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Review

# Sarcopenia in Asia: Consensus Report of the Asian Working Group for Sarcopenia

Liang-Kung Chen MD, PhD [a,*], Li-Kuo Liu MD, PhD [a], Jean Woo MD [b], Prasert Assantachai MD, PhD [c], Tung-Wai Auyeung MD [b], Kamaruzzaman Shahrul Bahyah MD [d], Ming-Yueh Chou MD [e], Liang-Yu Chen MD [a], Pi-Shan Hsu MD [f], Orapitchaya Krairit MD [g], Jenny S.W. Lee MD [b], Wei-Ju Lee MD, MSc [h], Yunhwan Lee MD, PhD [i], Chih-Kuang Liang MD [e], Panita Limpawattana MD, PhD [j], Chu-Sheng Lin MD [k], Li-Ning Peng MD, MSc [a], Shosuke Satake MD, PhD [l], Takao Suzuki MD, PhD [m], Chang Won Won MD, PhD [n], Chih-Hsing Wu MD [o], Si-Nan Wu MD [p], Teimei Zhang MD, PhD [p], Ping Zeng MD [p], Masahiro Akishita MD, PhD [q], Hidenori Arai MD, PhD [r,*]

[a] *Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, Taipei, Taiwan*
[b] *The S H Ho Centre for Gerontology and Geriatrics, The Chinese University of Hong Kong, Hong Kong, China*
[c] *Department of Preventive and Social Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand*
[d] *Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia*
[e] *Geriatric Medicine Center, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[f] *Department of Family Medicine, Taichung Hospital, Ministry of Health and Welfare, Taichung, Taiwan*
[g] *Department of Internal Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*
[h] *Department of Family Medicine, Taipei Veterans General Hospital Yuanshan Branch, I-Land, Taiwan*
[i] *Department of Preventive Medicine and Public Health, Ajou University School of Medicine, Suwon, South Korea*
[j] *Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*
[k] *Center for Geriatrics and Gerontology, Taichung Veterans General Hospital, Taichung, Taiwan*
[l] *Department of Comprehensive Geriatric Medicine, National Center for Geriatrics and Gerontology, Obu, Japan*
[m] *Research Institute, National Center for Geriatrics and Gerontology, Obu, Japan*
[n] *Department of Family Medicine, Kyung Hee University School of Medicine, Seoul, South Korea*
[o] *Department of Family Medicine, National Cheng Kung University Hospital and College of Medicine, Tainan, Taiwan*
[p] *Beijing Institute of Geriatrics, Beijing Hospital, Ministry of Health, Beijing, China*
[q] *Department of Human Health Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan*
[r] *Department of Geriatric Medicine, Graduate School of Medicine, University of Tokyo, Tokyo, Japan*

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A B S T R A C T

Sarcopenia, a newly recognized geriatric syndrome, is characterized by age-related decline of skeletal muscle plus low muscle strength and/or physical performance. Previous studies have confirmed the association of sarcopenia and adverse health outcomes, such as falls, disability, hospital admission, long term care placement, poorer quality of life, and mortality, which denotes the importance of sarcopenia in the health care for older people. Despite the clinical significance of sarcopenia, the operational definition of sarcopenia and standardized intervention programs are still lacking. It is generally agreed by the different working groups for sarcopenia in the world that sarcopenia should be defined through a combined approach of muscle mass and muscle quality, however, selecting appropriate diagnostic cutoff values for all the measurements in Asian populations is challenging. Asia is a rapidly aging region with a huge population, so the impact of sarcopenia to this region is estimated to be huge as well. Asian Working Group for Sarcopenia (AWGS) aimed to promote sarcopenia research in Asia, and we collected the best available evidences of sarcopenia researches from Asian countries to establish the consensus for sarcopenia diagnosis. AWGS has agreed with the previous reports that sarcopenia should be described as

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* Address correspondence to Liang-Kung Chen, MD, PhD, Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, No. 201, Sec 2, Shihpai Road, Taipei, Taiwan; or Hidenori Arai, MD, PhD, Department of Human Health Sciences, Kyoto University Graduate School of Medicine, 53 Kawahara-cho, Shogoin, Sakyo-ku 606-8507, Kyoto, Japan.

*E-mail addresses:* lkchen2@vghtpe.gov.tw (L.-K. Chen), harai@kuhp.kyoto-u.ac.jp (H. Arai).


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low muscle mass plus low muscle strength and/or low physical performance, and we also recommend outcome indicators for further researches, as well as the conditions that sarcopenia should be assessed. In addition to sarcopenia screening for community-dwelling older people, AWGS recommends sarcopenia assessment in certain clinical conditions and healthcare settings to facilitate implementing sarcopenia in clinical practice. Moreover, we also recommend cutoff values for muscle mass measurements (7.0 kg/m$^2$ for men and 5.4 kg/m$^2$ for women by using dual X-ray absorptiometry, and 7.0 kg/m$^2$ for men and 5.7 kg/m$^2$ for women by using bioimpedance analysis), handgrip strength (<26 kg for men and <18 kg for women), and usual gait speed (<0.8 m/s). However, a number of challenges remained to be solved in the future. Asia is made up of a great number of ethnicities. The majority of currently available studies have been published from eastern Asia, therefore, more studies of sarcopenia in south, southeastern, and western Asia should be promoted. On the other hand, most Asian studies have been conducted in a cross-sectional design and few longitudinal studies have not necessarily collected the commonly used outcome indicators as other reports from Western countries. Nevertheless, the AWGS consensus report is believed to promote more Asian sarcopenia research, and most important of all, to focus on sarcopenia intervention studies and the implementation of sarcopenia in clinical practice to improve health care outcomes of older people in the communities and the healthcare settings in Asia.


Sarcopenia has been accepted as a new geriatric syndrome,[1] and the knowledge related to sarcopenia is growing rapidly worldwide. Over the past 20 years of sarcopenia research after the first introduction by Rosenberg et al,[2] the etiology, pathophysiology, risk factors, and consequences of sarcopenia have gradually become clearer.[3] Moreover, a number of therapeutic approaches and clinical trials have been developed and are still evolving.[4–7] Most importantly, the association of sarcopenia with poorer health status and adverse outcomes had triggered a new approach for health promotion and health care of older people. The escalation of elderly population worldwide further strengthened the clinical importance of sarcopenia, which is even more significant in Asia because of the rapid demographic transition in this highly populated continent.[8–10]

Sarcopenia has been described as an age-related decline in skeletal muscle mass as well as muscle function (defined by muscle strength or physical performance),[11] which may result in reduced physical capability,[12–14] poorer quality of life, impaired cardiopulmonary performance,[15,16] unfavorable metabolic effects,[17] falls,[18] disability, and mortality in older people,[19,20] as well as high health care expenditure.[21] Furthermore, sarcopenia is also associated with multimorbidity,[22,23] cigarette smoking,[22,24] low body mass index,[25] underweight,[26] physical inactivity,[12] and low serum levels of testosterone in men.[27,28] In general, the association between sarcopenia and functional decline is more significant in men than in women,[29,30] which deserves further research for therapeutic consideration. Since Asia is the most populated and fastest aging region in the world, sarcopenia will pose great impacts to Asian populations in the near future.[31,32] Therefore, experts and researchers of sarcopenia from China, Hong Kong, Japan, South Korea, Malaysia, Taiwan, and Thailand organized the Asian Working Group for Sarcopenia (AWGS) and had several meetings in Taipei, Seoul, and Kyoto to promote further research development of sarcopenia in Asia since March 2013. This article will focus on the epidemiology of sarcopenia in Asian countries and to propose a diagnostic algorithm based on currently available evidence in Asia.

## Diagnosis of Sarcopenia and Its Impact to Asia

Asia is a huge and densely populated continent with a wide range of ethnicities, cultural, social, religious backgrounds, and lifestyles. Because of the rapid population aging and the population size, the impact of sarcopenia in Asia may be stronger than in other continents. However, the status of population aging and economic development varies extensively in different Asian countries. Therefore, developing a consensus for sarcopenia diagnosis and clinical approaches based on available evidence is of great importance for sarcopenia research in the future.

In 2010, European Working Group on Sarcopenia in Older People (EWGSOP) proposed an operational definition and diagnostic strategy for sarcopenia that had become the most widely used in the world.[33] The EWGSOP definition required measurements of muscle mass, muscle strength, and physical performance for the diagnosis of sarcopenia, which is compatible with current understanding about sarcopenia. Based on the discussion of the AWGS meetings, we decided to take similar approaches for sarcopenia diagnosis, but unlike EWGSOP, we recommended measuring both muscle strength (handgrip strength) and physical performance (usual gait speed) as the screening test (Figure 1). Although the recommended approaches for measurements of muscle mass, muscle strength, and physical performance by AWGS were similar to the EWGSOP definition, the cutoff values of these measurements in Asian populations may differ from those in Caucasians because of ethnicities, body size, lifestyles, and cultural backgrounds. Therefore, developing an Asian consensus in sarcopenia diagnosis based on the evidence derived from Asian populations is essential for research and therapeutic approaches to sarcopenia in Asia.

## Strategy for Sarcopenia Screening and Assessment

In principle, AWGS followed the diagnostic approach of EWGSOP, and we added some Asian perspectives in sarcopenia diagnosis and research. In the previous studies from Western countries, the prevalence of sarcopenia in older people was around 20% among people aged 65 years and older and may reach 50%–60% in octogenarians.[34] EWGSOP recommends routine screening for sarcopenia among community-dwelling people aged 65 years and older. On the other hand, the International Working Group on Sarcopenia (IWGS) specifies certain conditions for sarcopenia assessment, including (1) noted decline in function, strength, "health" status, (2) self-reported mobility-related difficulty, (3) history of recurrent falls, (4) recent unintentional weight loss (>5%), (5) post-hospitalization, and (6) other chronic conditions (eg, type 2 diabetes, chronic heart failure, chronic obstructive pulmonary disease, chronic kidney disease, rheumatoid arthritis, and cancer).[35] Moreover, IWGS recommends assessing patients with reduced physical functioning (or weakness) or patients with habitual gait speed <1.0 m/s (by 4-m course) to assess body composition by dual x-ray absorptiometry (DXA). Nonambulatory patients or those who cannot rise from a chair unassisted should be considered to be sarcopenic without DXA measurements. Since sarcopenia is defined as an age-related condition, assessment of sarcopenia is limited to people aged 65 years and older only in the

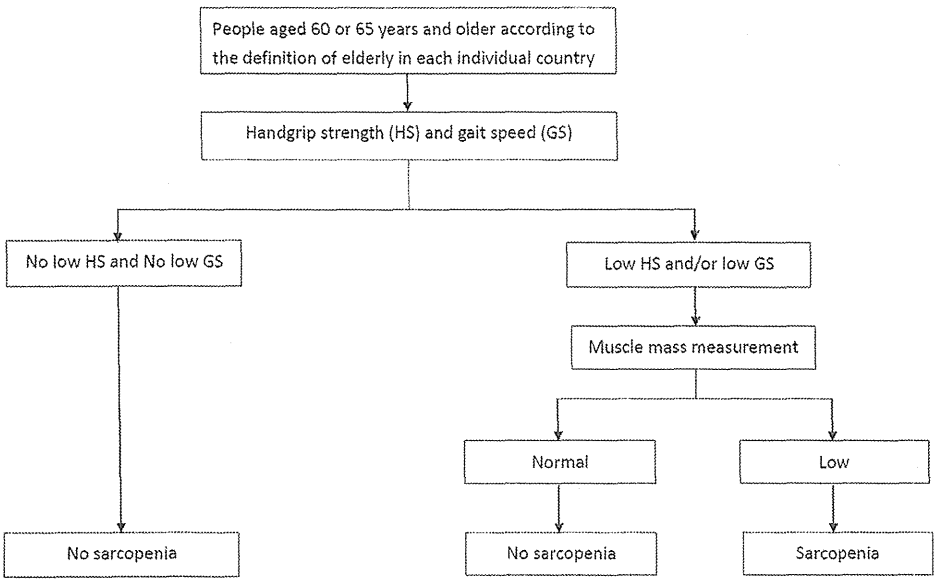


**Fig. 1.** Recommended diagnostic algorithm of Asian Working Group for Sarcopenia.

EWGSOP criteria, but IWGS does not specify the age for sarcopenia diagnosis.

In Asia, because of the different states of aging, not all countries use the same age cutoff to define elderly populations. Therefore, AWGS recommends using 60 or 65 years as the age for sarcopenia diagnosis according to the definitions of elderly in each country. Although muscle aging is a continuous process, most previous studies supported the idea that loss of muscle mass and muscle strength becomes pronounced around the age of 50,[36] progresses faster after the age of 60,[37] and accelerates even faster after the age of 75.[38] The overall benefits of sarcopenia screening or assessment programs are dependent on the outcomes of effective intervention programs. AWGS emphasizes the benefits of intervention programs in addition to sarcopenia screening and assessment; therefore, we recommend screening for sarcopenia among community-dwelling older people as well as older people with certain clinical conditions in all healthcare settings. Table 1 summarized the recommended strategy for sarcopenia screening and assessment of AWGS by dividing cases into 2 categories (ie, community settings and specific chronic conditions in all healthcare settings). From the perspective of public health, sarcopenia screening for community-dwelling older people would facilitate health promotion and disability prevention in their communities, and the assessment of sarcopenia in clinical settings would facilitate strategies for the intervention in clinical practice. AWGS would like to emphasize the prognostic significance of sarcopenia in clinical practice through assessment under certain clinical conditions. However, the benefits of identification of and interventions for sarcopenia remain to be determined.

**Table 1**
Strategy of Sarcopenia Screening and Assessment for Older People (60 or 65 Years of Age and Older) in Asia

| Community Settings |
|---|
| People aged 60 or 65 years and older (according to the definitions of elderly in each individual country) living in communities |
| **Specific Clinical Conditions in All Healthcare Settings** |
| Presence of recent functional decline or functional impairment |
| Unintentional body weight loss for over 5% in a month |
| Depressive mood or cognitive impairment |
| Repeated falls |
| Undernutrition |
| Chronic conditions (eg, chronic heart failure, chronic obstructive pulmonary disease, diabetes mellitus, chronic kidney disease, connective tissue disease, tuberculosis infection, and other chronic wasting conditions) |

## Suggested Outcome Indicators in Sarcopenia Research

The EWGSOP definition suggests using physical performance, muscle strength, and muscle mass as the primary treatment outcome indicators for sarcopenia intervention trials, whereas activities of daily living, quality of life, metabolic and biochemical markers, inflammatory markers, global impression of change by subject or physician, falls, admission to nursing home or hospital, social support, and mortality as secondary outcome indicators.[33] While most epidemiologic studies in sarcopenia research to date have taken a static approach, the state of sarcopenia may change over time and this dynamic approach may provide different considerations in developing sarcopenia intervention programs. Therefore, AWGS also recommends a dynamic approach for sarcopenia research by measuring changes in (1) muscle mass, strength, and function, (2) physical performance, (3) frailty status, (4) instrumental activities of daily living, and (5) basic activities of daily living over a given period of time as outcome indicators for sarcopenia research. In addition to the above-mentioned outcome indicators, AWGS also recommends using fear of falling and incontinence as outcome indicators for sarcopenia research (Table 2).

## Assessment Techniques and Suggested Cutoff Values

Assessment of sarcopenia in Asian populations presents a great challenge because of the lack of outcome-based studies. However, determining appropriate cutoff values for sarcopenia diagnosis in Asia is critical to promote further sarcopenia research and treatment in Asia. Consequently, AWGS focused on the best available evidence to determine cutoff values for the diagnosis of sarcopenia in Asia. If, however, no outcome-based data are available, AWGS would recommend standardized approaches for cutoff value determination.

**Table 2**
Outcome Indicators for Sarcopenia Research Recommended by AWGS

| Static Approach |
|---|
| Activities of daily living |
| Quality of life |
| Inflammatory markers |
| Falls |
| Frailty status |
| Mobility disorders |
| Admission to hospitals |
| Admission to long term care facilities |
| Mortality |
| **Dynamic Approach** |
| Changes in muscle mass |
| Changes in muscle strength |
| Changes in physical performance |
| Changes in frailty status |
| Changes in instrumental activities of daily living |
| Changes in activities of daily living |

AWGS, Asian Working Group for Sarcopenia.

## Muscle Mass

EWGSOP recommends DXA, computed tomography (CT), magnetic resonance imaging (MRI), and bioimpedance analysis (BIA) for sarcopenia research. Currently, the precision of DXA, CT, and MRI has been well recognized, but the precision of BIA in measuring muscle mass is controversial. BIA was developed to estimate the volume of body fat and lean body mass, but not appendicular muscle mass. Although the accuracy of BIA in sarcopenia diagnosis has been validated,[39–41] it is heavily dependent on the accuracy of the equation of the equipment and the conditions of assessments, eg, temperature, humidity, skin condition, etc.[42] Nevertheless, the high cost, CT-generated radiation exposure, and inconvenience for community screening have limited the applications of CT and MRI despite both CT and MRI have both been considered gold standards for evaluation of body composition. On the other hand, DXA is also considered an appropriate alternative approach to distinguish between fat, bone mineral, and lean tissues. Currently, DXA may be the most widely used method for muscle mass measurement in sarcopenia research. Despite the minimal radiation exposure from DXA, using DXA in community screening of sarcopenia is still difficult. Newly developed models of BIA equipment may obtain measurements of appendicular muscle mass with precision.[43,44] Portability, reasonable cost, fast processing, noninvasiveness, radiation-free functions, and convenience of use made BIA suitable for community sarcopenia assessment. Results of multiple segment fat-free mass estimation using BIA are highly associated with that measured using DXA among elderly Taiwanese.[45] Although using BIA equipment with validated equations is recommended for sarcopenia research in EWGSOP criteria, the equations of BIA equipment in Western countries are not derived from Asian populations. Strasser et al[46] proposed measurement of muscle thickness, especially of musculus vastus medialis, by musculoskeletal ultrasound to be a reliable method for the estimation of sarcopenia, which deserves further research for applications in Asian studies. In current Asian studies, the most commonly used BIA machines were manufactured by only 2 companies, and the results were quite consistent. Because of its portability and reasonable cost, BIA may be considered the main approach in sarcopenia assessment in community-based screening programs. Therefore, AWGS supports using BIA for sarcopenia diagnosis and evaluation of the effect of intervention programs, but AWGS suggests researchers to provide coefficient of variance, inter- and intra-examiner reliability whenever possible to facilitate subsequent international comparisons.

In terms of cutoff value determination, most current Asian studies have adopted the classical approach for muscle mass measurement (ie, below 2 standard deviations of the mean muscle mass of young adults). However, Asian studies reported an extremely low prevalence of sarcopenia through this approach, especially in older women.[26,47,48] Lau et al[26] also found that the relative total skeletal muscle of Hong Kong Chinese (total skeletal muscle /height$^2$) was 17% lower among young Chinese men than that of Caucasian men.[26] A potential cohort effect may exist in this approach since younger people in Asia today leading a westernized or more urbanized lifestyle while older Asian people have carried out a traditional lifestyle since adulthood. This cohort effect may be derived from the economic development, urbanization, and development of public transportation in Asia in recent decades. Older Asian people today may have walked and performed more physical activities because of the underdevelopment of public transportation and living conditions since their early adulthood, so their muscle mass may be maintained better than that of the younger generation. On the other hand, because of the relatively higher adiposity of Asian people in comparison with Caucasians, appendicular muscle mass may be overestimated by DXA. Overall, AWGS recommends using 2 standard deviations below the mean muscle mass of young reference group or the lower quintile as the cutoff value determination. Moreover, AWGS recommends using height-adjusted skeletal muscle mass instead of weight-adjusted skeletal muscle mass, and the suggested cutoff values were 7.0 kg/m$^2$ in men and 5.4 kg/m$^2$ in women by using DXA. By using BIA, the suggested cutoff values were 7.0 kg/m$^2$ in men and 5.7 kg/m$^2$ in women, defined by appendicular skeletal muscle mass/height$^2$.

## Muscle Strength

Measuring handgrip strength is considered a feasible and convenient measure of muscle strength because of cost, availability, ease of use, and its association with leg strength. Wu et al[49] presented the norm of handgrip strength in Taiwan, which disclosed that the mean grip strength of the study sample in Taiwan was significantly lower (male 25%, female 27%) than consolidated norms derived from largely Caucasian populations. Although some papers published in Taiwan using this adjusted cutoff value based on EWGSOP definition for sarcopenia research,[50] some unpublished papers from Japan, Hong Kong, and China recommended using 25 kg for men and 18 or 16 kg for women as the cutoff values for handgrip strength. Currently, handgrip strength is the most widely used measure for muscle strength in Asian sarcopenia research (Table 3), and AWGS also recommends using it for the measurement of muscle strength. Although knee flexion/extension and peak expiratory flow are also recommended for sarcopenia research in EWGSOP criteria, they are less commonly used. In Thailand, the cutoff points of quadriceps strength had been defined based on the outcome of mobility decline. The cutoff points of <18 kg in men and <16 kg in women can discriminate those had normal and abnormal various sarcopenia-related variables. Because of the lack of outcome-based cutoff values, AWGS recommends using the lower 20th percentile of handgrip strength of the study population as the cutoff value for low muscle strength before outcome-based data is available. Low handgrip strength is suggested to be defined as <26 kg for men and <18kg for women by AWGS.

## Physical Performance

A wide range of tests for physical performance are recommended in EWGSOP criteria, including the Short Physical Performance Battery (SPPB), usual gait speed, the 6-minute walk test, the stair climb power test, and the timed-up-and-go test (TUG).[51] Timed usual gait is highly predictive for the onset of disability,[52] and other adverse health

**Table 3**
Measurable Variables and Cutoff Points in Asian Populations

| Criterion | Measurement Method | Cutoff Points by Sex | Reference Group Definition | Prevalence of Sarcopenia | Country/ Ethnicity | Reference |
|---|---|---|---|---|---|---|
| Muscle mass | DXA | ASM/height$^2$<br>Class 1 and class 2 sarcopenia<br>Men: 7.77 and 6.87 kg/m$^2$<br>Women: 6.12 and 5.46 kg/m$^2$ | Based on values 1 and 2 SD below the sex-specific means of the study reference data (n = 529) | Class 1 and class 2 sarcopenia in subjects 70–85 years of age:<br>Men: 6.7%, 56.7%<br>Women: 6.3%, 33.6% | Japan | 69 |
| | | ASM/height$^2$<br>Men <5.72 kg/m$^2$<br>Women <4.82 kg/m$^2$ | Based on 2 SD below the mean of young Asians in study (n = 111) | In older Chinese ≥70 years of age<br>Men: 12.3%<br>Women: 7.6% | Chinese | 26 |
| | | ASM/height$^2$<br>Men: 7.40 kg/m$^2$<br>Women: 5.14 kg/m$^2$ | Based on 2 SD below the sex-specific mean of a younger population (n = 145) | In older subjects ≥ 60 years of age<br>Men: 6.3%<br>Women: 4.1% | Korea | 70 |
| | | SMI (%)<br>Men: 35.71%<br>Women: 30.70% | Based on 2 SD below the sex-specific mean of a younger population (n = 145) | Men: 5.1%<br>Women: 14.2% | | |
| | | Using the residuals method | | Men: 15.4%<br>Women: 22.3% | | |
| | | ASM/height$^2$<br>Class I and class II sarcopenia<br>Men: 7.50 and 6.58 kg/m$^2$<br>Women: 5.38 and 4.59 kg/m$^2$ | Based on 1 and 2 SD below the mean of young adults in study (n = 2513) | Class I and class II sarcopenia<br>Men: 30.8% and 12.4%<br>Women: 10.2% and 0.1% | Korea | 48 |
| | | ASM/body weight (%)<br>Class I and class II sarcopenia<br>Men: 32.2% and 29.1%<br>Women: 25.6% and 23.0% | Based on 1 and 2 SD below the mean of young adults in study | Men: 29.5% and 9.7%<br>Women: 30.3% and 11.8% | Korea | 48 |
| | | ASM/body weight (%)[1]<br>Men: 29.53%<br>Women: 23.20% | Based on 2 SD of sex-specific young normal people | | Korea | 71 |
| | | Use SMI (% of skeletal muscle index) but not mentioned the cutoff points in the manuscript | Based on 2 SD of sex-specific young normal people | Sarcopenia class I, II, overall<br>Men: 32.5%, 15.7%, 35.33 %<br>Women: 30.5%, 10%, 34.74 % | Thailand | 72 |
| | | RASM index<br>Men: 7.27 kg/m$^2$<br>Women: 5.44 kg/m$^2$ | Based on the lower 20% of study group | Men: 10.8%<br>Women: 3.7% | Taiwan | 47 |
| | | SMI (% of skeletal muscle index)<br>Men: 37.4%<br>Women: 28.0% | Based on the lower 20% of study group | Men: 14.9%<br>Women: 19% | | |
| | BIA | SMI<br>Men <8.87 kg/m$^2$<br>Women <6.42 kg/m$^2$ | Based on 2 SD below the normal sex-specific mean for young people | 18.6% in elderly women and 23.6% in elderly men age 65 and older | Taiwan | 40 |
| | | ASM/height$^2$<br>Men <7.0 kg/m$^2$<br>Women <5.8 kg/m$^2$ | Based on 2 SD below young adult values | Men: 11.3%<br>Women: 10.7% using EWGSOP criteria | Japan | 15 |
| | | ASM/height$^2$<br>Women ≤ 6.42 kg/m$^2$ | | Women: 22.1% | Japan | 6 |
| | | ASM/height$^2$<br>Men <6.75 kg/m$^2$<br>Women <5.07 kg/m$^2$ | Based on 2 SD below young adult values | Men: 21.8%<br>Women: 22.1% using EWGSOP criteria | Korea/Health ABC data | 15 |
| Muscle strength | Handgrip strength | Men: 30.3 kg<br>Women: 19.3 kg | Based on lowest quartile of study group | | Japan | 13 |
| | | Men <22.4 kg<br>Women <14.3 kg | Based on EWGSOP recommendation and adjusted according to Asian data[46] | | Taiwan | 50 |
| | Knee extension | Women ≤1.01 Nm/kg | | | Japan | 6,73 |
| Physical performance | Gait speed | Gait speed<br>Men <1.27 m/s<br>Women <1.19 m/s | Based on the lowest quartile of study group, gait speed obtained from the middle 5 m of a total of 11 m walking | Men: 11.3%<br>Women: 10.7% using EWGSOP criteria | Japan | 13 |
| | | Gait speed ≤ 1 m/s | | | Taiwan | 50 |
| | | Gait speed ≤ 1.22 m/s | | Women: 22.1% | Japan | 6,73 |
| | SPPB | SPPB scores <9 | | | Korea | 74 |

ASM, appendicular skeletal muscle mass; BIA, bioimpedance analysis; DXA, dual x-ray absorptiometry; EWGSOP, European Working Group on Sarcopenia in Older People; Health ABC, The Health Aging and Body Composition Study; RASM, relative appendicular skeletal muscle; SD, standard deviation; SPPB, Short Physical Performance Battery; SMI, skeletal muscle mass index.

[1]SMI (%) = total skeletal muscle mass (kg)/weight (kg) × 100.

[2]The author also named it modified skeletal muscle mass index (SMI).

events like severe mobility limitation and mortality.[53] TUG is an assessment of ambulation and dynamic balance. Poorer TUG has been demonstrated to be associated with poorer physical and mental function and mood status, as well as low fat-free mass by BIA measurements.[54] Although TUG has been proposed as a suitable measurement for physical performance in EWGSOP, abnormal TUG may result from a great variety of underlying conditions. AWGS is more conservative in the use of TUG as a measurement for physical

performance, and we recommend using 6-meter usual gait speed for measurement of physical performance.

Ideally, determination of the cutoff values of these measurements should be based on longitudinal outcome-based studies instead of a simply statistical approach.[55] Although the association between sarcopenia and functional decline or even mortality has been established,[56] selection of universal outcome indicators in subsequent research may facilitate international comparisons. Table 3 summarized the epidemiology and proposed cut-off points in different cases of Asian sarcopenia research. EWGSOP has developed a suggested algorithm based on gait speed measurement with a cutoff point of <0.8 m/s.[33] The association of slow usual gait speed in the elderly with adverse clinical outcomes has been reported extensively, but the application was also dependent on the determination of appropriate cutoff points. Meanwhile, the prevalence of low muscle mass in the Asian population as determined using the classical approach is very low, which is confusing. The potential cohort effect may partially explain the phenomenon of older people today engaging in more physical activities than younger people, which made the prevalence of sarcopenia lower than expected. Specific consideration of this potential cohort effect deserves further attention in the diagnosis of sarcopenia in Asia. Although there is a potential gender difference in the cutoff value of usual gait speed and a wide range of walking speed (from 0.6 to 1.2 m/s) being reported in this special issue, AWGS suggested using ≤0.8 m/s as the cutoff for low physical performance after extensive consideration of data available in Asian studies.

## Therapeutic Implications

Physical activities, including aerobics, endurance exercise,[57] and resistance exercise training[58,59] have been demonstrated to significantly increase muscle mass and strength in sarcopenic older people. Although the recommended frequency of exercise training to improve muscle strength and functional performance has been shown,[60] a consensus has not yet been reached concerning the content of the prescribed exercise and the most optimal frequency and intensity. Inappropriate exercise training in the elderly may result in unfavorable adverse outcomes such as musculoskeletal complaints,[61] which is not uncommon. Further research should be focused on the development of suitable exercise prescription, especially for older people at risk of functional decline or sarcopenia. The Society for Sarcopenia, Cachexia, and Wasting Disease developed nutritional recommendations for the prevention and management of sarcopenia, which combined exercise with adequate protein and energy intake.[62] A leucine-enriched balanced essential amino acid or balanced amino acid supplementation is suggested for sarcopenia. Recently, Kim et al[6] demonstrated that exercise and amino acid supplementation (3 g of a leucine-rich essential amino acid mixture twice a day) together may actually be effective in enhancing muscle strength, variables of muscle mass, and walking speed in sarcopenic women. Aside from exercise and nutritional supplementation, the pharmaceutical approach to sarcopenia is still under development. Growth hormone replacement was not successful because the effect of increased muscle mass by growth hormone replacement was not associated with the improvement of muscle performance,[63–65] unless it is used for growth hormone deficiency patients for a period longer than 12 months.[66–68] In addition, the effects of antimyostatin antibodies on sarcopenia have been demonstrated and may be marketed in a few years. Therefore, sarcopenia should be treated through a multilevel approach employing combined physical activities and nutritional supplementation. Currently, there is no well-established evidence for pharmaceutical approach for sarcopenia intervention, but a few agents may be available in future.

## Future Challenge and Conclusion

Sarcopenia significantly impacts daily activities, functional status, disability, and quality of life in older populations. Although Asian populations are rapidly ageing, from the clinical practice or public health points of view, the understanding of and preparation for sarcopenia remain inadequate. Hence, this consensus collected as many Asian studies as possible and offers a working diagnosis of sarcopenia for Asian people. The main aims of AWGS were to promote sarcopenia research in Asian countries through providing recommended diagnostic strategies and cutoff values based on Asian studies, and to foster the importance of implementing sarcopenia in clinical practice and in community health promotion programs.

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ORIGINAL ARTICLE

# Association between serum uric acid and lumbar spine bone mineral density in peri- and postmenopausal Japanese women

S. Ishii · M. Miyao · Y. Mizuno · M. Tanaka-Ishikawa · M. Akishita · Y. Ouchi

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**Abstract**
*Summary* Previous studies on the association between uric acid and bone mineral density yielded conflicting results. In this study, we demonstrated positive association between uric acid and lumbar spine bone mineral density in peri- and postmenopausal Japanese women. Further research is needed to elucidate the underlying mechanism.
*Introduction* Oxidative stress has been implicated in the pathogenesis of osteoporosis. Uric acid, a potent antioxidant substance, has been associated with bone mineral density but previous studies have yielded conflicting results. The objective of the study was to examine the association between serum uric acid and lumbar spine bone mineral density (BMD).
*Methods* This was a retrospective analysis of medical records of 615 women, aged 45–75 years, who had lumbar spine BMD measurement by dual-energy X-ray absorptiometry as a part of health checkup from August 2011 to July 2012.
*Results* Mean serum uric acid level was 4.7 mg/dL. Serum uric acid level was positively and significantly associated with lumbar spine BMD independent of age, body mass index, smoking, drinking, physical activity, years after menopause, diabetes mellitus, hypertension, serum calcium, estimated glomerular filtration rate, plasma C-reactive protein, and serum alkaline phosphatase (standardized beta=0.078, $p=0.049$). Uric acid rapidly increased until the age of 60 years, and then decelerated but continued to increase thereafter. The association between lumbar spine BMD and uric acid remained significantly positive after excluding women older than 60 years.
*Conclusion* The present study showed that higher uric acid levels were linearly associated with higher lumbar spine BMD in peri- and postmenopausal Japanese women. Further research is needed to elucidate the underlying mechanism of the association between uric acid and BMD.

**Keywords** Bone mineral density · Menopause · Osteoporosis · Uric acid

S. Ishii (✉) · M. Akishita · Y. Ouchi
Department of Geriatric Medicine, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku Tokyo 113-8655, Japan
e-mail: ishiis-tky@umin.ac.jp

S. Ishii
e-mail: sishii76@gmail.com

M. Miyao · M. Tanaka-Ishikawa
Center for Health Check-up and Preventive Medicine, Kanto Central Hospital, 6-25-1 Ueyouga, Setagaya-ku Tokyo 158-8531, Japan

Y. Mizuno
Department of Endocrinology, Kanto Central Hospital, 6-25-1 Ueyouga, Setagaya-ku Tokyo 158-8531, Japan

## Introduction

Osteoporosis, a disease characterized by bone fragility and increased risk of fracture, has been chiefly attributed to the decline of ovarian function at menopause and resulting sex steroid deficiency [1]. On the other hand, oxidative stress has also been implicated in the pathogenesis of osteoporosis [1–12]. For example, observational studies suggested that a higher intake of the antioxidant vitamin C was associated with slower decline of bone mineral density (BMD) [10] and lower risk of hip and nonvertebral fractures [9], and that diminution in plasma antioxidant activity or high oxidative stress was observed in patients with osteoporosis compared with those without [4, 6, 8, 11, 12].

In agreement with accumulating evidence supporting the role of oxidative stress as one of the underlying mechanisms of osteoporosis, uric acid, a potent antioxidant substance [13], has been associated with osteoporosis. In a large population-based, cross-sectional study on older men, higher serum uric acid levels were significantly associated with higher BMD at

various sites including the lumbar spine and femoral neck, adjusting for covariates [14]. Higher serum uric acid levels were also associated with a lower prevalence of osteoporosis, vertebral fracture ascertained by lateral spine scans, and history of nonvertebral fracture [14]. Another large cross-sectional study replicated the association of uric acid positively with BMD and negatively with lower prevalence of vertebral fracture in postmenopausal women [15]. This study also demonstrated that uric acid suppressed osteoclastogenesis and reduced the production of reactive oxygen species in osteoclast precursors, providing important evidence that the positive association between uric acid and bone mineral density may be related to the antioxidant effect of uric acid. Moreover, in a longitudinal study on peri- and postmenopausal female twins, higher uric acid levels at baseline were associated with higher BMD at baseline and a slower rate of decline in BMD thereafter, independent of covariates [16].

However, there is also strong evidence linking hyperuricemia with increased risk of cardiovascular disease [17, 18] in which oxidative stress plays an important pathophysiological role [19, 20]. One of the proposed hypotheses explaining this paradox is related to a shift in the prooxidant/antioxidant properties of uric acid depending on its concentration. Experimental studies suggested that uric acid may become prooxidant under certain conditions [21, 22], particularly when it is supersaturated in blood. Therefore, it is conceivable that uric acid may confer protective antioxidant effects or detrimental prooxidant effects when, respectively, present at normal levels or at supersaturated concentrations [23]. One cross-sectional study on young men and women actually demonstrated that *higher* levels of serum uric acid were associated with *lower* BMD at the femoral neck in women after controlling for age, weight, and serum creatinine [24]. Interestingly, uric acid levels in most female participants were within the normal range. Estrogen has an antioxidant property [1] and also reduces serum uric acid by enhancing renal clearance [25]. Therefore, the finding of an inverse association between estrogen and uric acid may be attributable to the confounding effects of estrogen, considering that the women in this study were predominantly premenopausal. However, the effects of age and menopause on the association between uric acid and osteoporosis have not been empirically examined, and further research is needed.

In the present study, we examined the association between uric acid and BMD in peri- and postmenopausal Japanese women. We hypothesized that BMD and uric acid are linearly and positively associated independent of covariates including the menopausal status in the normal range of serum uric acid, but the association becomes inverse in the hyperuricemic range.

## Methods

### Subjects

This was a retrospective analysis of medical records obtained from Kanto Central Hospital which is a 470-bed urban teaching hospital in Tokyo funded and run by the Mutual Aid Association of Public School Teachers. Teachers who work at public schools and belong to the Association have health checkup annually at the Center for Health Check-up and Preventive Medicine of the Hospital since workers are required by law to have annual health checkup regardless of their age in Japan. Health checkup is performed in a standardized manner, consisting of consultation with a doctor, height and weight measurement, laboratory tests, and several studies including chest X-ray. Lumbar spine BMD measurement by dual-energy X-ray absorptiometry (DXA) is offered optionally for teachers with financial subsidy from the association.

We drew data from the medical records of 3,814 women aged between 45 and 75 years who received a health checkup at the Center from August 2011 to July 2012. Of the women, 638 (16.7 %) out of 3,814 had lumbar spine BMD measurement. Women with chronic kidney disease (estimated glomerular filtration rate (GFR) lower than 60 mL/min/1.73 $m^2$) ($n=10$) or who had received treatment for osteoporosis ($n=8$) were excluded from the analysis. Those who had received treatment for either hypothyroidism ($n=4$) or hyperthyroidism ($n=1$) were also excluded because of the effect of thyroid hormones on bone [26]. No women received oral steroids, loop diuretics, high-dose thiazide diuretics, hormone replacement therapy, or treatment for hyperuricemia or chronic liver disease. After exclusion, 615 women were included in the analysis. This study was approved by the Ethics Committee of Kanto Central Hospital.

### Measurements

Standardized interviews and self-reported questionnaires were used to obtain the following information: age (years), smoking habit (current smoker, past smoker, or never smoked), drinking habit [abstainer, infrequent (non-abstainer but one or less drink per week), and light (more than one drink per week but one or less per day), or moderate to heavy (more than one drink per day)], physical activity (any regular exercise or none), age at menopause, medical history, and use of prescription medication. Height and weight were measured using a fixed stadiometer and a digital scale, with the participant wearing light clothing. Body mass index (BMI) was calculated from weight and height.

Fasting blood samples were collected from each participant, and serum uric acid, creatinine, calcium, and alkaline phosphatase were measured using a standard technique with a medical autoanalyzer (BioMajesty JCA-BM2250). The assay

range for serum uric acid was 0.2–200 mg/dL. Plasma C-reactive protein (CRP) was measured using a latex immunoassay with the assay range of 0.2–4,000 mg/L. Estimated GFR was calculated from age, sex, and serum creatinine [27].

Subjects with a reported history of diabetes mellitus, fasting glucose of 126 mg/dL or higher, or glycosylated hemoglobin levels at 6.5 % or higher were classified as diabetic. Those with a reported history of hypertension, systolic blood pressure of 140 mmHg or higher, or diastolic blood pressure of 90 mmHg or higher were classified hypertensive.

## Bone mineral density measurements

BMD of the lumbar spine was measured by DXA using a GE Lunar Prodigy. A standard quality control program included daily calibrations with machine-specific phantoms to ensure machine accuracy of greater than 98 %.

## Statistical analysis

Uric acid becomes insoluble and supersaturated in bodily fluids above a concentration of about 7 mg/dL. The nonparametric locally weighted scatterplot smoothing (LOESS) method was used to determine whether the saturation point affects the functional form of the association between uric acid and BMD. The LOESS method generated a smooth curve of BMD as a function of uric acid. Visual inspection of the LOESS plot indicated that the relationship between BMD and uric acid was piecewise linear with an inflection (change of slope) at the uric acid value of 4.8, above which the slope appeared steeper (Fig. 1). We then fitted piecewise linear spline models to BMD as a function of uric acid with a fixed knot at 4.8. We also employed generalized additive models to examine the shape of the association between uric acid and BMD accounting for other covariates. The generalized additive model is an extension of the generalized linear model in which one or more independent variables can be modeled with nonparametric smooth functions [28].

The model was initially adjusted for age and BMI (model 1). Covariates for lifestyle risk factors for osteoporosis including physical activity; smoking and drinking habit; years after menopause (coded as 0 if subject had not experienced menopause) (model 2); comorbidity including diabetes mellitus and hypertension (model 3); and serum calcium, alkaline phosphatase (ALP), estimated GFR, and log (CRP) (model 4) were successively added to regression models. The selection of covariates was based on the literature review on factors affecting BMD [29–35].

There were missing values for physical activity in 180 women (29.3 %), years after menopause in 140 women (22.8 %), and drinking habit in 1 woman (0.2 %). These were imputed using the expectation–maximization (EM) algorithm [36].

Statistical analyses were performed using SAS, version 9.2 (SAS Institute, Inc., Cary, NC, USA) and R statistical software

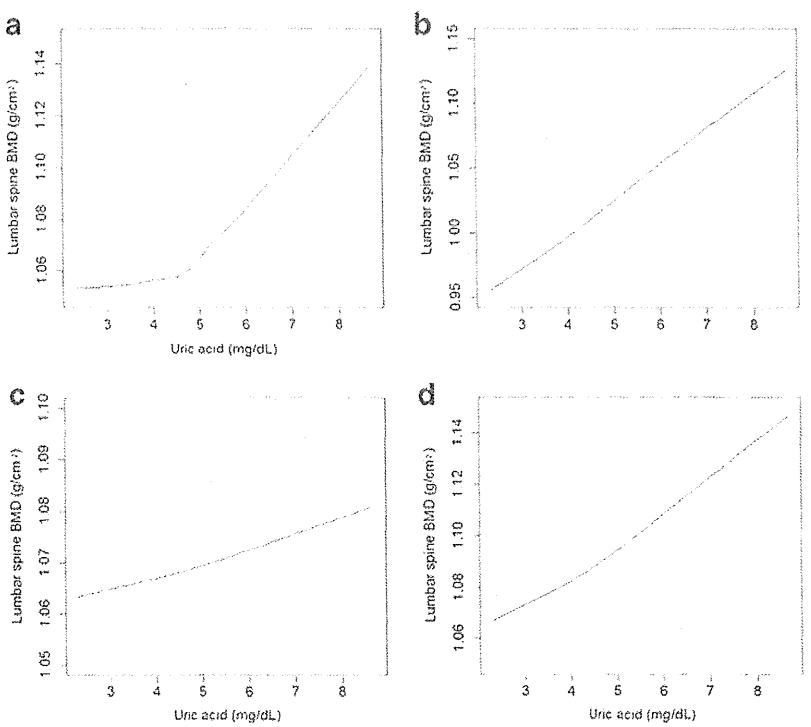


**Fig. 1** Plots of lumbar spine bone mineral density against uric acid level. **a** The LOESS plot. **b**–**d** The plots generated using generalized additive models accounting for age (**b**), body mass index (**c**), or estimated glomerular filtration ratio (**d**). The values of the covariates were fixed at their mean when the association between lumbar spine BMD and uric acid were plotted. *BMD* bone mineral density

version 2.15.2 (R Foundation, Vienna, Austria). All statistical tests were two-sided, and a $p$ value less than 0.05 was considered statistically significant.

## Results

Characteristics of study participants are shown in Table 1. Women included in the analysis were similar to those excluded from the analysis with respect to major characteristics. Of the 615 women included in the analysis, serum uric acid had a mean value of 4.7 mg/dL with standard deviation of 1.0 mg/dL. Only 12 women (2.0 %) had hyperuricemia (i.e., uric acid level higher than 7.0 mg/dL), and 19 (3.1 %) women were obese (i.e., BMI equal to or higher than 30 kg/m$^2$).

**Table 1** Characteristics of participants

| | Participants ($n$=615) |
|---|---|
| Uric acid (mg/dL) | 4.7±1.0 |
| Lumbar spine bone mineral density (g/cm$^2$) | 1.06±0.18 |
| Age (years) | 57.6±6.4 |
| Log (CRP in mg/L)[a] | 0.12±0.17 |
| BMI (kg/m$^2$) | 22.2±3.5 |
| Smoking | |
| Current | 19 (3.1) |
| Ex | 53 (8.6) |
| Never | 543 (88.3) |
| Drinking[b] | |
| Abstainer | 219 (35.7) |
| Infrequent | 188 (30.6) |
| Light | 171 (27.9) |
| Moderate to heavy | 36 (5.9) |
| Activity[b] | |
| Sedentary | 283 (65.1) |
| Active | 152 (34.9) |
| Postmenopausal[b] | 373 (78.5) |
| Age at menopause in postmenopausal women (years) | 50.9±3.8 |
| Diabetes | 44 (7.2) |
| Hypertension | 114 (18.5) |
| Serum calcium (mg/dL) | 9.3±0.3 |
| Estimated GFR (mL/min/1.73 m$^2$) | 97.8±21.6 |
| ALP (IU/L) | 223.5±66.3 |

For continuous variables, the mean is shown with standard deviation. For categorical variables, the number (percentage) is shown. Percentages may not add up to 100 because of rounding errors

*BMD* bone mineral density, *CRP* C-reactive protein, *BMI* body mass index, *GFR* glomerular filtration rate, *ALP* alkaline phosphatase, *IU* international unit

[a] The natural log (base e) was taken for CRP due to skewed distribution

[b] There were missing values for physical activity in 180 women (29.3 %), years after menopause in 140 women (22.8 %), and drinking habit in 1 woman (0.2 %)

### Association between BMD and uric acid

In piecewise linear regression of BMD as a function of uric acid with a fixed knot at uric acid level of 4.8 mg/dL, the change in slope at the knot was not statistically significant in univariate analysis and all four models of multivariate analyses ($p$ values=0.31–0.79). The generalized additive models also demonstrated that uric acid was approximately linearly associated with BMD when accounting for each of age, BMI, or estimated GFR (Fig. 1). Therefore, the knot was subsequently dropped. The resulting multiple linear regression models fitted simple linear relationship between uric acid and BMD. Serum uric acid levels were significantly and positively associated with lumbar spine BMD adjusting for age and BMI (model 1, Table 2). The association between uric acid and BMD remained significant after successively adjusting for lifestyle risk factors and years after menopause (model 2); comorbidity (model 3); and serum calcium, estimated GFR, log (CRP), and ALP (model 4). Serum uric acid levels explained 0.48–0.63 % of variance in BMD ($R^2$=0.187–0.258).

### Effect modification

One of the presumed mechanisms of the association between BMD and uric acid is the antioxidant property of uric acid. Considering the complicated and interrelated relationship between oxidative stress and inflammation, we postulated that the degree of inflammation modifies the association between BMD and uric acid. To test this hypothesis, we examined the interaction between log (CRP) and uric acid, but it was not significant ($p$=0.22).

**Table 2** Adjusted associations of serum uric acid with lumbar spine bone mineral density ($n$=615)

| | Beta[a] | %V[b] | $p$ | $R^2$ |
|---|---|---|---|---|
| Model 1 | 0.084 | 0.63 | 0.03 | 0.187 |
| Model 2 | 0.081 | 0.57 | 0.04 | 0.199 |
| Model 3 | 0.084 | 0.61 | 0.03 | 0.206 |
| Model 4 | 0.078 | 0.48 | 0.049 | 0.258 |

Model 1—adjusted for age, BMI; model 2—adjusted for age, BMI, smoking, drinking, physical activity, and years after menopause; model 3—adjusted for age, BMI, smoking, drinking, physical activity, years after menopause, diabetes, and hypertension; model 4—adjusted for age, BMI, smoking, drinking, physical activity, years after menopause, diabetes, hypertension, serum calcium, estimated GFR, log (CRP), and ALP. Abbreviations are as in Table 1

[a] Standardized beta coefficient

[b] Variance of lumbar spine bone mineral density explained by uric acid

### Sensitivity analysis

Previous studies have demonstrated that menopause is associated with changes in both BMD and uric acid. Women have a minimal decline in BMD until 1–2 years prior to the final menstrual period when they begin to experience a rapid decline in BMD. The decline in BMD decelerates 1–2 years after the final menstrual period, but continues [37]. On the other hand, postmenopausal status was associated with higher levels of uric acid [38, 39]. Therefore, the associations of age with BMD and uric acid in this study sample of peri- and postmenopausal women may not be linear. The LOESS plots of BMD and uric acid as a function of age demonstrated that both of the relationships were piecewise linear, with an inflection at around the age of 60 (Fig. 2a, b). Uric acid rapidly increased with increasing age until age 60 years, then decelerated but continued to increase. Similarly, lumbar spine BMD declined rapidly with increasing age, but the rate of decline slowed down at the age of 60 years but continued to decline. As a sensitivity analysis, we examined the association between uric acid and BMD after excluding 177 women older than 60. The analysis demonstrated significant and positive associations between BMD and uric acid in all models, with effect sizes slightly larger than those observed in the main analyses, supporting the robustness of our scientific conclusion (Table 3).

We also conducted another sensitivity analysis after excluding 281 women with any missing values in covariates. This sensitivity analysis revealed slightly larger effect sizes of the association between UA and BMD than those in the main analyses, but the associations failed to reach statistical significance (data not shown).

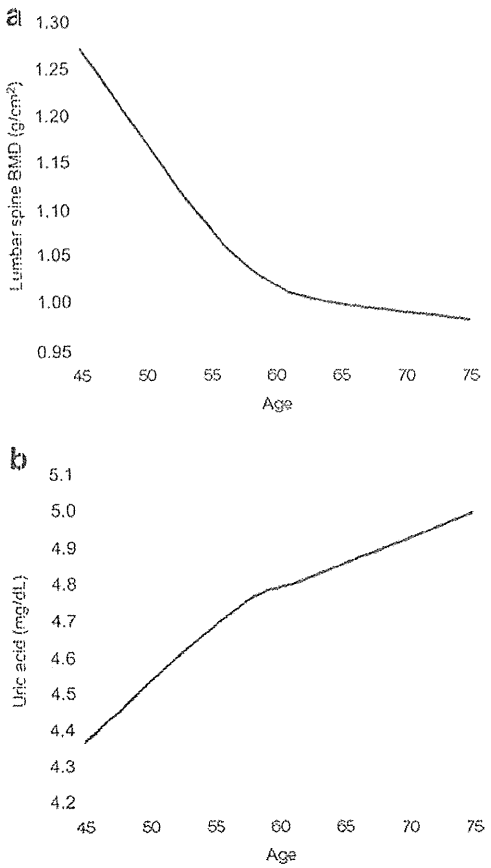


**Fig. 2** LOESS plots of bone mineral density and uric acid against age. *BMD* bone mineral density

## Discussion

In this cross-sectional analysis of 615 peri- and postmenopausal women aged between 45 and 75 years, higher serum levels of uric acid were significantly associated with higher values of BMD in the lumbar spine, independent of covariates including years after menopause. One standard deviation (1.0 mg/dL in this study population) increment in uric acid was associated with an approximately 0.08 standard deviation increase in lumbar spine BMD. We also demonstrated rapid changes in uric acid and BMD with increasing age until the age of 60, and the rate of changes slowed down thereafter. The positive association between BMD and uric acid remained significant after excluding women older than 60 years.

Our study confirms and extends a previous study that has demonstrated a positive association between BMD and uric acid in peri- and postmenopausal women [15, 16]. We showed that uric acid was positively and linearly associated with lumbar spine BMD, and therefore not only the presence of hyperuricemia but also the magnitude of uric acid elevation plays an important role. Addition of years after menopause did not significantly affect the uric acid–BMD association. We did not observe any sharp inflection point (i.e., change of slope) in the association between uric acid and BMD, incongruent with our hypothesis that the association between uric acid and

**Table 3** Adjusted associations of serum uric acid with lumbar spine bone mineral density after excluding 177 women older than 60 years ($n$=438)

| | Beta[a] | %V[b] | $p$ | $R^2$ |
|---|---|---|---|---|
| Model 1 | 0.103 | 0.96 | 0.02 | 0.284 |
| Model 2 | 0.091 | 0.73 | 0.04 | 0.294 |
| Model 3 | 0.101 | 0.89 | 0.02 | 0.304 |
| Model 4 | 0.107 | 0.91 | 0.02 | 0.359 |

Model 1—adjusted for age and BMI; model 2—adjusted for age, BMI, smoking, drinking, physical activity, and years after menopause; model 3—adjusted for age, BMI, smoking, drinking, physical activity, years after menopause, diabetes, and hypertension; model 4—adjusted for age, BMI, smoking, drinking, physical activity, years after menopause, diabetes, hypertension, serum calcium, estimated GFR, log (CRP), and ALP. Abbreviations are as in Table 1

[a] Standardized beta coefficient

[b] Variance of lumbar spine bone mineral density explained by uric acid

BMD becomes inverse in the hyperuricemic range. However, it should be noted that only a small portion of women in this study had hyperuricemia, and further study is needed to determine if the association between BMD and uric acid in the hyperuricemic range may differ from that in the physiologic range.

We also demonstrated that there was a period of rapid increase in uric acid until the age of 60 years when the rate of increase slowed. The observed trajectory of uric acid is consistent with menopause-related changes, rather than changes secondary to chronological aging. This is congruent with previous studies showing that uric acid levels were higher in postmenopausal women compared with pre- or perimenopausal women [38, 39]. We observed a similar menopause-related change in BMD, consistent with previous studies [37]. However, the inflection (i.e., change of slope) was observed at around the age of 60 for both uric acid and BMD in the present study, which appears too far apart from the mean age at menopause of approximately 51 years. The possible explanations for the discrepancy include reporting error and the nature of cross-sectional data, which are predisposed to recall bias and are unable to separate the effects of aging from secular trend. Hence, a longitudinal study is warranted to determine the precise trajectory of uric acid during the menopause transition.

This study has several limitations. First, the study design was cross-sectional and did not allow us to infer a cause–effect relationship between uric acid level and BMD. However, one previous longitudinal study demonstrated that higher serum uric acid levels were associated with slower annual decline in BMD in peri- and postmenopausal women [16]. Second, we employed an EM algorithm to impute missing values in covariates. Missing values occurred mostly in two variables—physical activity and age at menopause. Sensitivity analysis excluding women with any missing values in covariates yielded similar, albeit not significant, effect sizes of the association between BMD and uric acid, indirectly supporting the robustness of the approach. The association failed to reach statistical significance due to the reduced number of women included in the sensitivity analysis. Third, the data were obtained from the medical records of female teachers who had received health checkup annually and were therefore expected to be generally in good health and health conscious. In fact, the prevalence of comorbidity such as hypertension and diabetes, and the smoking rate were lower than those in the general population [40–42]. In addition, the women in this study had lower weight compared with peri- and postmenopausal Australian women in a previous study on uric acid and BMD [16]. Thus, the observed associations of uric acid with menopause and BMD were less likely to be confounded by obesity and other comorbidity, but the generalizability of the findings to other populations may be limited. In addition, BMD measurement was performed voluntarily, which could introduce selection bias. However, women in the analysis were comparable to those excluded from the analysis, most of whom had not had BMD measurement and excluded. Fourth, the observed association was marginally significant. We speculate that it is mostly likely due to relatively small sample size because the finding was consistent throughout various models. Lastly, any observational studies like this one cannot be free of possible confounding due to uncontrolled or unmeasured variables. Several important variables such as bone turnover markers, PTH, and serum 25-hydroxyvitamin D were not measured or available for the analysis.

Despite these limitations, the study has several strengths. Even though this was a retrospective analysis, the data were drawn from medical records for health checkup, which were in general free of missing values except for a few measurements. These measurements were performed voluntarily or as a part of optional examinations. The main finding was robust to the inclusion of a variety of covariates including years after menopause and exclusion of older women.

In conclusion, the present study showed that higher uric acid levels in the physiologic range of uric acid are linearly associated with higher lumbar spine bone mineral density in peri- and postmenopausal Japanese women. Further research is needed to elucidate the precise underlying mechanism of the association between uric acid and bone mineral density and to determine if the positive association between BMD and uric acid is still observed in the hyperuricemic range.

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**Conflicts of interest** None.

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Geriatr Gerontol Int 2014; 14: 159–166

ORIGINAL ARTICLE — EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

# Association of decreased sympathetic nervous activity with mortality of older adults in long-term care

Koji Shibasaki,[1] Sumito Ogawa,[1] Shizuru Yamada,[2] Katsuya Iijima,[1] Masato Eto,[1] Koichi Kozaki,[2] Kenji Toba,[3] Masahiro Akishita[1] and Yasuyoshi Ouchi[1]

[1]*Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo,* [2]*Department of Geriatric Medicine, Kyorin University School of Medicine, Tokyo, and* [3]*National Center for Geriatrics and Gerontology, Obu, Japan*

**Aim:** To investigate the relationship between physical function, mortality and autonomic nervous activity measured by heart rate variability of elderly in long-term care.

**Methods:** Cross-sectional and longitudinal studies were carried out at hospitals and health service facilities for the elderly in Nagano prefecture, Japan, from July 2007 to March 2011. A total of 105 long-term care older adults and 17 control older adults with independent physical function were included. The Functional Independence Measure (FIM) and Barthel Index were determined as indices of physical function. Twenty-four-hour Holter monitoring was carried out. From RR intervals in electrocardiograms, heart rate and standard deviations of all NN intervals in all 5-min segments of the entire recording, power spectral density, low frequency, high frequency and low frequency/high frequency (LF/HF) were calculated.

**Results:** FIM score and Barthel Index were 46 ± 26 and 30 ± 31, respectively, in long-term care elderly. FIM and Barthel index were significantly correlated with heart rate and the standard deviations of all NN intervals after adjustment for age, sex, cardiovascular risk factors and FIM. Furthermore, LF/HF was significantly decreased in long-term care elderly compared with control elderly after adjustment for covariates. In addition, decrease in LF/HF was an independent risk factor for mortality.

**Conclusion:** Low LF/HF activity was observed in long-term care elderly and was related to an increase of overall mortality. **Geriatr Gerontol Int 2014; 14: 159–166.**

**Keywords:** heart rate variability, long-term care, mortality, motor activity, sympathetic nervous system.

## Introduction

The number of older adults who require long-term care (LTC) has been increasing in Japan, and it was reported that there were 4.67 million older adults in LTC in 2008.[1] One of the characteristics of older adults in long-term care is physical and cognitive dysfunction. Physical dysfunction, including slow gait, low handgrip strength, low physical activity, weight loss and exhaustion, are reported to be associated with increased overall mortality.[2] In Japan, LTC elderly is defined as those who require assistance with walking, moving, and washing their face, body and mouth, representing functional disability and high mortality.[3] Thus, it is important to maintain or increase physical function in LTC elderly.

The underlying causes of physical dysfunction in Japanese LTC elderly include cerebrovascular disease, dementia, fractures, falls, weakness as a result of aging, and arthritis.[3] Recent studies have shown that these diseases with physical dysfunction are associated with low sympathetic nervous system activity.[4–7]

Skin sympathetic reactivity (SSR) reflects sympathetic nervous system activity. Muslumanoglu *et al.* showed that low SSR was associated with greater severity of paralysis, and depression of sympathetic reflex activity was associated with moderate or severely limited motor function in the chronic phase of ischemic cerebrovascular disease in elderly patients.[5] In addition, low plasma norepinephrine and low iodine-131-meta-iodobenzylguanidine ($^{123}$I-MIBG) uptake were observed in patients with Lewy body dementia compared with normal healthy subjects.[6,7] RR intervals in the electrocardiogram are utilized to evaluate heart rate variability

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Correspondence: Dr Sumito Ogawa MD PhD, Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Email: suogawa-tky@umin.ac.jp

(HRV), which reflects autonomic nervous system activity.[8] In practice, low frequency/high frequency (LF/HF), a marker of sympathovagal balance or sympathetic modulation, showed a positive correlation with respiratory and skeletal muscle strength in chronic obstructive pulmonary disease.[4] Furthermore, decreased LF/HF was related to overall mortality in frail older adults.[9]

In addition to measurement of SSR, norepinephrine spillover and $^{123}$I-MIBG scintigraphy uptake, HRV has recently been used as a marker of autonomic nervous function.[8] HF was reported to reflect parasympathetic nervous system activity and LF/HF to represent sympathovagal balance or sympathetic modulation. In addition, decreased HRV was associated with cardiovascular disease (CVD),[10] cardiac death[11] and all-cause mortality.[9] Whereas HRV is known to decrease with the aging process,[12,13] little is known about the relationship between sympathetic nervous activity and mortality in LTC elderly.

In the Framingham heart study, a cohort study in American community-dwelling people, mortality and HRV were investigated in older adults, and it was not shown that low LF/HF correlated with mortality,[14] whereas in a cohort study of frail older adults, low LF/HF was significantly correlated with both frailty and mortality in the Women's Health and Aging Study-I (WHAS-I).[9]

Aging attenuates sympathetic nervous modulation,[12,13] and previous studies suggested that low sympathetic nervous activity might be associated with physical and cognitive dysfunction. However, only some of the subjects were frail or LTC elderly,[9,14] and there is little evidence describing the relationship between physical function, mortality and sympathetic nervous activity in LTC elderly. In particular, few studies have focused on the specific characteristics of sympathetic nervous activity in LTC elderly. Therefore, we investigated the relationship between sympathetic nervous activity, measured by HRV, and physical function and mortality in older adults in LTC.

## Methods

### *Study design and participants*

The present observational study analyzed 105 consecutive older adults in LTC aged 75 years or older who were admitted to a rehabilitation unit or a health service facility for older adults that provided rehabilitation. All hospitals and health service facilities were located in Nagano prefecture, Japan. Inclusion criteria were older adults in LTC aged 75 years or older receiving rehabilitation. Exclusion criteria were treatment of acute phase diseases within the past 2 weeks, arrhythmia, administration of anti-arrhythmia drugs or β-blockers, malignancy and neurodegenerative diseases other than dementia. As a control for the present study, we recruited 17 elderly outpatients with intact activities of daily living (ADL) who were matched for age, sex and CVD risk factors. The same inclusion and exclusion criteria were used for these control subjects. Medical records were reviewed to obtain information about the medical history of CVD, such as hypertension, diabetes mellitus, hyperlipidemia, chronic heart failure and ischemic heart disease, which was confirmed by the patients or their family. The present study protocol was approved by the institutional review board of the facility. Written informed consent was obtained from all participants or their families.

### *Heart rate variability*

Ambulatory Holter recording was carried out for 24 h using QR2100 (Fukuda ME Kogyo, Tokyo, Japan) and processed with HS1000VL (Fukuda ME Kogyo). For time domain analysis, the standard deviations of all NN intervals in all 5-min segments of the entire recording (SDANN) were calculated, and frequent domain analysis was carried out with fast Fourier transform. From the power spectral density, low frequency (LF; 0.04~0.15 Hz), high frequency (HF; 0.15~0.40 Hz) and low frequency/high frequency (LF/HF) were determined.

### *Anthropometric, physical function and hematological measures*

Height, weight and body mass index (BMI) were measured before Holter monitoring. The Functional Independence Measure (FIM)[15] and Barthel Index[16] were determined in order to assess physical function. Venous blood samples were obtained from participants in the morning after an overnight fast. Blood cell counts and serum levels of chemical parameters were determined by a commercial laboratory (Health Science Research Institute, Yokohama, Japan).

### *Statistical analysis*

Data were analyzed using SPSS software version 11.0.1J (SPSS Japan, Tokyo, Japan). Mann–Whitney *U*-test for continuous variables and $\chi^2$-test for categorical variables were used to compare controls and LTC elderly. Pearson's correlation coefficient was calculated, and standardized multiple regression analysis of HRV indices was carried out with age, sex, FIM, Barthel Index and blood nutritional data as covariates. Multiple regression analysis was used to calculate Cox hazard ratio, with adjustment for age, sex, clinical risk factors and FIM. Kaplan–Meier survival rate was computed for HRV indices.

**Table 1** Characteristics of long-term care elderly and healthy elderly controls

| | LTC elderly | Controls | *P* |
|---|---|---|---|
| No. participants | 105 | 17 | |
| Age (years) | 86.5 ± 6.0 (75–100) | 86.3 ± 9.1 (75–103) | 0.311 |
| Sex, male (%) | 29 (27.6) | 6 (35.3) | 0.999 |
| Body mass index | 19.5 ± 3.3 | 22.0 ± 3.5 | 0.009 |
| Cardiovascular risk factors, *n* (%) | | | |
| Hypertension | 57 (54.3) | 11 (64.7) | 0.590 |
| Diabetes mellitus | 13 (12.4) | 2 (11.8) | 0.999 |
| Hyperlipidemia | 14 (13.3) | 3 (17.6) | 0.921 |
| Chronic heart failure | 12 (11.4) | 1 (5.9) | 0.792 |
| Ischemic heart disease | 15 (14.3) | 1 (5.9) | 0.572 |
| Physical function | | | |
| FIM | 46 ± 26 | 116 ± 24 | <0.001 |
| Barthel Index | 30 ± 31 | 92 ± 16 | <0.001 |
| Blood nutritional data | | | |
| Albumin (g/dL) | 3.5 ± 0.5 | 3.9 ± 0.3 | <0.001 |
| Hemoglobin (g/dL) | 12.0 ± 1.8 | 12.4 ± 2.2 | 0.188 |
| Total cholesterol (mg/dL) | 177 ± 40 | 175 ± 34 | 0.892 |
| Heart rate variability indices | | | |
| SDANN | 85.0 ± 34.3 | 112.1 ± 27.2 | 0.001 |
| Heart rate (b.p.m.) | 73.1 ± 12.1 | 71.5 ± 7.4 | 0.878 |
| LF ($ms^2$) | 36.1 ± 25.3 | 42.4 ± 37.5 | 0.274 |
| HF ($ms^2$) | 65.9 ± 56.3 | 60.7 ± 52.3 | 0.813 |
| LF/HF | 0.69 ± 0.27† | 0.87 ± 0.31 | 0.023 |

Values are mean ± standard deviation. †After adjusted for age, sex, cardiovascular risk factors and Function Independent Measure (FIM), low frequency/high frequency (LF/HF) were significantly lower in long-term care elderly than healthy controls ($P = 0.049$). HF, high frequency; LF, low frequency; SDANN, standard deviations of the all NN intervals in all 5-min segments of the entire recording.

## Results

We registered 105 elderly in LTC, and assessed HRV from 24-h Holter monitoring. The underlying diseases of older adults in LTC for rehabilitation were cerebrovascular disease ($n = 59$, 56.2%), disuse syndrome ($n = 26$, 24.8%), fracture ($n = 19$, 18.1%) and dementia ($n = 1$, 1.0%). The proportions of underlying diseases were similar to those reported in Japanese older adults in LTC.[3]

The background data of the present study are shown in Table 1. In LTC elderly, mean age was 86.5 ± 6.0 years, blood nutritional data including albumin, hemoglobin and total cholesterol were at the lower limit of the normal range, and physical function represented by FIM and Barthel Index was significantly lower (46 ± 26 and 30 ± 31, respectively) than that in elderly controls (116 ± 24 and 92 ± 16, respectively). Scores for each FIM item were as follow: eating 3.7 ± 2.2, grooming 2.6 ± 1.8, bathing 1.5 ± 1.1, upper body dressing 2.5 ± 1.7, lower body dressing 2.2 ± 1.6, toileting 2.7 ± 2.0, bladder management 2.6 ± 2.1, bowel management 2.4 ± 2.0, bed to chair transfer 3.0 ± 1.9, toilet transfer 2.4 ± 1.7, shower transfer 1.5 ± 1.4, locomotion (ambulatory or wheelchair level) 2.0 ± 1.8, stairs 1.2 ± 0.8, cognitive comprehension 3.6 ± 2.2, expression 3.6 ± 2.2, social interaction 3.2 ± 2.2, problem solving 2.8 ± 1.9 and memory 2.8 ± 1.9. These score showed that the overall participants required moderate care supporting physical and cognitive function. In addition, BMI, albumin, SDANN and LF/HF were significantly decreased in LTC elderly compared with elderly controls. After adjustment for covariance, of all HRV indices, only LF/HF was significantly lower in LTC elderly (Table 1). Data of HRV indices were obtained every 5 min, and averaged every 3 h to examine the circadian rhythm in both LTC elderly and healthy controls. A significant decrease of LF/HF was observed in the night-time in healthy controls, whereas there was a loss of circadian rhythm in LTC elderly (Fig. 1).

Multiple regression analysis showed that the associations between heart rate, SDANN and physical function (Barthel Index and FIM) were independent of age, sex, and CVD. Furthermore, albumin and hemoglobin were also correlated with heart rate and SDANN. In contrast, LF, HF and LF/HF were not significantly correlated with physical function and blood nutritional data (Table 2).

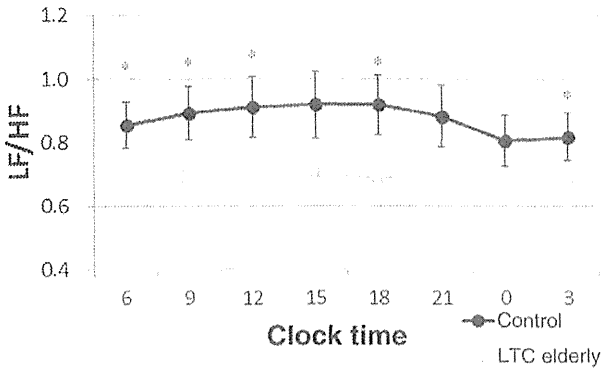


**Figure 1** The activity of low frequency/high frequency (LF/HF) in long-term care (LTC) elderly and controls. The RR interval data were measured every 5 min, and averaged every 3 h. $^{*}P < 0.05$, mean ± SEM.

Next, we followed the survival of LTC elderly, and 23 people died among 105 LTC elderly during a mean follow-up period of 8.9 months. The major cause of death was pneumonia ($n = 12$). There was no sign of stroke among the study participants, and one participant with acute myocardial infarction was observed during the follow-up period. Mortality according to HRV indices divided by the average is shown in Table 3. After adjustment for covariates, of all HRV indices, only LF/HF was associated with mortality. Kaplan–Meier survival curves also showed an association between decreased LF/HF and high mortality (Fig. 2). In addition to adjusted covariates, BMI, Barthel Index, and blood nutritional data were not different between the high LF/HF group and low LF/HF group (data not shown).

## Discussion

In the present study, we investigated the relationship between physical function, mortality and sympathetic nervous activity measured by HRV in Japanese LTC elderly, and it was shown that LF/HF was significantly decreased in LTC elderly after adjustment for age, sex, CVD risk factors and FIM compared with elderly controls. In addition, the circadian rhythm of LF/HF was lost in LTC elderly, and low LF/HF was associated with overall mortality.

In a previous study, low LF/HF was associated with both frailty and mortality in community-dwelling people of whom one-third were frail elderly,[9] and these associations were consistent with the present data. Additionally, low LF/HF was also shown in LTC elderly, and was independent of physical function.

Elevated heart rate or low SDANN leads to cardiovascular disease and low physical function,[17,18] and the same relationship was also observed in LTC elderly. Furthermore, low albumin and low hemoglobin were observed in the high heart rate group, and limited physical function was observed in LTC elderly. These results are supported by a previous report.[19] So it might be possible to improve the physical function of LTC elderly by maintaining their nutritional state. The high LF/HF group has been reported to show high physical function and muscle mass,[4,20] whereas the present data did not show this association. One of the reasons for this discrepancy is thought to be the effect of aging. Aging generally attenuates LF/HF, and the patients in the present study were older than those in other studies.[9,14] Another reason might be autonomic nervous system disturbance. In particular, the circadian rhythm of LF/HF was impaired in LTC elderly.

Circadian imbalance of LF/HF has been shown in some disorders, such as Parkinson's disease, type 2 diabetes mellitus (T2DM) and ischemic stroke;[21–23] and furthermore, physical activity also influences HRV indices.[24,25] In the present study, LTC elderly with Parkinson's disease were excluded, and CVD risk factors including T2DM were matched between LTC elderly and healthy controls, as stroke and physical activity might affect LF/HF. However, the influence of both conditions on LF/HF is controversial. High physical activity and good posture led to high LF/HF activity,[26] whereas it was also suggested that LF/HF was not affected by physical activity.[13] The effect of LF/HF on stroke is also controversial.[23,27,28] In ischemic stroke patients, LF/HF was higher than healthy controls in some studies,[27,28] whereas another study suggested that LF/HF was lower in patients.[23] So the mechanism of LF/HF circadian rhythm disturbance is not clear, though its recovery might be important to increase physical function in LTC elderly. Other reasons why LF/HF and physical function did not show a correlation in LTC elderly might to be the effects of stroke, insufficient exposure to daylight and posture at daytime. All participants were aged over 75 years in the present study, and there is a possibility that asymptomatic lacunar infarction might be observed. It has also been suggested that lacunar infarction disturbs the autonomic nervous system, leading to a decrease in LF/HF and the related value of the autonomic nervous system, resulting in a disappearance of the correlation between physical activity and LF/HF. In addition, exposure to daylight was known to be one of the most powerful rhythmic regulators in the environment.[29] All participants in the present study spent their time indoors for rehabilitation and care. Furthermore, it is known that the supine position increases HF and decreases LF/HF,[30] and LTC elderly participants who were at rehabilitation units or health service facilities might spend more time in bed compared with outpatient controls, leading to low LF/HF and disappearance of the correlation between LF/HF and physical activity in the present study.

**Table 2** Multiple regression analysis of heart rate variability indices with physical function and blood nutritional data after adjusted for age, sex and cardiovascular risk factors

| | HR | SDANN | LF | HF | LF/HF |
|---|---|---|---|---|---|
| FIM | −0.25* | 0.28* | 0.19 | 0.15 | −0.08 |
| Barthel Index | −0.27* | 0.29* | 0.08 | 0.04 | 0.00 |
| Body mass index | −0.05 | 0.05 | 0.00 | −0.08 | 0.19 |
| Albumin | −0.21* | 0.25* | 0.05 | −0.02 | 0.11 |
| Hemoglobin | −0.20* | 0.27* | 0.12 | 0.12 | 0.05 |
| Total cholesterol | −0.01 | −0.05 | −0.13 | −0.17 | 0.03 |

*$P < 0.05$, analyzed in 105 long-term care elderly. FIM, function independent measure; HF, high frequency; HR, heart rate; LF, low frequency; SDANN, standard deviations of the all NN intervals in all 5-min segments of the entire recording.

**Table 3** Proportional hazards regression analysis of the impact of heart rate variability measure on overall mortality

| | Hazard ratio† | 95% Confidence interval | *P* |
|---|---|---|---|
| Unadjusted | | | |
| SDANN (ms) | 1.84 | 0.77–4.38 | 0.171 |
| LF ($ms^2$) | 1.61 | 0.59–4.38 | 0.353 |
| HF ($ms^2$) | 2.14 | 0.72–6.34 | 0.169 |
| LF/HF | 4.73 | 1.59–14.06 | 0.005 |
| Age, sex and cardiovascular risk factors adjusted for association with mortality | | | |
| SDANN (ms) | 1.53 | 0.60–3.86 | 0.372 |
| LF ($ms^2$) | 1.65 | 0.57–4.78 | 0.357 |
| HF ($ms^2$) | 2.60 | 0.82–8.22 | 0.105 |
| LF/HF | 3.37 | 1.02–11.07 | 0.046 |
| Age, sex, FIM and cardiovascular risk factors adjusted for association with mortality | | | |
| SDANN (ms) | 1.19 | 0.44–3.17 | 0.736 |
| LF ($ms^2$) | 1.49 | 0.50–4.41 | 0.475 |
| HF ($ms^2$) | 2.85 | 0.83–9.83 | 0.097 |
| LF/HF | 3.61 | 1.08–12.10 | 0.038 |

Based on 23 deaths among 105 participants. Mean values of heart rate variability measure are in Table 1. †Hazard ratio of death rates of participants whose heart rate variability were less than average. FIM, function independent measure; HF, high frequency; HR, heart rate; LF, low frequency; SDANN, standard deviations of the all NN intervals in all 5-min segments of the entire recording.

Recent studies showed that decreased HRV indices including LF, HF and LF/HF were associated with CVD risk factors, and decreased LF was an independent predictor of death in elderly people.[31,32] However, the present findings showed that, of all HRV indices, only LF/HF was associated with mortality. This result is supported by a previous study in which, of HRV indices, LF/HF was associated with both frailty and mortality.[9] The major difference between the present study and other studies is whether or not the participants included frail LTC elderly. All participants were LTC elderly in the present study and WHAS-I, which was reported by Varadhan *et al.* and consisted of one-third frail elderly, whereas in other studies the participants were community-dwelling older adults with intact ADL, and they did not consider physical function.[14,32,33] These results suggest that the significance of LF/HF might differ between LTC elderly and elderly with intact ADL and physical function.

There is a discrepancy in the results derived from studies of LTC elderly and studies of elderly with intact physical function regarding sympathetic nervous activity. Exercise activates the sympathetic nervous system, leading to an increase in blood pressure, muscle blood