



Longitudinal Changes in Physical and Cognitive Functions among Participants with and without Rheumatoid Arthritis in Community-Dwelling Middle-Aged and Older Adults

Mikako Yasuoka¹, Chikako Tange², Yukiko Nishita², Makiko Tomida², Ryota Watanabe^{1,3,4}, Hiroshi Shimokata^{2,5}, Rei Otsuka², Masayo Kojima^{1,6}

¹Department of Frailty Research, Research Institute, National Center for Geriatrics and Gerontology, Obu, Japan

²Department of Epidemiology of Aging, Research Institute, National Center for Geriatrics and Gerontology, Obu, Japan

³Center for Well-Being and Society, Nihon Fukushi University, Nagoya, Japan

⁴Department of Social Preventive Medical Sciences, Center for Preventive Medical Sciences, Chiba University, Chiba, Japan

⁵Graduate School of Nutritional Sciences, Nagoya University of Arts and Sciences, Nisshin, Japan

⁶Department of Public Health, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Corresponding Author:

Rei Otsuka, PhD

Department of Epidemiology of Aging,
Research Institute, National Center for
Geriatrics and Gerontology, 7-430
Morioka, Obu, Aichi 474-8511, Japan

E-mail: otsuka@ncgg.go.jp

ORCID:

<https://orcid.org/0000-0001-6184-570X>

Received: November 22, 2022

Revised: February 24, 2023

Accepted: March 4, 2023

Background: This study evaluated the chronological changes in physical and cognitive functions in middle-aged and older adults with and without rheumatoid arthritis (RA). **Methods:** This population-based case-control longitudinal study included individuals aged 40–79 years at baseline who agreed to participate. We identified 42 participants with RA and randomly selected 84 age- and sex-matched controls. Physical function was assessed according to gait speed, grip strength, and skeletal muscle mass. Cognitive function was assessed based on the information, similarities, picture completion, and digit symbol substitution test scores of the Wechsler Adult Intelligence Scale-Revised Short Form. The general linear mixed models comprised the fixed effects of the intercept, case, age, time in years since baseline, and casextime interaction, which were used to examine longitudinal changes in physical and cognitive functions. **Results:** Regardless of RA status, grip strength decreased and the picture completion score increased in the group aged <65 years, while skeletal muscle mass index and gait speed decreased in the group aged ≥65 years. The interaction of casexfollow-up years for grip strength in the group aged ≥65 years was significant ($p=0.03$). The decline in grip strength in the control group (slope= -0.45) was greater than that in the RA group (slope= -0.19). **Conclusion:** Chronological changes in physical and cognitive functions were comparable between participants with and without RA; however, the decline in grip strength in the control group was greater among older adults with RA.

Key Words: Physical examination, Cognition, Rheumatoid arthritis, Aging

INTRODUCTION

Alterations in physical and cognitive functions with age are generally related to adverse health outcomes. Skeletal muscle mass,¹⁾ grip strength,²⁾ and gait speed³⁾ gradually decrease with age. Structural and functional changes related to disability^{4,5)} increase the risk of mortality.⁶⁻⁸⁾ Cognitive function comprises multiple do-

main components that change with age.⁹⁾ Some domains of cognitive function, such as memory, information processing speed, search speed, and verbal memory, are associated with survival in later adulthood.¹⁰⁻¹²⁾

Rheumatoid arthritis (RA) is a chronic inflammatory disease. Patients with RA experience pain, and insufficient disease control may result in cartilage damage.¹³⁾ Skeletal muscle mass, gait speed, and grip strength are lower in patients with RA than in communi-

ty-dwelling adults because of this burden.¹⁴⁾ Additionally, the estimated number of older patients with RA is increasing^{15,16)} due to a surge in late-onset RA¹⁷⁾ and decreasing mortality.¹⁸⁾ The number of older patients with RA and the number of patients with RA having a high risk of disability are increasing. However, the association between RA and cognitive function is unclear. Opposing mechanisms are involved in the association between RA and cognitive function, and evidence of the association between the two is limited. A population-based case-control study reported an inverse association between a history of RA and Alzheimer disease.¹⁹⁾ Other studies have shown higher risks of dementia in patients with RA,²⁰⁻²²⁾ chronic inflammation with neurological involvement, accelerated atherosclerosis, and subsequent cognitive impairment.²³⁾ Biological disease-modifying antirheumatic drugs and anti-tumor necrosis factor drugs may have beneficial effects on cognitive impairment.²⁴⁾

Most previous studies have not matched the controls for comparisons of physical and cognitive functions and have not monitored the changes in these functions using longitudinal data. Hence, in this study, we aimed to identify longitudinal changes in physical and cognitive functions in participants with RA compared with those in community-dwelling adults. We evaluated middle-aged and older adults separately because changes in physical function vary between the two age groups.²⁵⁻²⁷⁾

MATERIAL AND METHODS

Study Participants

This study was conducted as part of the National Institute for Longevity Sciences—Longitudinal Study of Aging (NLS-LSA).²⁸⁾ This population-based prospective cohort study screens for aging and age-related diseases. In this project, the normal aging process was assessed using detailed questionnaires, medical checkups, anthropometric measurements, physical fitness tests, and nutritional examinations. The participants were a random sample of community-dwelling adults who were stratified based on age and sex. They were aged 40–79 years at the time of their initial participation and lived in Obu-shi and Higashiura-cho, Aichi Prefecture, Japan. These participants were followed up every 2 years from the first (November 1997–April 2000) to the second (April 2000–May 2002), third (May 2002–May 2004), fourth (June 2004–July 2006), fifth (July 2006–July 2008), sixth (July 2008–July 2010), and seventh (July 2010–July 2012) study waves. When participants could not be followed up, new age-(decade) and sex-matched participants were randomly recruited from the second to seventh study waves, and individuals aged 40 years were newly recruited every year. The study protocol was approved by the Com-

mittee of Ethics of Human Research of the National Center for Geriatrics and Gerontology (No. 1633). Written informed consent was obtained from all participants. Also, this study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.²⁹⁾

The total number of NLS-LSA participants was 3,983. We included individuals who did not report having medical conditions that could affect physical and cognitive functions, such as a history of stroke, heart disease, cancer, or dementia, using a self-administered questionnaire at baseline. Individuals were categorized into the RA and control groups. Participants with RA (RA group) were defined as those who answered that they had received RA treatment, had been treated for RA, or were not currently treated but had been treated for RA previously in the fifth to seventh study wave questionnaires because we did not distinguish between RA and other forms of arthritis, such as osteoarthritis, until the fourth study wave. The baseline for participants with RA was defined as the study wave in which they first answered that they had RA or arthritis. We excluded participants with RA who did not join the NLS-LSA more than twice. We selected the controls as follows: first, we randomly selected controls without RA whose age and sex matched those of participants with RA in the first wave in a ratio of 2:1. After excluding the participants selected as controls in the first study wave, we selected controls in the second study wave in the same manner as that in the first study wave. When those in the control group did not participate in the NLS-LSA more than twice, we selected other control participants. We repeatedly selected controls until the sixth study wave. Finally, 42 participants with RA and 84 controls were chosen.

Measurements

Physical function (baseline and follow-up survey)

Appendicular lean mass (ALM), grip strength, and gait speed were assessed as physical functions. ALM was assessed using a dual-energy X-ray absorptiometer (QDR-4500; Hologic, Bedford, MA, USA).³⁰⁾ The skeletal muscle mass index (SMI) was calculated as the ALM divided by the height squared (kg/m^2). Grip strength was measured using a handgrip dynamometer (T.K.K.4301a; Takei, Niigata, Japan). In this assessment, the participants were instructed to hold a hand grip dynamometer while standing with their arms at their sides and their elbows extended and to squeeze with maximum force, alternating the left and right hands twice.³¹⁾ A maximum of two readings from each hand was used as the measurement result. Gait speed was assessed using a walking analysis system (YW-3; Yagami Co., Aichi, Japan).³²⁾ The participants walked at a comfortable speed on an 11-m straight walkway, in-

cluding acceleration and deceleration. The start and end times to walk 10 m were recorded using light sensors, and habitual gait speed was measured three times by calculating the time in meters per second. The gait speed was determined from the first trial wherein stride length, pitch, and gait speed were measured simultaneously and used as the measurement result.

Cognitive function (baseline and follow-up survey)

Cognitive abilities were assessed using the Japanese version of the Wechsler Adults Intelligence Scale-Revised Short Form (WAIS-R-SF).³³⁾ The WAIS-R-SF consists of information, similarity, picture completion, and digit symbol substitution scales. Trained clinical psychologists or graduate students specializing in psychology administered the test to the participants individually. The information test evaluates general knowledge about people, places, and events (29 items; possible range, 0–29). The similarities test assesses logical abstract thinking by asking participants to state how similar two things are to each other (14 items; possible range 0–28). The picture completion test gauges visual perception and long-term visual memory by asking participants to spot the missing elements in a series of drawings (21 items, possible range 0–21). The digit symbol substitution test measures processing speed by asking participants to write as many symbols as possible that correspond to a given number in 90 seconds (possible range 0–93). In all tests, higher scores indicate better cognitive function.

Covariates (baseline)

At baseline, data on age, sex (male, female), education level (≥ 12 years, < 12 years), and history of hypertension or diabetes mellitus (none, presence) were collected using a self-administrated questionnaire. Body weight and height were measured using digital scales to the nearest 0.1 kg and 0.1 cm, respectively. The participants were requested to wear light clothing and no shoes. Body mass index (BMI) was calculated as the body weight in kilograms divided by the square of the height in meters. According to BMI, the participants were categorized into three groups: < 18.5 , ≥ 18.5 and < 25 , and ≥ 25 kg/m^{2,34)}.

Statistical Analysis

The participants were classified into two age groups: < 65 years (40–64 years) and ≥ 65 years (65–79 years) at baseline because the slope of decreasing physical function differs between middle-aged and older adults.²⁵⁻²⁷⁾ We analyzed the data according to these groups. When certain variables were missing for a participant, the entire data for that participant in the same wave were deleted. Subsequent analysis was performed by age group. The baseline characteristics in the RA and control groups were examined

using t-test or chi-square tests in each age group. General linear mixed models were used to evaluate the effects of RA presence on longitudinal changes in physical and cognitive functions. The model used in this study included fixed terms for the intercept, case (RA or control), age (at baseline), time (time in years since baseline), and case \times time interaction. The case \times time interaction was expected to indicate whether the change in physical and cognitive functions varied according to the presence or absence of RA. A history of hypertension or diabetes, BMI categories (for physical function),³⁵⁾ and education categories (for cognitive function)³⁶⁾ were considered covariates. Additionally, the models included random intercepts and slope terms that captured participant-specific deviations.

All statistical data were analyzed using SAS System (version 9.3; SAS Institute, Cary, NC, USA). Two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Table 1 shows the baseline characteristics of the RA and control groups according to age. The physical and cognitive functions at baseline did not differ significantly between the two groups in either age group. The follow-up time in the RA group was significantly longer than that in the control group aged ≥ 65 years.

Table 2 presents the results of the general linear mixed-model parameter estimates for physical function in each age group. The parameter estimates of fixed effects for the follow-up years declined significantly for grip strength (both $p < 0.001$) in both age groups and for SMI ($p < 0.01$) and gait speed ($p = 0.01$) in the group aged ≥ 65 years. The average grip strength of the RA group aged ≥ 65 years was significantly lower than that of the control group ($p = 0.01$). The interaction effect of case \times time was significant for grip strength in the group aged ≥ 65 years. Fig. 1 illustrates the grip strength changes in the group aged ≥ 65 years, which were estimated by substituting baseline age, follow-up years, and the effects of the case \times time interaction (Fig. 1). The slope of the grip strength change in the control group was steeper (slope = -0.45) than that in the RA group (slope = -0.19). Regarding cognitive abilities, the information ($p < 0.001$) and similarity ($p = 0.01$) scores increased with follow-up years in the group aged < 65 years. The average picture completion score increased with follow-up years in both age groups ($p < 0.001$ for < 65 years; $p = 0.03$ for ≥ 65 years). However, no significant difference in cognitive function scores was observed between the RA and control groups. Furthermore, no significant effects of case \times time interaction for each cognitive domain were observed in either age group (Table 3).

Table 1. Baseline characteristics of the RA and control groups

	Aged < 65 years			Aged ≥ 65 years		
	RA (n = 25)	Control (n = 50)	p-value	RA (n = 17)	Control (n = 34)	p-value
Age (y)	53.2 ± 7.8	53.2 ± 7.7		72.3 ± 4.2	72.3 ± 4.2	
Sex, female	20 (80.0)	40 (80.0)		11 (64.7)	22 (64.7)	
BMI (kg/m ²)	22.9 ± 2.8	21.9 ± 3.1	0.16	23.3 ± 2.9	23.3 ± 2.9	1.00
SMI (kg/m ²)	6.8 ± 1.1	6.7 ± 1.0	0.53	6.8 ± 1.0	6.8 ± 1.0	0.97
Grip strength (kg)	28.4 ± 10.7	29.1 ± 7.1	0.73	24.2 ± 9.5	27.8 ± 8.0	0.16
Gait speed (m/s)	1.3 ± 0.2	1.4 ± 0.2	0.40	1.3 ± 0.2	1.2 ± 0.2	0.53
Cognitive abilities score						
Information	15.5 ± 5.3	14.1 ± 5.9	0.33	12.2 ± 4.0	13.3 ± 4.7	0.42
Similarities	15.4 ± 4.5	13.5 ± 5.4	0.14	10.7 ± 4.3	10.6 ± 4.0	0.96
Picture completion	12.7 ± 3.8	12.3 ± 2.6	0.59	9.6 ± 3.5	9.9 ± 3.7	0.77
Digit symbol substitution	58.2 ± 15.5	59.6 ± 13.0	0.70	39.5 ± 10.4	41.6 ± 9.6	0.47
Follow-up time (y)	10.5 ± 2.6	9.1 ± 3.4	0.09	7.2 ± 3.1	5.2 ± 3.2	0.04
Number of participations for the study	5.6 ± 1.5	5.3 ± 1.7	0.49	4.0 ± 1.6	3.4 ± 1.5	0.22
Education (y)						
< 12	6 (24.0)	11 (22.0)	0.85	15 (88.2)	22 (64.7)	0.10
History of hypertension or diabetes	4 (16.0)	10 (20.0)	0.14	5 (29.4)	18 (52.4)	0.14

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

RA, rheumatoid arthritis; BMI, body mass index; SMI, skeletal muscle mass index.

Table 2. General linear mixed model of fixed effects for physical function

	SMI			Grip strength			Gait speed		
	β	SE	p-value	β	SE	p-value	β	SE	p-value
Aged < 65 years									
Case	-0.13	0.17	0.45	-1.40	1.24	0.26	-0.07	0.04	0.053
Time (follow-up years)	-0.01	0.01	0.24	-0.31	0.06	<0.001	0.00	0.00	0.72
Case × time	-0.01	0.02	0.37	-0.02	0.10	0.84	0.00	0.00	0.20
Aged ≥ 65 years									
Case	-0.13	0.14	0.34	-3.68	1.46	0.01	0.04	0.04	0.41
Time (follow-up years)	-0.03	0.01	<0.01	-0.45	0.07	<0.001	-0.01	0.00	0.01
Case × time	0.02	0.01	0.12	0.26	0.11	0.03	0.01	0.01	0.44

SMI, skeletal muscle mass index; SE, standard error.

Adjusted for sex, age at baseline, history of hypertension or diabetes, body mass index, and random effect.

Case (0=control, 1=RA).

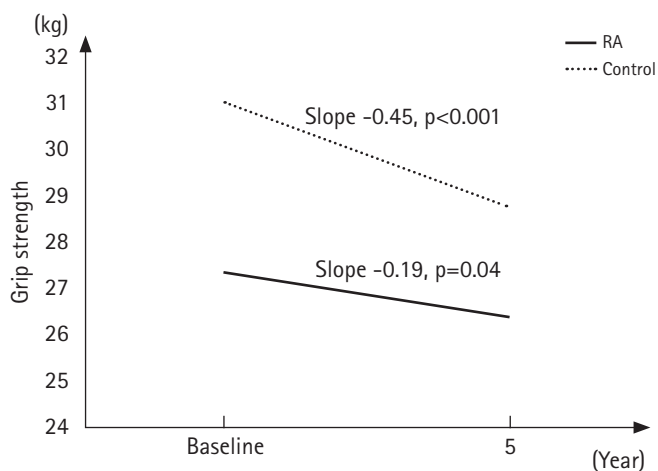


Fig. 1. Model-estimated 5-year changes in grip strength in the group aged ≥ 65 years by the rheumatoid arthritis (RA) and control groups. The solid lines are estimates for RA group, and the dashed lines are estimates for individuals without RA.

DISCUSSION

This study examined the longitudinal changes in physical function and cognitive abilities among the RA group compared to those in non-RA controls selected from a large community-based cohort. The interaction between case and follow-up time for grip strength in the group aged ≥ 65 years was significant. The decline in grip strength in the control group was greater than that in the RA group. Our results did not reveal greater decreases or increases in physical or cognitive function in the RA group compared with those in the control group.

Furthermore, except for grip strength, we did not observe significant differences in physical and cognitive functions between the RA and control groups. In this study, grip strength decreased in both groups, with parameter estimates of grip strength for follow-up years of -0.31 and -0.45 for the groups aged < 65 years and

Table 3. General linear mixed model of fixed effects for cognitive abilities

	Information			Similarities			Picture completion			Digit symbol substitution		
	β	SE	p-value	β	SE	p-value	β	SE	p-value	β	SE	p-value
Aged < 65 years												
Case	0.71	1.21	0.56	0.67	1.09	0.54	-0.02	0.70	0.98	-1.78	2.38	0.46
Time (follow-up years)	0.16	0.05	<0.001	0.15	0.06	0.01	0.20	0.03	<0.001	0.14	0.08	0.09
Case \times time	-0.06	0.08	0.48	-0.07	0.10	0.50	-0.03	0.05	0.58	-0.06	0.14	0.69
Aged \geq 65 years												
Case	-0.71	1.35	0.60	0.44	1.18	0.71	-0.13	1.02	0.90	0.40	2.61	0.88
Time (follow-up years)	0.01	0.07	0.85	-0.01	0.10	0.91	0.19	0.09	0.03	-0.17	0.13	0.19
Case \times time	-0.02	0.11	0.89	0.19	0.15	0.22	-0.03	0.14	0.81	0.05	0.20	0.80

SE, standard error.

Adjusted for sex, age at baseline, history of hypertension or diabetes, body mass index, and random effect.

Case (0=control, 1=RA).

\geq 65 years, respectively. This result was unexpected; moreover, previous studies have suggested an association of chronic inflammation with disability and dementia^{20,21,37} and reported that the changes in grip strength in RA populations were not affected by age but by other factors such as disease duration and disease activity.³⁸ A meta-analysis of the general population aged 20–100 years and RA population aged 31–65 years showed that grip strength decreased gradually with age, with a steeper decline at 50 years of age.³⁸ In contrast, the grip strength in the RA group was lower than that in the general population, did not show a steeper decline during middle age, and was associated with disease duration.³⁸ Our results were similar to those of a previous report showing that the grip strength of the RA group was lower than that of the control group and that the decline in the grip strength for the RA group was slower than that of the control group. The reduced grip strength might be due to disease duration or factors other than aging. The decline in grip strength in the RA group was slower than that in the control group, which was caused by the low grip strength of the RA group at the beginning of the follow-up. This may be because the case \times time interaction for grip strength was significant in the group aged \geq 65 years. Longitudinal studies are required to clarify the changes in grip strength in the RA and control groups.

Our results revealed a significant inverse association between SMI and aging in the group aged \geq 65 years but not in the group aged < 65 years. Longitudinal changes in SMI did not differ significantly between the RA and control groups. A cross-sectional study of healthy community-dwelling adults aged 40–79 years reported that SMI decreased gradually from middle age.³⁹ A 12-year follow-up longitudinal study in community-dwelling adults aged 40–79 years showed that SMI decreased with age, except in middle-aged men.³⁰ The association between SMI and aging in our study is in line with the previously reported results. In our study, gait speed decreased significantly in the group aged \geq 65 years but

did not decrease in the group aged < 65 years. Gait speed began to decrease in approximately the 60s.²⁶ The change in SMI and gait speed with age did not differ significantly in the RA and control groups, and the decline in gait speed in the RA group also likely occurred in the control group.

Crystallized intelligence increased with follow-up years in both the RA and control groups aged < 65 years. The picture completion score, which reflects fluid intelligence, also increased with age in age groups. A cross-sectional study of participants aged 18–99 years showed that crystallized intelligence increased until the sixth decade and was maintained or decreased slightly thereafter, while fluid intelligence declined from middle age.⁴⁰ Our results on crystallized intelligence were consistent with those reported previously.⁴⁰ The difference in picture completion may be affected by participant memory. As our study participants answered the same questions repeatedly, their knowledge of the previous questions and answers might have influenced their subsequent correct answers. Chronic inflammation causes atherosclerosis and cognitive impairment.^{23,41} In contrast, antirheumatic drugs may exert beneficial effects on cognitive impairment.²⁴ The findings regarding the association between RA and cognitive function remain debatable. We do not have a clear explanation for the lack of difference in the change in cognitive function between the RA and control groups.

This study has several limitations. First, the participants were recruited from a random sample of community-dwelling middle-aged and older adults. However, they were relatively physically or mentally healthy because they could repeatedly participate in the study at our institution. Additionally, the number of study participants was small. Therefore, our findings cannot be extrapolated to patients with RA with severe disabilities. Second, we did not define RA based on diagnostic criteria,⁴² which might have led to misclassification. Third, the follow-up time in the RA group was longer than that in the control group aged \geq 65 years. However,

these differences may not have affected the results of the analysis because the 2-year interval of each wave might have affected the difference and the number of participants did not differ significantly between the RA and control groups. Finally, patients with RA might have stiffness or deformity in their fingers, which might have caused decreased grip strength. Information on disease severity, duration, finger stiffness or deformity, and use of disease-modifying antirheumatic drugs was not collected. Although we did not collect information on the factors that affect physical function, participants with RA might have maintained their physical function because their baseline characteristics were not significantly different from those of the control group.

Chronological changes in physical and cognitive functions with aging are comparable between participants with RA and community dwellers without RA; however, the grip strength of those in the participants with RA showed a greater decline in older adults without RA.

ACKNOWLEDGMENTS

We thank all the participants and our colleagues in the NILS-LSA.

CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

FUNDING

This work was supported by the National Center for Geriatrics and Gerontology under Research Funding for Longevity Science (21-18, 21-19) and JSPS KAKENHI Grant Number JP20H03954.

AUTHOR CONTRIBUTIONS

Conceptualization, MY, MK; Data curation, CT, YN, MT, HS, RO; Methodology, MY, CT, RO, MK; Formal analysis, MY, CT, YN, MT; Funding acquisition, HS, RO, MK; Investigation, CT, YN, MT, HS, RO; Resources, RO; Data curation, RO; Writing – Original Draft, MY, CT, RW, RO, MK; Writing – Review & Editing, MY, CT, YN, MT, RW, HS, RO, MK.

REFERENCES

1. Jackson AS, Janssen I, Sui X, Church TS, Blair SN. Longitudinal changes in body composition associated with healthy ageing: men, aged 20-96 years. *Br J Nutr* 2012;107:1085-91.
2. Frederiksen H, Hjelmborg J, Mortensen J, McGue M, Vaupel JW, Christensen K. Age trajectories of grip strength: cross-sectional and longitudinal data among 8,342 Danes aged 46 to 102. *Ann Epidemiol* 2006;16:554-62.
3. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, et al. Gait speed and survival in older adults. *JAMA* 2011;305:50-8.
4. Bianchi L, Ferrucci L, Cherubini A, Maggio M, Bandinelli S, Savino E, et al. The predictive value of the EWGSOP definition of sarcopenia: results from the InCHIANTI study. *J Gerontol A Biol Sci Med Sci* 2016;71:259-64.
5. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc* 2002;50:889-96.
6. Bohannon RW. Hand-grip dynamometry predicts future outcomes in aging adults. *J Geriatr Phys Ther* 2008;31:3-10.
7. Brown JC, Harhay MO, Harhay MN. Sarcopenia and mortality among a population-based sample of community-dwelling older adults. *J Cachexia Sarcopenia Muscle* 2016;7:290-8.
8. Veronese N, Stubbs B, Volpato S, Zuliani G, Maggi S, Cesari M, et al. Association between gait speed with mortality, cardiovascular disease and cancer: a systematic review and meta-analysis of prospective cohort studies. *J Am Med Dir Assoc* 2018;19:981-8.
9. Salthouse TA. What and when of cognitive aging. *Curr Dir Psychol Sci* 2004;13:140-4.
10. Anstey KJ, Luszcz MA, Giles LC, Andrews GR. Demographic, health, cognitive, and sensory variables as predictors of mortality in very old adults. *Psychol Aging* 2001;16:3-11.
11. Davis D, Cooper R, Terrera GM, Hardy R, Richards M, Kuh D. Verbal memory and search speed in early midlife are associated with mortality over 25 years' follow-up, independently of health status and early life factors: a British birth cohort study. *Int J Epidemiol* 2016;45:1216-25.
12. Pavlik VN, de Moraes SA, Szklo M, Knopman DS, Mosley TH Jr, Hyman DJ. Relation between cognitive function and mortality in middle-aged adults: the atherosclerosis risk in communities study. *Am J Epidemiol* 2003;157:327-34.
13. Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, et al. Rheumatoid arthritis. *Nat Rev Dis Primers* 2018;4:18001.
14. Brance ML, Di Gregorio S, Pons-Estel BA, Quagliato NJ, Jorfen M, Berbotto G, et al. Prevalence of sarcopenia and whole-body composition in rheumatoid arthritis. *J Clin Rheumatol* 2021;27(6S):S153-60.
15. Hunter TM, Boytsov NN, Zhang X, Schroeder K, Michaud K, Araujo AB. Prevalence of rheumatoid arthritis in the United States adult population in healthcare claims databases, 2004-2014. *Rheumatol Int* 2017;37:1551-7.
16. Kojima M, Nakayama T, Tsutani K, Igarashi A, Kojima T, Suzuki

- S, et al. Epidemiological characteristics of rheumatoid arthritis in Japan: prevalence estimates using a nationwide population-based questionnaire survey. *Mod Rheumatol* 2020;30:941-7.
17. Kato E, Sawada T, Tahara K, Hayashi H, Tago M, Mori H, et al. The age at onset of rheumatoid arthritis is increasing in Japan: a nationwide database study. *Int J Rheum Dis* 2017;20:839-45.
 18. van den Hoek J, Boshuizen HC, Roorda LD, Tjhuis GJ, Nurmo-hamed MT, van den Bos GA, et al. Mortality in patients with rheumatoid arthritis: a 15-year prospective cohort study. *Rheumatol Int* 2017;37:487-93.
 19. Kao LT, Kang JH, Lin HC, Huang CC, Lee HC, Chung SD. Rheumatoid arthritis was negatively associated with Alzheimer's disease: a population-based case-control study. *PLoS One* 2016; 11:e0168106.
 20. Chen KT, Chen YC, Fan YH, Lin WX, Lin WC, Wang YH, et al. Rheumatic diseases are associated with a higher risk of dementia: a nation-wide, population-based, case-control study. *Int J Rheum Dis* 2018;21:373-80.
 21. Lin TM, Chen WS, Sheu JJ, Chen YH, Chen JH, Chang CC. Autoimmune rheumatic diseases increase dementia risk in middle-aged patients: a nationwide cohort study. *PLoS One* 2018; 13:e0186475.
 22. Wallin K, Solomon A, Kareholt I, Tuomilehto J, Soininen H, Kivipelto M. Midlife rheumatoid arthritis increases the risk of cognitive impairment two decades later: a population-based study. *J Alzheimers Dis* 2012;31:669-76.
 23. Im CH, Kim NR, Kang JW, Kim JH, Kang JY, Bae GB, et al. Inflammatory burden interacts with conventional cardiovascular risk factors for carotid plaque formation in rheumatoid arthritis. *Rheumatology (Oxford)* 2015;54:808-15.
 24. Sood A, Raji MA. Cognitive impairment in elderly patients with rheumatic disease and the effect of disease-modifying anti-rheumatic drugs. *Clin Rheumatol* 2021;40:1221-31.
 25. Kozakai R, Nishita Y, Otsuka R, Ando F, Shimokata H. Age-related changes in physical fitness among community-living middle-aged and older Japanese: a 12-year longitudinal study. *Res Q Exerc Sport* 2020;91:662-75.
 26. Lauretani F, Russo CR, Bandinelli S, Bartali B, Cavazzini C, Di Iorio A, et al. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. *J Appl Physiol* (1985) 2003;95:1851-60.
 27. Sternang O, Reynolds CA, Finkel D, Ernsth-Bravell M, Pedersen NL, Dahl Aslan AK. Factors associated with grip strength decline in older adults. *Age Ageing* 2015;44:269-74.
 28. Shimokata H, Ando F, Niino N. A new comprehensive study on aging: the National Institute for Longevity Sciences, Longitudinal Study of Aging (NILS-LSA). *J Epidemiol* 2000;10(1 Suppl): S1-9.
 29. Noh JH, Jung HW, Ga H, Lim JY. Ethical guidelines for publishing in the *Annals of Geriatric Medicine and Research*. *Ann Geriatr Med Res* 2022;26:1-3.
 30. Shimokata H, Ando F, Yuki A, Otsuka R. Age-related changes in skeletal muscle mass among community-dwelling Japanese: a 12-year longitudinal study. *Geriatr Gerontol Int* 2014;14 Suppl 1:85-92.
 31. Kozakai R, Ando F, Kim HY, Yuki A, Otsuka R, Shimokata H. Sex-differences in age-related grip strength decline: a 10-year longitudinal study of community-living middle-aged and older Japanese. *J Phys Fit Sports Med* 2016;5:87-94.
 32. Nakamoto M, Otsuka R, Yuki A, Nishita Y, Tange C, Tomida M, et al. Higher gait speed and smaller sway area decrease the risk for decline in higher-level functional capacity among middle-aged and elderly women. *Arch Gerontol Geriatr* 2015;61: 429-36.
 33. Kobayashi S, Fujita K, Maekawa H, Dairoku H, Misawa G. Japanese Wechsler Adult Intelligence Scale-Revised Short Forms. Tokyo, Japan: Nihon Bunka Kagakusha; 1993.
 34. World Health Organization. Obesity and overweight [Internet]. Geneva, Switzerland: World Health Organization; 2021 [cited 2023 Feb 15]. Available from: <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>.
 35. Schaap LA, Koster A, Visser M. Adiposity, muscle mass, and muscle strength in relation to functional decline in older persons. *Epidemiol Rev* 2013;35:51-65.
 36. Clouston SA, Smith DM, Mukherjee S, Zhang Y, Hou W, Link BG, et al. Education and cognitive decline: an integrative analysis of global longitudinal studies of cognitive aging. *J Gerontol B Psychol Sci Soc Sci* 2020;75:e151-60.
 37. Tada M, Yamada Y, Mandai K, Hidaka N. Correlation between frailty and disease activity in patients with rheumatoid arthritis: data from the CHIKARA study. *Geriatr Gerontol Int* 2019;19: 1220-5.
 38. Beenakker KG, Ling CH, Meskers CG, de Craen AJ, Stijnen T, Westendorp RG, et al. Patterns of muscle strength loss with age in the general population and patients with a chronic inflammatory state. *Ageing Res Rev* 2010;9:431-6.
 39. Yamada M, Moriguchi Y, Mitani T, Aoyama T, Arai H. Age-dependent changes in skeletal muscle mass and visceral fat area in Japanese adults from 40 to 79 years-of-age. *Geriatr Gerontol Int* 2014;14 Suppl 1:8-14.
 40. Tucker-Drob EM, de la Fuente J, Kohncke Y, Brandmaier AM, Nyberg L, Lindenberger U. A strong dependency between changes in fluid and crystallized abilities in human cognitive aging. *Sci Adv* 2022;8:eabj2422.

41. Shin SY, Katz P, Wallhagen M, Julian L. Cognitive impairment in persons with rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012;64:1144-50.
42. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24.