to our study results. In addition, according to a recent study, among older adults, men were more likely to report limitations in performing household activities than women. This effect may be another explanation for frailty in men living alone. Thus, cultural factors such as gender roles may have influenced the natural course of frailty.

In men and women, those living with spouse and children had a lower prevalence of frailty. Since this cohort study lacked such specific questions, it was difficult to determine whether participants lived with grandchildren. However, considering the age of the participants living with children, it is likely that they were living with their grandchildren. Therefore, caring for grandchildren might have beneficial health effects. A study in China reported that older adults caring for grandchildren had better self-rated health and fewer limitations than those who did not. However, because the relationship between living with children and frailty was not statistically significant, no definitive conclusions could be reached.

Our study had some limitations. First, it was a cross-sectional study. Hence, the causality of the result must be carefully considered. Further prospective longitudinal studies would be helpful to verify our results. Second, we could not take into account how long the participants had lived alone. This could be another confounding factor because the duration of widowhood was related to health in a cohort study in India. Third, only three of the 2,128 participants (0.1%) reported being unmarried. As this proportion was significantly small, the effects were almost none, and we excluded the three people. However, further studies considering marriage and frailty are warranted to determine this relationship. Finally, considering the age of the participants, they most likely had grandchildren. Further investigation of the effects of living with grandchildren on frailty is needed.

Nevertheless, this study was the first to reveal that living with a spouse was crucial for the prevention of frailty in men, while living with a spouse and children was beneficial for the prevention of...
Cohabitan ts and Frailty

FRAILETY IN WOMEN.

Effective intervention methods for the prevention of frailty remain scarce in Korea. The results of this study indicate that additional methods related to cohabitants should be developed for the prevention of frailty.

In conclusion, men living with a spouse or with a spouse and children had a lower prevalence of frailty, whereas women living with a spouse and children together had a lowered prevalence of frailty.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

FUNDING

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AUTHOR CONTRIBUTIONS

Conceptualization, HS, SK, CWW; Data curation, SK, CWW; Funding acquisition, CWW; Investigation, CWW, SK; Methodology, HS, CWW, SK, MK, EJ, YJL; Writing original draft, HS; Writing review & editing, HS, SK, CWW.

REFERENCES


Red Cell Distribution Width as a Predictor of Functional Outcome in Rehabilitation of Older Stroke Patients

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¹Fliman Geriatric Rehabilitation Hospital, Haifa, Israel
²The Ruth and Bruce Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel

Background: Red cell distribution width (RDW) is a prognostic marker in vascular diseases. While increased RDW predicts mortality and outcomes after ischemic stroke, evidence regarding its prognostic significance in stroke rehabilitation is lacking. Thus, the present study investigated the relationship of RDW with stroke, orthopedic, and deconditioning rehabilitation outcomes.

Methods: This prospective comparative study included three groups (stroke, orthopedic, and deconditioning) of older adult patients hospitalized for rehabilitation. The patients in each group were divided into two subgroups according to whether they had high (>14.5%) or normal (≤14.5%) RDW levels on admission. Functional outcome was assessed by total and motor FIM (Functional Independence Measure) score changes and efficiency at admission and on discharge.

Results: Of the 234 eligible patients, 108 (46.2%) had high RDW. Of the 50 stroke rehabilitation patients, 13 (26%) had high RDW. FIM change and efficiency scores were significantly lower in patients with high RDW only in the stroke rehabilitation group. However, multiple linear regression analysis showed that high RDW was not independently associated with total and motor FIM gain or total and motor FIM efficiency.

Conclusion: High RDW levels on admission to rehabilitation were associated with poor rehabilitation outcome in stroke patients but were not an independent risk factor for rehabilitation outcomes.

Key Words: Stroke, Red cell distribution width, Rehabilitation, Recovery of function
dergoing surgery after a hip fracture. Studies in geriatric populations have also identified RDW as a predictor of all-cause mortality, as well as mortality in patients with ischemic stroke treated with intravenous thrombolysis, older patients with sepsis and in older patients undergoing non-cardiac surgery.

The present study explored the prognostic potential of RDW for rehabilitation by investigating the associations between RDW and short-term functional outcomes among older patients hospitalized for rehabilitation.

MATERIALS AND METHODS

Setting and Study Design

Data were collected over a 6-month period at the Fliman Rehabilitation Geriatric Hospital (a 150-bed public geriatric facility affiliated with the Technion - Israel Institute of Technology, Medical School in Haifa, Israel. This study included all patients over 65 years of age admitted consecutively to the five geriatric rehabilitation wards. The only exclusion criteria were non-ambulatory status before hospitalization and unwillingness to participate. We obtained approval for the study from our local institutions and the Ministry of Health Helsinki committee. The study protocol was approved by the Institutional Review Board at Fliman Geriatric Hospital (No. 920150002).

Patient hemoglobin levels, MCV, and RDW were measured on admission. When more than two RDW measurements were available, the second was taken as the last RDW measurement during hospitalization. Anemia was defined as hemoglobin levels < 13 g/dL in men and 12 g/dL in women, based on the World Health Organization criteria. RDW was reported as the coefficient of variation (in percent) of red blood cell volume. The normal range for RDW in our laboratory is 11.5% to 14.5%. We divided the patients into high (> 14.5%) or normal (≤ 14.5%) RDW groups based on measurements on admission.

Data Collection and Outcome Measures

We approached all potential participants in the hospital and assigned them to groups after the baseline evaluation. Patients were analyzed in three subgroups: namely, the stroke group (patients hospitalized for stroke rehabilitation), orthopedic group (patients hospitalized for orthopedic rehabilitation), and deconditioning group (patients hospitalized after deconditioning for general rehabilitation).

Baseline information was gathered during in-person interviews to ascertain ambulatory function just before hospitalization and associated comorbidities and to perform cognitive screening assessment. We applied the Clinical Dementia Rating (CDR) scale to assess cognitive impairment. Comorbid conditions were determined from the participant or proxy respondent (in interviews) and from medical records using a list derived from the Charlson Comorbidity Index.

In the stroke group, details of the stroke were gathered at the time of inclusion, including the National Institutes of Health Stroke Scale (NIHSS) score at arrival in the emergency room. The Functional Independence Measure (FIM) was the primary study outcome measure. The FIM is a performance-based disability measure that assesses the level of disability in terms of assistance required to perform basic activities of daily living. The FIM consists of 18 items designed to assess the amount of assistance required for safely performing self-care (6 items), sphincter control (2 items), transfers (3 items), locomotion (2 items), communication (2 items), social adjustment and cooperation (3 items), and cognition and problem-solving (3 items). Good reliability and validity have been demonstrated in studies involving orthopedic conditions, older adults, and individuals with cognitive impairment. The validity and reliability of the FIM were also established specifically among adults receiving inpatient rehabilitation. We also used the FIM motor score (13 items) because previous studies have reported low responsiveness for the FIM cognition score. The FIM was completed by trained nurses at admission and discharge from rehabilitation. The rate of functional gain (FIM efficiency) was calculated as the total FIM change (discharge FIM score minus the admission FIM score) divided by the length of rehabilitation stay (days).

Statistical Analysis

Baseline characteristics were examined to determine pre-hospitalization functional status, comorbidities, and health status. Categorical data are presented as proportions. Chi-square tests were used to compare differences in categorical variables. The primary analysis examined recovery over time as measured according to FIM and FIM motor scores. We examined functional recovery at each evaluation point (admission and discharge) using all participants available at that time point. The overall changes within groups were examined by paired-sample t-test or Wilcoxon signed-rank test, while differences in changes between groups were assessed by independent sample t-test or Mann–Whitney U test. To test the associations between possible confounders and FIM measures, a multiple regression analysis was performed using possible confounders (congestive heart failure and baseline hemoglobin, albumin, and creatinine levels) with variables entered in a single stage. The p-value for statistical significance level was less than 0.05.
RESULTS

Data were available for 231 patients admitted, including 50 patients in the stroke group, 125 patients in the orthopedic group, and 56 in the deconditioning group. The demographic characteristics and clinical data of these patients are shown in Table 1.

We observed no significant differences in mean age or sex proportions between groups. In the stroke group, the baseline hemoglobin level was higher in patients with normal RDW compared to that in patients with high RDW (13.2 ± 1.9 vs. 11.3 ± 1.9 g/dL). Moreover, patients in the stroke group with normal RDW had a significantly higher albumin level, lower creatinine level, of better cognitive status (CDR). In the orthopedic group, patients with normal RDW had a significantly higher baseline hemoglobin level and lower Charlson Comorbidity Index. In the deconditioning group, patients with normal RDW had a significantly higher baseline hemoglobin level, lower Charlson Comorbidity Index, and higher percentage of patients with cancer.

In the stroke group, total and motor FIM changes were significantly higher in the low RDW group (32.4 ± 18.2 vs. 18.1 ± 12.9 and 26.5 ± 16.0 vs. 15.2 ± 13.1, respectively; p = 0.012 and p = 0.028, respectively); additionally, these patients had higher total (1.17 ± 0.88 vs. 0.57 ± 0.62; p = 0.015) and motor (0.99 ± 0.74 vs. 0.47 ± 0.58; p = 0.027) FIM efficiency scores compared to those in the high RDW group (Table 2). In contrast, in the orthopedic and deconditioning groups, we observed no significant differences in FIM gains and efficiency between the high and low RDW groups.

As the group of stroke patients with normal RDW had a lower prevalence of anemia, higher albumin levels, and lower creatinine levels, we performed multiple linear regression analysis to test for predictors of high FIM change and FIM efficiency scores. As the confounders included as covariates are influenced by age, we checked and found no multicollinearity (Table 3). Our results suggested that high RDW was not independently associated with worse total and motor FIM change scores (β coefficient = -4.76, p = 0.47 and β coefficient = -2.47, p = 0.68, respectively). High RDW was also not independently associated with worse total and motor FIM efficiency scores (β coefficient = -0.18, p = 0.58 and β coefficient = -0.10, p = 0.72, respectively). None of the other variables tested, including age, sex, congestive heart failure, and baseline hemoglobin, albumin, and creatinine levels were predictive of higher FIM change or efficiency.

DISCUSSION

The present prospective study of a consecutive cohort of patients hospitalized for rehabilitation focused on the relationship between RDW and rehabilitation outcome as assessed by FIM score. The results showed significant differences in functional gains during rehabilitation between patients with normal and high RDW hospitalized for stroke rehabilitation. We found that high RDW was associated with small gain and low efficiency of total and motor FIM during rehabilitation. The association between high RDW and functional outcomes was not observed in other rehabilitation patients (orthopedic and deconditioning). To our knowledge, this is the first study to compare the effects of high RDW on rehabilitation outcomes in these patients and to suggest its negative effects on functional outcomes. These results did not remain statistically significant after multiple regression analysis accounting for the effects of confounders including age, sex, and baseline hemoglobin, albumin, and creatinine levels. This finding supports the assumption that high RDW is not an independent risk factor of rehabilitation outcomes in stroke patients.

Most previous investigations of RDW in stroke patients were retrospective studies in patients with acute ischemic stroke that analyzed RDW as a predictor of long-term mortality. Among patients with ischemic stroke, higher RDW was predictive of higher mortality. Previous studies reported an association between higher RDW and worse functional outcome 3 months and 1 year after the stroke; however, the relative weights of mortality and rehabilitation on that outcome from these studies remain unclear.

Despite our finding that high RDW was associated with small gain and low efficiency of total and motor FIM during rehabilitation in stroke patients multiple linear regression analysis did not support its role as a specific predictor of stroke rehabilitation outcome. We propose that the role of RDW as a predictor of successful rehabilitation is not specifically implicated in the pathogenesis or process of stroke and that it should instead be interpreted as a general prognostic marker as it was associated with mortality in the general population, patients with ischemic heart disease, and those with metabolic syndrome and heart failure, among others. Other factors, including oxidative stress, impaired iron mobilization, inflammation, undernutrition, and impaired renal function are some of the pathophysiological mechanisms postulated as mediators of the association between elevated RDW and clinical endpoints.

The underlying mechanisms by which RDW predicts adverse clinical endpoints remain unknown. Red blood cell transports oxygen to tissues such as peripheral muscle. Increased RDW signifies increased numbers of red blood cells with incomplete oxygen binding to hemoglobin such as premature erythrocytes in iron deficiency anemia. Higher RDW levels may affect oxygen transport capacity, resulting in adverse clinical outcomes. Recent studies...
<table>
<thead>
<tr>
<th>Variable</th>
<th>Stroke group (n = 50)</th>
<th>Orthopedic group (n = 125)</th>
<th>Deconditioning group (n = 56)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>75.6 ± 7.6</td>
<td>79.8 ± 7.0</td>
<td>77.8 ± 9.4</td>
<td>0.100</td>
</tr>
<tr>
<td>Female</td>
<td>16 (43.2)</td>
<td>8 (61.5)</td>
<td>22 (66.2)</td>
<td>0.260</td>
</tr>
<tr>
<td>Sociodemographic characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS score at the ER</td>
<td>12.69 ± 5.81</td>
<td>13.21 ± 3.89</td>
<td>-</td>
<td>0.320</td>
</tr>
<tr>
<td>Number of chronic diseases</td>
<td>4.51 ± 1.17</td>
<td>4.92 ± 1.04</td>
<td>4.60 ± 1.43</td>
<td>0.270</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>2.43 ± 1.80</td>
<td>2.85 ± 1.90</td>
<td>2.34 ± 2.30</td>
<td>0.370</td>
</tr>
<tr>
<td>Delirium</td>
<td>1 (2.7)</td>
<td>1 (7.7)</td>
<td>5 (7.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Post-stroke state</td>
<td>12 (32.4)</td>
<td>5 (38.5)</td>
<td>10 (15.4)</td>
<td>0.740</td>
</tr>
<tr>
<td>CHF</td>
<td>4 (10.8)</td>
<td>6 (46.2)</td>
<td>17 (26.2)</td>
<td>0.046</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13 (35.1)</td>
<td>6 (46.2)</td>
<td>25 (36.1)</td>
<td>0.520</td>
</tr>
<tr>
<td>Cancer</td>
<td>9 (24.3)</td>
<td>1 (7.7)</td>
<td>11 (16.9)</td>
<td>0.260</td>
</tr>
<tr>
<td>COPD</td>
<td>1 (2.7)</td>
<td>2 (15.4)</td>
<td>7 (10.8)</td>
<td>0.160</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>1 (2.7)</td>
<td>0 (0.0)</td>
<td>3 (4.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Chronic diseases and medication use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline hemoglobin (g/dL)</td>
<td>13.2 ± 1.9</td>
<td>11.3 ± 1.9</td>
<td>10.8 ± 1.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Anemia (WHO)</td>
<td>16 (43.2)</td>
<td>10 (77.0)</td>
<td>58 (89.2)</td>
<td>0.037</td>
</tr>
<tr>
<td>Mean corpuscular volume (μm³)</td>
<td>86.7 ± 3.87</td>
<td>84.4 ± 4.4</td>
<td>88.1 ± 4.0</td>
<td>0.130</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.66 ± 0.45</td>
<td>3.22 ± 0.54</td>
<td>3.31 ± 0.40</td>
<td>0.009</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>22.1 ± 25.7</td>
<td>33.4 ± 48.9</td>
<td>59.1 ± 44.3</td>
<td>0.380</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.18 ± 1.15</td>
<td>1.23 ± 1.87</td>
<td>1.0 ± 0.93</td>
<td>0.007</td>
</tr>
<tr>
<td>Blood analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cognitive impairment (CDR = 0)</td>
<td>7 (19.0)</td>
<td>2 (15.4)</td>
<td>21 (32.3)</td>
<td>0.024</td>
</tr>
<tr>
<td>Mild cognitive impairment (CDR = 0.5)</td>
<td>13 (35.0)</td>
<td>4 (30.8)</td>
<td>19 (29.2)</td>
<td>0.077</td>
</tr>
<tr>
<td>Cognitive impairment (CDR = 1)</td>
<td>10 (77.0)</td>
<td>4 (30.8)</td>
<td>13 (20.0)</td>
<td>0.100</td>
</tr>
<tr>
<td>Cognitive impairment (CDR = 2)</td>
<td>7 (19.0)</td>
<td>0 (0.0)</td>
<td>10 (15.4)</td>
<td>0.000</td>
</tr>
<tr>
<td>Cognitive impairment (CDR = 3)</td>
<td>0 (0.0)</td>
<td>3 (23.1)</td>
<td>0 (0.0)</td>
<td>0.000</td>
</tr>
<tr>
<td>Rehabilitation period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization period (day)</td>
<td>35.7 ± 17.6</td>
<td>42.1 ± 18.8</td>
<td>35.3 ± 18.8</td>
<td>0.310</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%).

RDW, red cell distribution width; NIHSS, National Institutes of Health Stroke Scale; ER, emergency room; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; WHO, World Health Organization; CRP, C-reactive protein; CDR, Clinical Dementia Rating scale.
Table 2. Functional recovery of the participants (high vs. normal RDW) over time (unadjusted associations)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stroke group (n = 50)</th>
<th>Orthopedic group (n = 125)</th>
<th>Deconditioning group (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal RDW (n = 37)</td>
<td>High RDW (n = 13)</td>
<td>Normal RDW (n = 65)</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td>Total FIM change</td>
<td>32.4 ± 18.2</td>
<td>18.1 ± 12.9</td>
<td>25.8 ± 13.0</td>
</tr>
<tr>
<td>Motor FIM change</td>
<td>26.5 ± 16.0</td>
<td>15.2 ± 13.1</td>
<td>21.9 ± 11.9</td>
</tr>
<tr>
<td>Total FIM efficiency</td>
<td>1.17 ± 0.88</td>
<td>0.57 ± 0.62</td>
<td>0.94 ± 0.70</td>
</tr>
<tr>
<td>Motor FIM efficiency</td>
<td>0.99 ± 0.74</td>
<td>0.47 ± 0.58</td>
<td>0.80 ± 0.70</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
RDW, red cell distribution width; FIM, Functional Independence Measure.

FIM efficiency = \frac{\text{Total FIM change}}{\text{Length of rehabilitation stay (day)}}

Table 3. Associations between baseline characteristics and study outcomes in the stroke group (normal and high RDW, adjusted analyses)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total FIM change</th>
<th>Total FIM efficiency</th>
<th>Motor FIM change</th>
<th>Motor FIM efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β coefficient</td>
<td>p-value</td>
<td>β coefficient</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>High RDW</td>
<td>-4.76 (-17.90, 8.40)</td>
<td>0.47</td>
<td>-0.18 (-0.83, 0.47)</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-2.47 (-14.38, 9.44)</td>
<td>0.68</td>
</tr>
<tr>
<td>Female</td>
<td>4.65 (-6.00, 15.30)</td>
<td>0.38</td>
<td>0.27 (-0.26, 0.79)</td>
<td>0.31</td>
</tr>
<tr>
<td>Age</td>
<td>0.0003 (-0.67, 0.67)</td>
<td>0.99</td>
<td>-0.002 (-0.04, 0.03)</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-0.14 (-0.75, 0.47)</td>
<td>0.65</td>
</tr>
<tr>
<td>CHF</td>
<td>-12.15 (-25.65, 1.35)</td>
<td>0.08</td>
<td>-0.48 (-1.14, 0.19)</td>
<td>0.15</td>
</tr>
<tr>
<td>Baseline hemoglobin</td>
<td>1.44 (-2.05, 4.92)</td>
<td>0.41</td>
<td>0.035 (-0.14, 0.21)</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.60 (-1.56, 4.74)</td>
<td>0.32</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.82 (-9.53, 17.17)</td>
<td>0.57</td>
<td>0.27 (-0.39, 0.93)</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.27 (-9.82, 14.36)</td>
<td>0.71</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.33 (-3.83, 4.48)</td>
<td>0.88</td>
<td>-0.041 (-0.25, 0.16)</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-0.30 (-4.06, 3.46)</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-0.06 (-0.23, 0.11)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

RDW, red cell distribution width; FIM, Functional Independence Measure; CI, confidence interval; CHF, congestive heart failure.

demonstrated inverse correlations between peak oxygen uptake and RDW, with peak oxygen uptake increasing and RDW decreasing before and after exercise training. A previous study showed that higher RDW levels were related to impaired exercise capacity and that exercise training decreased RDW in patients with chronic heart failure. These findings suggest that the mechanisms of RDW as a predictor of adverse clinical endpoints may be connected to erythrocyte proliferation in the bone marrow.

The mechanisms underlying the association between RDW and outcome of stroke rehabilitation but not in orthopedic or deconditioning rehabilitation are not fully understood. We hypothesize that, because erythropoiesis is affected by numerous chronic disease factors including inflammation, kidney diseases, malignancies, autoimmune diseases as well as oxidative stress and different acute-phase inflammatory markers, RDW mirrors chronic disease (as reflected in our data) and may, thus, be viewed as a nonspecific but outcome-relevant "chronic disease marker". Such a marker may be better reflected in chronic atherosclerotic patients, such as those with stroke.

Previous studies have analyzed the effects of RDW on survival. Most studies reporting the relationship between RDW and age found that a higher RDW was consistently associated with older age, which is a major determinant of survival. Assessment of the interaction between these variables revealed that the role of RDW in predicting mortality depends on age and confirmed the association between higher RDW values and increased mortality in most cases in older patients. This important bias needs to be addressed in studies analyzing the effect of RDW on survival.

The strengths of the present study are its prospective design including a large sample of patients who had experienced a stroke and underwent a rehabilitation program in a ward dedicated to the rehabilitation of older stroke patients. To the best of our knowledge, this study is the first to focus on the specific role of RDW value in rehabilitation. Another strength of the study was the use of the FIM as a structured assessment tool. This scale has benefits over other widely used scales. The use of the FIM to analyze our data was advantageous as it shows lower ceiling and floor effects compared to those of other scales. Thus, the FIM likely measured the functional gains during rehabilitation with greater accuracy.

However, this study also has several limitations that should be considered. First, the study cohort was restricted to older patients hospitalized for rehabilitation. Assessing the possibility that RDW value may provide prognostic information for rehabilitation only
in this cohort excluded a number of community-dwelling older adults and younger people who experienced a stroke but were not hospitalized in an institution dedicated to stroke rehabilitation. Second, although the natural history of functional recovery was described, the mediators of improvement cannot be concluded. For example, whether rehabilitation therapy or expertise were similar between groups was unknown, although we compared the time, in days, that patients spent in rehabilitation and in our hospital. Such patients usually receive the same rehabilitation program.

In conclusion, older patients with high RDW before being hospitalized for stroke rehabilitation had less recovery of functional status compared to adults who suffered a stroke but had normal RDW. However, high RDW was not an independent risk factor for rehabilitation outcomes.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, EZ, EA; Data curation, EZ, YP; Investigation, EZ, IS, YP, RS, SC, BNF, EA; Methodology, EZ, IS, EA; Project administration, EZ, EA; Supervision, EA; Writing-original draft, EZ, RS, SC, BNF, EA; Writing-review and editing, EA.

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INTRODUCTION

Breast cancer is one of the most common female malignancies with an increasing incidence not only in Western but also in Asian countries. In particular, the rate of older patients with breast cancer is rising with the increase in the number of older people. Although there are no set standards for aged patients, the tumor biological characteristics differ between patients aged over 70 or 80 years compared to those in younger patients. Lodi et al. reported larger tumor sizes, more frequent positive lymph nodes and distant metastases, and higher breast cancer-specific mortality in patients aged over 80 years than in patients aged 70 to 79 years. Jeon et al. reported larger tumor sizes and higher pathologic stages in patients aged over 75 years than in patients younger than 75 years.

While various guidelines have been recommended by countries and organizations for breast cancer diagnosis and treatment, it is difficult to apply uniform treatments to older patients with breast cancer who are more susceptible to comorbidities and have less ability to tolerate and adhere to treatment than younger people.

Thus, modified treatment is required in these cases. This case report describes an older patient with breast cancer who was maintained for 8 years with non-surgical primary treatments and minimized surgery. We also present some points to consider regarding older patients with breast cancer as the aging population grows.

CASE REPORT

In 2011, a 74-year-old woman visited our hospital with a palpable lesion in her right breast. Physical examination revealed a hard, movable, and non-tender mass. She was diagnosed with breast cancer 10 years ago. Laboratory studies revealed high hemoglobin A1c, serum glucose, and urine micro-albumin levels. She had diabetic retinopathy and had undergone pseudophakia surgery. She had symptoms of resting and postural regular tremors, especially in her finger, as well as intermittent tinnitus in both ears. She was diagnosed with lumbar stenosis and had difficulty in movement due to lumbago. She was taking various medications for her comorbidities. Although she had been recommend-
ed to undergo further breast studies a year earlier, she could not spare time to be examined because she was taking care of her husband, who had dementia.

The mammogram showed an irregular hyperdense mass in the right upper central deep breast (Fig. 1A, 1B). Ultrasound (US) of the palpable lesion showed an approximately 2.7-cm irregular hypoechoic mass in the right upper central breast located 3-cm from the right nipple (Fig. 1C). An additional 0.8-cm irregular hypoechoic mass was found on the right upper outer breast, 2.5-cm from the large palpable mass (Fig. 1D). Multifocal breast malignancy was strongly suspected. No suspicious lesions were identified in the left breast or either axilla. A US-guided core biopsy of the palpable mass in the right upper central breast confirmed invasive ductal carcinoma. The modified Black nuclear and histologic grade was 2 and immunohistochemical analyses showed estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and tumor suppressor p53-positivity, as well as moderate Ki-67 protein.

Surgery was recommended based on the imaging findings and pathology results. Since the two masses were located 2.5-cm apart, the range of surgery was wider than if only one mass was removed. Even when considering the separate removal of the two masses, one of the lesions required additional preoperative procedures for breast localization due to its small size. Therefore, regardless of which method was selected, general anesthesia was required for surgery. However, the patient refused any operation due to her co-morbidities and her need to care for her husband. Thus, endocrine and radiation therapy were chosen as treatment alternatives. F-18 fluorodeoxyglucose (FDG) PET-CT was performed to confirm that there was no distant metastasis and bone mineral densitometry was performed before medication was administered. She underwent radiation therapy with a total of 5,000 cGy (25 fractions in 5 weeks) to the whole breast followed by 1,600 cGy (8 fractions over 2 weeks) for the breast mass. She was prescribed a selective estrogen receptor modulator, Fareston (Orion Corporation, Espoo, Finland), along with Dicamax (DalimBiotech, Seoul, Korea) and Bonviva (Roche, Basel, Switzerland) to manage osteoporosis.

At 3- and 9-month follow-ups after treatment initiation, the right upper central palpable mass had gradually decreased in size and was not observed at all in the US conducted one and a half years later (Fig. 2). The right upper outer small lesion had slightly decreased at the 9-month follow-up after treatment initiation and was measured at the smallest size 2 years 4 months later (Fig. 3A). The patient continued to take medication, accompanied by breast US and physical examinations. At the 4 years 4 months follow-up, the right upper central mass remained invisible; however, the right upper outer lesion, which had been somewhat stable, began to increase in size (Fig. 3B). On the subsequent follow-ups, the lesion size increased continuously (Fig. 3C, 3D). We recommended surgery again due to the clear growing trend of the mass. However, the patient was very reluctant to undergo general anesthesia. Therefore, we instead performed an excision under local anesthesia and finally removed the remaining mass 5 years 7 months since the first diagnosis of breast malignancy. The mass was confirmed as invasive ductal carcinoma, measuring 2.0 × 1.0 × 1.0 cm. Immunohistochemistry showed ER and PR positivity, and borderline HER2 positivity. After surgery, the patient was prescribed an aromatase inhibitor, Femara (Novartis, Basel, Switzerland), as well as Dicamax and Fosamax (Merck Sharp & Dohme Corp., Kenilworth, NJ, USA) to manage osteoporosis. A follow-up study conducted in July 2019, 2 years after the surgery and 8 years after the first diagnosis, showed no signs of recurrence or metastasis.

Fig. 1. Initial mammogram and ultrasonography of the patient. (A, B) Right craniocaudal and mediolateral oblique mammogram showing an irregular hyperdense mass in the right upper central deep breast with a spiculated margin. (C) On ultrasound, the palpable lesion shows an approximately 2.7-cm irregular hypoechoic mass with angular margin and microcalcifications in the right upper central breast. (D) An additional small irregular hypoechoic mass was found in her right upper outer breast, with an angular margin and vertical orientation.
This report was approved by the Institutional Review Board of our hospital, with informed consent from the patient waived.

DISCUSSION

Breast cancer is one of the most common female cancers worldwide, accounting for 24.2% of new cases in 2018. Statistics compiled in Korea in 2017 also showed breast cancer to be the most common type of cancer in women, representing 20.3% of new female cancers. The rate of breast cancer has been rising constantly since 1999 when statistics first started to be compiled in Korea. As a result, the proportion of older patients with breast cancer has also increased, with the incidence of breast cancer at age 70 years or older increasing from 5.34% (444/5,708 cases) in 2003 to 9.87% (2,148/21,747 cases) in 2016.

Many countries have developed their own guidelines for breast cancer diagnosis and treatment. The Korean Society for Breast Cancer announced its 8th medical recommendation in 2019. The policy for older patients is that sentinel lymph node biopsy or axillary lymph node dissection can be selectively conducted if the information on the axillary lymph node does not affect the patient’s treatment decision. Postoperative radiation therapy is not conducted in patients aged over 70 years with tumors measuring less than 3-cm, negative axillary lymph nodes, positive hormone receptors, and clear resection margins, taking into account the comorbidities and life expectancy; and endocrine therapy alone is also possible. For patients aged 70 years and older, chemotherapy is individually determined based on the patient’s comorbidities and general condition. The National Comprehensive Cancer Network (NCCN) separately provides guidelines for “older adult oncology” in which patients with high risks of dying or suffering from cancer to receive palliative care. In treatable conditions, patient ability to withstand cancer treatment or comprehensive geriatric assessment should be evaluated in advance.

In our case, the treatment choices included breast conserving surgery with or without radiation therapy or mastectomy, sentinel lymph node biopsy with or without axillary lymph node dissection, endocrine therapy based on ER/PR positivity, and/or chemotherapy.

Endocrine therapy is a useful non-surgical treatment for ER-positive older patients. A study in women aged over 75 years who took...
hormonal therapy without surgery despite being surgical candidates, reported that the reasons for primary endocrine therapy included older age, increased comorbidities, and patient choice. The International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialist (EUSOMA) updated their recommendations in 2012 to support the use of primary endocrine therapy for patients with hormone receptor-positive tumors with short life expectancy or who are unfit for or refuse surgery. Endocrine therapy can significantly reduce the mass size although at a slower rate than that with chemotherapy. Primary endocrine therapy can control tumor growth for approximately 18 to 24 months. The time to onset of response may take several months or longer. Radiation therapy is usually offered to patients with tumors larger than 5-cm, locally advanced tumors, close surgical margins near the tumors, and more than four positive axillary lymph nodes to lower local recurrence. Poleszczuk et al. reported that preoperative radiotherapy for early-stage breast cancer may improve disease-free survival without decreasing overall survival. They suggested preoperative radiotherapy followed by preoperative endocrine therapy and lumpectomy. The NCCN Guidelines recommend that considerations for older patients undergoing radiation therapy depend on the anatomic site being radiated and the dose/fractionation chosen.

In this case, radiotherapy and endocrine therapy were administered simultaneously and a decrease in one of the mass was confirmed at 3-month follow-up. Thus, we could not determine which treatment had a greater effect. However, since radiation therapy was implemented in the early stages of treatment and endocrine therapy continued, we believe that endocrine therapy played a major role in stabilizing the remaining mass for approximately 5 years before it increased in size. The ultimate treatment for breast cancer is surgery. This patient underwent surgery for the mass under local anesthesia due to her reluctance regarding general anesthesia.

In conclusion, although surgery is the ultimate treatment for breast cancer, a modified treatment process could be considered for older patients with physical limitations and complex comorbidities. The patient’s choice or rejection of surgery are also important reasons for considering alternative treatments. Hormonal or radiation therapy could be an important primary treatment in those cases. If the lesions remain and the patient is cooperative, close follow-ups can be implemented to detect lesion progression. If the lesion is small enough and general anesthesia is risky for the patient, surgery with local anesthesia may be a possible alternative.

**ACKNOWLEDGMENTS**

**CONFLICT OF INTEREST**

The researchers claim no conflicts of interest.

**AUTHOR CONTRIBUTIONS**

Conceptualization, JKA; Writing-original draft, JKA; Writing-review & editing, JJW, HYK.

**REFERENCES**

Acute Hydronephrosis owing to A Giant Fecaloma in an Older Patient

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²Department of Nephrology, Hallym University Sacred Heart Hospital, Anyang, Korea

Hydronephrosis with acute urinary tract obstruction can lead to serious complications such as obstructive nephropathy or pyelonephritis. We report the first case of hydronephrosis caused by a giant fecaloma in an 83-year-old woman accompanied with chronic constipation in Korea. The patient with a fever presented to the emergency room and was diagnosed with right hydronephrosis. Computed tomography revealed a markedly dilated rectum with a giant fecaloma compressing the right vesicoureteric junction. Hydronephrosis was resolved through manual disimpaction of the fecaloma and simultaneous lavage with rectal tubes, which improved the acute pyelonephritis and renal function. Chronic constipation can lead to giant fecaloma threatening urinary tract patency, especially in older patients with immobility or dehydration. Therefore, clinicians should consider this condition as a rare but possible cause of hydronephrosis in older patients with chronic constipation.

Key Words: Hydronephrosis, Fecal impaction, Elderly

INTRODUCTION

Acute urinary tract obstruction can cause acute kidney damage and urinary tract infections, which can lead to potentially fatal complications. Although rare, acute urinary tract obstruction can be caused by compression of the gastrointestinal (GI) tract. Some cases of acute urinary tract obstruction by giant fecalomas caused by chronic constipation have been reported in patients with immobility and dehydration.² In addition, constipation and fecal impaction are common clinical problems in older adults.²

Even with its clinical relevance, chronic constipation is rarely suspected as a predisposing cause of urinary tract obstruction. To date, there have been no reports of fecaloma-related acute hydronephrosis owing to chronic constipation in Korea. Here, we report a case of acute hydronephrosis owing to a giant fecaloma in an older patient.

CASE REPORT

An 83-year-old woman with a fever presented to the emergency room. She had a 10-year history of chronic constipation and was in a long-term bedridden state owing to a previous history of right femur fracture, cerebral infarction, and dementia. She had no history of abdominal surgery, inflammatory bowel disease, or anatomical abnormalities of the GI tract. Some cases of acute urinary tract obstruction by giant fecalomas caused by chronic constipation have been reported in patients with immobility and dehydration.¹ In addition, constipation and fecal impaction are common clinical problems in older adults.²

Even with its clinical relevance, chronic constipation is rarely suspected as a predisposing cause of urinary tract obstruction. To date, there have been no reports of fecaloma-related acute hydronephrosis owing to chronic constipation in Korea. Here, we report a case of acute hydronephrosis owing to a giant fecaloma in an older patient.

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urine analysis.

Serum blood urea nitrogen (BUN) and creatinine concentrations were mildly increased to 43.0 mg/dL and 0.93 mg/dL, respectively. Blood and urine microbiological cultures grew *Escherichia coli* sensitive to all tested antibiotic agents. A Foley catheter was introduced into the urinary bladder, and the remaining urine volume was 50 mL. Computed tomography revealed a markedly dilated rectum with a giant fecaloma compressing the right lower ureter and vesicoureteric junction, resulting in right hydronephrosis (Fig. 1). Through the manual release of the fecaloma and simultaneous enema with rectal tubes, fecal impaction and rectal dilatation were resolved. Subsequently, hydroureteronephrosis was resolved, which was confirmed by ultrasonography (Fig. 2). Acute pyelonephritis and renal function improved and the patient’s BUN and serum creatinine concentrations decreased to 19.6 mg/dL and 0.69 mg/dL, respectively. In addition, the serum C-reactive protein concentration decreased to 7.77 mg/L. The patient was discharged in good medical condition with normal renal and bowel functions.

The present case report was reviewed by the Institutional Review Board of Hallym University Sacred Heart Hospital (No. HALLYM 2020-05-011), and informed consent was obtained from the patient for publication.

DISCUSSION

Fecal impaction can be caused by GI tract damage owing to Hirschsprung disease, prior intestinal surgeries, and anorectal malformations.\(^3\)\(^,\)\(^5\) However, chronic constipation is also a common cause of fecal impaction, especially in older adults.\(^6\) A fecaloma is a mass of inspis-

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Fig. 1. Hydroureteronephrosis caused by a giant fecaloma in the rectum. (A) Computed tomography (CT) of the abdomen-pelvis showing hydronephrosis in the right kidney. (B) CT of the abdomen-pelvis showing a huge distended rectum containing a giant fecaloma pushing the urinary bladder anteriorly and compressing the vesicoureteral junction. (C) CT of the abdomen-pelvis showing right hydroureter owing to a markedly dilated rectum caused by the huge fecaloma. (D) Giant fecaloma is visible in the kidney-ureter-bladder image.

Fig. 2. Kidney ultrasound demonstrating a longitudinal view of normalized kidneys and a shape with the resolution of hydronephrosis in the right kidney.
sated stool that results from the accumulation of feces in the rectum or rectosigmoid colon. Fecalomas are much harder in consistency than a fecal impaction and can cause a mass effect that compresses adjacent anatomical structures, leading to potentially fatal complications unless appropriately treated. 1-7 In the literature, fecalomas can reportedly lead to bowel ischemia, bowel perforation, and peritonitis. 7,8 However, obstructive nephropathy with compression by fecalomas owing to chronic constipation is rarely reported. 8,9 Fecaloma can result in a marked dilatation of the rectosigmoid colon, subsequently leading to extrinsic ureteral compression and acute urinary tract obstruction owing to anterior displacement of the bladder base. 10 Bedridden patients with immobility owing to neurological or traumatic sequelae are at a higher risk of developing urinary tract obstruction caused by chronic constipation-induced fecalomas, especially if they are superimposed by insufficient fluid intake, dehydration, or administration of drugs that decrease GI tract motility. 11-14 Moreover, patients with schizoaffective disorders who are receiving antipsychotic, anticholinergic, tricyclic antidepressant, and antiserotonergic medication are also at a higher risk. 12-15 Consistent with these reports, our patient was also bedridden owing to a previous cerebral infarction and femur fracture; she also had a history of chronic constipation. Moreover, her medical records confirmed that the patient had been taking analgesics for the femur fracture. Because it was difficult to communicate with the patient owing to advanced dementia, we assumed that she could not complain about her symptoms until hydronephrosis resulting from the giant fecaloma occurred.

Besides unilateral or bilateral acute kidney injury, urinary tract obstruction caused by giant fecalomas can lead to acute pyelonephritis or emphysematous pyelonephritis; therefore, urgent treatment, including the removal of the cause, is necessary. 8 Most fecal impactions are successfully treated by conservative methods such as laxatives, manual disimpaction, including digital evacuation, or transrectal enemas. 14,16 In cases refractory to conservative methods, an endoscopic approach for removing fecalomas has also been described. 15,16 Surgery is required only in severe cases. 13 Fortunately, conservative treatment with rectal enema and digital evacuation was successful in our patient.

Although extremely rare, fecal impaction should be considered in the differential diagnosis of acute obstructive nephropathy, especially in older patients with limited mobility, history of cerebrovascular accidents, and intake of agents that decrease bowel movements. Chronic constipation can lead to giant fecaloma threatening urinary tract patency, especially in older people with immobility and dehydration or those who are taking analgesics that decrease GI motility. Although giant fecalomas are rare causes of acute obstructive nephropathy or pyelonephritis, physicians should consider them as possible causes of hydronephrosis in older patients with chronic constipation.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, HSL; Data curation, NJ, HSL; Investigation, NJ, HSL; Methodology, NJ, HSL; Project administration, HSL; Supervision, HSL; Writing—original draft, NJ, HSL; Writing—review & editing, NJ, HSL.

REFERENCES


Tackling Instrumental Activities of Daily Living: Time to Start Rethinking Items

Soong-nang Jang
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I read with great pleasure the Letter to the Editor by Kim and Won regarding our study as the authors are dedicated researchers who develop instruments and pursue important issues concerning functional status and frailty measurements in Korea. I respect these scholars and have used the Korean versions of the Activities of Daily Living (K-ADL) and Instrumental Activity of Daily Living (K-IADL) scales developed by Dr. Won in my previous studies on disability. The motivation for our item response theory (IRT) research was prompted during international comparative studies on disability rates. Each country has somewhat different IADL items and differential item functioning (DIF) even for the same items. Thus, there might be potential measurement biases in disability comparisons across international surveys of aging. Without considering DIF, the disability rates of specific societies may not be free with possible misinterpretation. However, we realized that IRT analyses of the K-ADL and K-IADL were lacking.

Regimes, politics, and policies are ultimately rooted in the psychosocial background of a society such that the social-cultural context cannot be easily changed. In terms of understanding cultural differences, empirical analysis results should be accumulated more closely. Identifying a policy direction that fits the cultural and practical perspectives will ensure compliance and sustainability of healthy aging policies. To better understand how societies’ care for older adults works, it is necessary to expand institutional variation and conduct international comparative studies as a wider scope of political, policy, and social elements to confirm the relevance that allows a clearer association between individual and social factors for healthy aging.

Items in certain scales might be biased with respect to difficulty and/or discrimination. Item bias is the degree to which the items comprising a measurement scale are systematically related to various exogenous variables (e.g., age, gender, and socioeconomic position) after conditioning for the latent variable of interest. Item difficulty bias occurs when one group, such as women, responds higher on a certain item after being matched to men on the total scale score. Item discrimination bias occurs when the item difficulty bias (between two groups matched for the latent variable) increases or decreases as a function of the level of the latent variable.

If the current Korean older generations, such as baby boomers, progress to “gender egalitarians” (as Kim & Won mentioned), it is reasonable to consider changing some of the response options and items in the K-IADL. For example, “household chores” and “preparing meals” require consideration regarding whether response options, such as “never have done before” or “don’t do even though I can”, have to be maintained only because they are “men”. Many Korean researchers have excluded three items related to household tasks (household chores, preparing meals, and doing laundry) from the K-IADL in their analyses of men because of these niggling additional responses. However, for analysis, whether it remains valid and justifiable to remove items corresponding to household tasks only in men requires further evaluation. I would like to specifically ask the following research question: which items should be excluded from men, and which items should be excluded from women and why? My aim was not to assess gender differences in the status of disability for each ADL and IADL item but rather to examine the reliability of the scales according to gender.

Our findings indicated that only two items in the K-IADL (Grooming and Take medications) did not show a response bias. The IADLs were originally designed to assess a more complex range of functioning, in that they require more skill, judgment, and independence than those required for ADLs. They measure an individual’s functioning in the social world and the world outside the home. Given this, can we achieve the value of IADLs with only two valid items? Item bias analyses often use a “purified subscale” method, in which the purified subscale is defined as the total scale score minus the biased items. Our study was performed to as-
sess whether the choice of refined scale is clear in real data. We believe this is the beginning; the ultimate implication is that additional research is needed on how to improve K-IADL items.

Finally, it is important to have a clear conceptual framework for any measure. ADLs and IADLs are useful for measuring progress toward healthcare goals and encouraging geriatricians caring for patients to shift their attention toward providing comprehensive help for their older patients with disabilities. For this fundamental value of ADLs and IADLs, we can describe “disability” according to “how much help is needed” in the K-ADL and K-IADL. The IADL scale fits well for disability when qualifying phrases concerning social and cultural factors are included.

It may not be possible to completely control for bias in all measurements. However, the establishment of item invariance is of prime importance for drawing unbiased inferences in gerontological research using multi-item functional status measurements. The results have methodological and substantive implications for the suitable use of IADL for all ages, genders, and socioeconomic positions. There is a need to rethink the K-IADL for comprehensive geriatric care and long-term care services. Improved measurements may help clarify scientific evidence for the development of policies toward healthy aging societies.

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CONFLICT OF INTEREST
The author claims no conflicts of interest.

REFERENCES


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We would like to invite members of the Korean Geriatric Society and anyone who are interested.

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- All manuscripts must be written in clearly understandable English. Authors whose first language is not English are requested to have their manuscripts checked for grammatical and linguistic correctness before submission. Correct medical terminology should be used, and jargon should be avoided.
- The use of abbreviations should be minimized and restricted to those that are generally recognized. When using an abbreviated word, it should be spelled out in full on first usage in the manuscript, followed by the abbreviation in parentheses.
- Numbers should be written in Arabic numerals, but must be spelled out when placed at the beginning of a sentence.
- Drugs and chemicals should be referred to using standard chemical or generic terms. The names and locations (city, state, and country only) of manufacturers of equipment and non-generic drugs should be given.
- Measurements should be described using the metric system, and hematologic and biochemical markers using the International System of Units. All units must be preceded by one space, except for the following symbols: percentage (%), temperature (°C), and degree (°).

All authors of a manuscript must have agreed to its submission and are responsible for its content, including appropriate citations and acknowledgements; they must also have agreed that the corresponding author has the authority to act on their behalf on all matters pertaining to the publication of the paper. By publishing in this journal, the authors agree that the Korean Geriatrics Society
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Table 1. Recommended maximums for articles submitted to AGMR

<table>
<thead>
<tr>
<th>Type of article</th>
<th>Abstract (word)</th>
<th>Text (word)</th>
<th>Reference</th>
<th>Table &amp; figure</th>
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<tr>
<td>Original article</td>
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<td>Review</td>
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<td>Case report</td>
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<td>Editorial</td>
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a) Maximum number of words is exclusive of the abstract, references, tables, and figure legends.

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