

## Sedentary behavior is associated with arteriosclerosis in frail older adults

Nariaki Shiraishi<sup>1</sup>, Yusuke Suzuki<sup>2</sup>, Isao Kuromatsu<sup>3</sup>, Hitoshi Komiya<sup>2</sup>  
and Masafumi Kuzuya<sup>4</sup>

<sup>1</sup>Department of Rehabilitation, Faculty of Health Science, Nihon Fukushi University, Handa, Japan

<sup>2</sup>Centre for Community Liaison and Patient Consultations, Nagoya University Hospital, Nagoya, Japan

<sup>3</sup>Department of Urology, Nagoya Central Hospital, Nagoya, Japan

<sup>4</sup>Department of Community Healthcare and Geriatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan

### ABSTRACT

This prospective, cross-sectional, cohort observational study was conducted to evaluate the associations between sedentary behavior and arteriosclerosis-related vascular issues in community-dwelling frail older adults. We included 116 Japanese community-dwelling older adults (92 females and 24 males) who availed daycare at two long-term care insurance facilities in the cities of Yokkaichi and Handa between 2017 and 2019. An unpaired *t*-test and the chi-square test were used for intergroup comparisons. Logistic regression analysis was conducted with cardio-ankle vascular index as the dependent variable, sedentary behavior as the explanatory variable, and the other evaluated factors as covariates. Long-time sedentary behavior (based on the median value for all participants) was associated with high cardio-ankle vascular index after adjusting for age, sex, body mass index, ankle-brachial index, and walking MET-minutes in 1 week (odds ratio 3.086, 95% confidence interval 1.275–7.467,  $p=0.012$ ). After adjusting for other variables (care needs certificate, skeletal muscle mass index, body fat percentage, grip strength, 4-m walking duration, etc), there was a significant association between long-time sedentary behavior and high cardio-ankle vascular index values (odds ratio 4.977, 95% confidence interval 1.497–16.554,  $p=0.009$ ). The results study confirmed an association between long-time sedentary behavior in frail older adults and the degree of arterial stiffness assessed by the cardio-ankle vascular index. Interventions in older adults that focus on daily sedentary time to prevent the onset and exacerbation of geriatric syndromes secondary to the progression of arteriosclerosis warrant further investigation.

Keywords: sedentary behavior, arteriosclerosis, cardio-ankle vascular index, frail older adults

#### Abbreviations:

CAVI: cardio-ankle vascular index

OR: odds ratio

CI: confidence interval

MMSE: Mini-Mental State Examination

IPAQ: International Physical Activity Questionnaire

ABI: ankle-brachial pressure index

SMI: skeletal mass index

MNA: Mini-Nutritional Assessment

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Corresponding Author: Nariaki Shiraishi, PhD

Department of Rehabilitation, Faculty of Health Science, Nihon Fukushi University, 26-2, Higashihaemi-cho, Handa 475-0012, Japan

Tel: +81-569-20-0111, E-mail: n-shira@n-fukushi.ac.jp

## INTRODUCTION

In 2018, the World Health Organization (WHO) reported that the global population of adults >60 years is expected to increase from 600 million in 2000 to 2 billion by 2050.<sup>1</sup> Population aging is predicted to progress in super-aging developed and developing nations at an accelerated rate.<sup>2</sup> Therefore, the prolongation of active life expectancy while maintaining the functional independence of individuals has generated global attention and is becoming one of the most important agendas for many nations.<sup>3</sup> Epidemiological studies have shown that the maintenance of physical activity and exercise in old age reduces the risk of non-communicable diseases such as cardiovascular disease and cancer, and thereby lowers mortality rates among older adults.<sup>4</sup> The United States National Institute of Health guidelines (2018) reported that moderate-to-high-intensity exercise for more than 150 minutes per week reduced cardiovascular disease-related and all-cause mortalities by 30% and 75%, respectively.<sup>5</sup> Recent studies among older individuals have shown the effect of regular exercise on the prevention of cognitive or physical decline.<sup>4</sup> However, the importance of regular exercise in old age has not received much attention despite a global health report by the WHO, which indicated that reduced physical activity and a sedentary lifestyle, defined as reclining and lying down (posture) or having low energy expenditure, is the fourth major risk factor for mortality, after hypertension, smoking, and hyperglycemia. Moreover, a sedentary lifestyle has been implied to have a significant involvement in the development of cardiovascular disease, diabetes, and cancer.<sup>3,6</sup> Reduced physical activity due to improved convenience in daily life and eventual extension of sedentary hours during the daytime is an emerging serious health concern.<sup>7</sup> Moreover, a report suggested that reduced physical activity conferred a similar or higher health risk to that of smoking.<sup>8</sup> Moderate-intensity exercises can counter physical inactivity; however, they only account for approximately 5% of the time adults spend being awake, which is largely comprised of low-intensity physical activity (35–40%) or sedentary behaviors (55–60%).<sup>9</sup> Therefore, extending low-level physical activities to replace sedentary behaviors could be a key aspect in maximizing the effect of exercise. The correction of sedentary behavior has increasingly drawn attention since 2000 for the prevention of childhood obesity and cardiovascular and metabolic diseases.<sup>4,10,11</sup> Recently, sedentary behaviors have been shown to be associated with various health risks related to cardiovascular diseases, cancer, metabolic syndrome, and overall mortality in older people.<sup>12–14</sup> Particularly, reduced physical activity level and sedentary behaviors were associated with cardiovascular diseases secondary to atheromatous arteriosclerosis, for which the disability-adjusted survival years was estimated to incur a loss of approximately USD 13.4 million in 2013.<sup>15</sup>

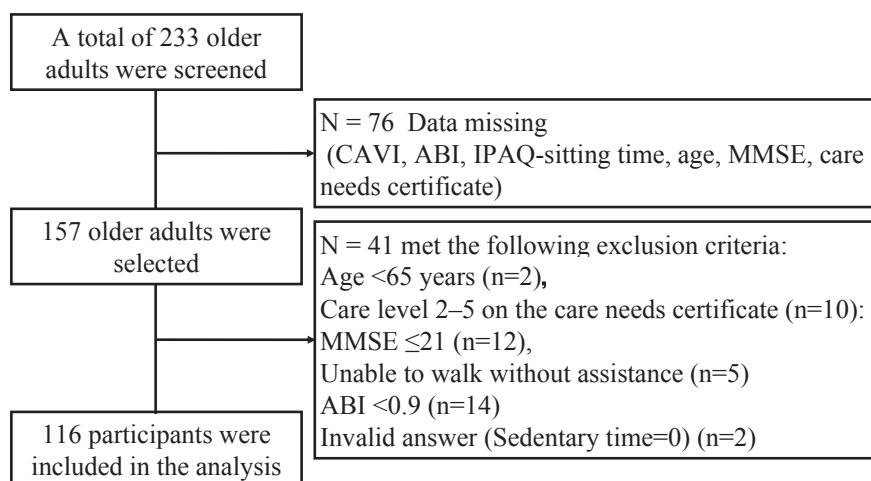
Until now, studies on the association between sedentary behavior and arteriosclerosis have focused only on healthy older adults. Healthy older adults with and without daily life restrictions have been included in the same group for analyses in previous studies.<sup>15,16</sup> Therefore, the extrapolation of the findings of previous studies to mildly disabled frail older adults with physical restrictions, remains questionable.

Therefore, this study was conducted to evaluate the associations of sedentary behaviors with vascular risks from arteriosclerosis in community-dwelling frail older adults.

## MATERIALS AND METHODS

*Participants and Study Design*

This prospective, cross-sectional, cohort study screened 233 older adults who availed daycare at two long-term care insurance facilities in the cities of Yokkaichi and Handa between 2017 and 2019. The participants' ages and sexes were recorded; their heights, body weights, and grip strengths were measured; and their cognitive functions were assessed using the Mini-Mental State Examination (MMSE). The exclusion criteria were as follows: unavailability of the abbreviated version of the International Physical Activity Questionnaire (IPAQ), age <65 years, certified care needs level >II (required monitoring or minor assistance for instrumental activities of daily living,<sup>17</sup> otherwise independent in basic activities of daily living), inability to walk independently indoors, MMSE score <21, those who returned invalid answers (sedentary time = 0), and an ankle-brachial pressure index (ABI) <0.9 because of concerns about the low precision of the cardio-ankle vascular index (CAVI).<sup>18</sup> The final analysis dataset included data from 116 older adults (Fig. 1). All study participants provided written informed consent for study participation. The study protocol was designed and implemented in compliance with the Declaration of Helsinki and was approved by the ethical bodies at both study centers (Ethics Committee of Studies on Human Subjects, Nihon Fukushi University [approval number 17-35] and Ethics Committee of Human Studies, Nagoya University [approval number 14294]).



**Fig. 1** Flowchart depicting the selection of participants in this study

CAVI: cardio-ankle vascular index

ABI: ankle-brachial index

IPAQ: International Physical Activity Questionnaire

MMSE: Mini-Mental State Examination

*Measurements*

All assessments and measurements were undertaken at the long-term care insurance facilities. The basic variables included age, sex, comorbidities, and care level. Body component-related variables included height, body weight, skeletal muscle mass volume of the four extremities, and total body fat volume. The volumes of skeletal muscle mass and body fat were measured by

biometric impedance analysis with a body-composition analysis equipment (Inbody430, Inbody Japan, Tokyo, Japan). Skeletal muscle mass volume divided by the square of the height provided the skeletal mass index (SMI), the total fat volume divided by body weight was recorded as the body fat percentage, and the body mass index (BMI) was calculated using the weight and height. Other assessments included nutritional assessments (Mini Nutritional Assessment [MNA]),<sup>19</sup> motor function determined by the 4-meter (4-m) walking duration, cognitive function determined by the MMSE, depression determined by the Geriatric Depression Scale 15 (GDS15), and active/sedentary state from the walking/sedentary time determined by the IPAQ. Sedentary behavior was assessed by asking about the average total time per day that participants spent in a sitting position during the weekdays of the past week. Participants were instructed to include all the time spent at work or at home regardless of the purpose. The GDS15 sets a range of 0–4 as “normal,” 5–9 as “mild,” and 10+ as “severe.” Walking time is expressed in MET-minutes in 1 week. The degree of arteriosclerosis was assessed with a device for measuring pulse wave velocity (Vasera VS-3000, Fukuda Denshi Co., Ltd., Tokyo, Japan). The CAVI and ABI were measured using Vasera VS-3000, and measurements were obtained with participants in the supine position and with cuffs attached to both arms for blood pressure measurements, a microphone was attached to the sternal surface at the second intercostal level for recording cardiac sounds, and electrodes were attached to each ankle for recording an electrocardiogram (the electrical waves on the right side were used for analysis).

### *Statistical Analysis*

As there were no standard criteria for the classification of sedentary time, the participants were divided into a long-time sedentary group ( $\geq 7.1$  hours of inactivity) and a non-long-time sedentary group ( $< 7.1$  hours of inactivity), based on a median of 7.1 hours/day for all participants. Furthermore, participants were assigned to the two subgroups based on the CAVI and ABI, with cutoff scores of 9.5 and 1.11, respectively (upon dividing the data equally). Intergroup comparisons of age, height, weight, BMI, limb SMI, body fat percentage, grip strength, 4-m walking duration, MNA, MMSE, and walking MET-minutes in 1 week were undertaken using the unpaired *t*-test. The sex, certified care need level, ABI, CAVI, GDS15, and comorbidities were analyzed using the chi-square test. Because the CAVI did not follow normal distribution, a logistic regression analysis was adopted to investigate the association between the CAVI and sedentary behavior, making the CAVI a dependent variable, the sedentary time as explanatory variable, and the other evaluated factors as covariates.

A multiple imputation approach was used to mitigate potential biases due to missing information, under the missing at random assumption (ie, the missing data mechanism depends only on the observed variables). We generated five imputed datasets and pooled the results in accordance with the standard Rubin’s rule.<sup>20</sup>

SPSS Statistics version 25 (IBM, Armonk, NY, USA) was used for the statistical analyses, and the SPSS missing values module was used for the calculation of the multiple imputations. A *p*-value less than 0.05 was considered statistically significant.

## RESULTS

In total, 116 older adults who met the inclusion criteria participated in this study. The mean age (95% confidence interval [CI]) was 80.3 years (79.1–81.5), and 79.3% ( $n=92/116$ ) were females. Table 1 presents the characteristics of the long-time sedentary and non-long-time sedentary groups. Data were missing in 1 case (0.9%) for body fat percentage, in 1 case (0.9%) for MNA,

in 2 cases (1.7%) for walking MET-minutes in 1 week, and in 8 (6.9%) cases for the GDS15. Participants in the long-time sedentary group had shorter mean walking MET-minutes duration in 1 week (258.0 [95% CI 161.9–354.1] MET-minutes/week vs 563.5 [321.8–805.3] MET-minutes/week,  $p=0.021$ ), higher CAVI values (60.0% vs 39.3%,  $p=0.026$ ), and greater prevalence of diabetes mellitus (16.4% vs 4.9%,  $p=0.043$ ) than the non-long-time sedentary group.

**Table 1** Comparison of variables between non-long sedentary group and long sedentary group

	Total	Non-long-time sedentary group	Long-time sedentary group	<i>p</i>
	n=116	n=61	n=55	
Age	80.3 (79.1–81.5)	80.6 (78.8–82.4)	80.0 (78.3–81.6)	0.623
Height (cm)	151.3 (150.0–153.0)	149.4 (147.3–152.1)	153.0 (150.6–155.4)	0.057
Body weight (kg)	52.1 (50.2–54.0)	51.0 (48.7–53.4)	53.2 (50.2–56.2)	0.247
BMI	22.7 (22.0–23.3)	22.7 (21.9–23.6)	22.6 (21.6–23.6)	0.911
Body fat percentage (%)	29.8 (28.2–31.4)	30.4 (28.2–32.6)	29.1 (26.7–31.6)	0.425
Missing value (%)	1 (0.9%)	1 (1.6%)	0 (0%)	
Skeletal muscle mass index	5.9 (5.8–6.1)	5.9 (5.7–6.1)	6.0 (5.8–6.3)	0.418
Missing value (%)	1 (0.9%)	1 (1.6%)	0 (0%)	
Grip strength (kg)	19.2 (17.9–20.5)	20.0 (18.1–21.8)	18.4 (16.7–20.1)	0.218
4-m walking time (sec)	5.0 (5.0–6.2)	6.0 (4.9–7.1)	5.2 (4.7–5.7)	0.168
MMSE	27.9 (27.5–28.3)	27.9 (27.4–28.5)	27.8 (27.3–28.4)	0.808
MNA	24.3 (23.7–25.0)	24.4 (23.5–25.4)	24.2 (23.3–25.1)	0.709
Missing value (%)	1 (0.9%)	1 (1.6%)	0 (0%)	
ABI	1.11 (1.09–1.12)	1.11 (1.09–1.13)	1.10 (1.08–1.13)	0.882
CAVI	9.42 (9.16–9.69)	9.18 (8.83–9.53)	9.69 (9.30–10.10)	0.054
Walking MET-minutes/week	416.1 (281.6–550.7)	563.5 (321.8–805.3)	258.0 (161.9–354.1)	0.021
Missing value (%)	2 (1.7%)	2 (3.3%)	0 (0%)	
Sedentary time (hour)	7.4 (6.7–8.1)	4.3 (3.8–4.7)	10.8 (10.2–11.5)	<0.001
Sex				0.229
Male	24	10	14	
Female	92	51	41	
Care needs certificate				0.272
Not eligible	48	29	19	
Need support level 1	36	17	19	
Need support level 2	19	7	12	
Need care level 1	13	8	5	
ABI category				0.427
≤1.11	63	31	32	
≥1.12	53	30	23	
CAVI category				0.026
≤9.5	59	37	22	

≥9.6	57	24	33	
GDS category				0.526
normal	71	42	29	
mild	31	15	16	
severe	6	4	2	
Missing value (%)	8 (6.9%)	0	8 (14.5%)	
Osteoarthritis	41	21	20	0.827
Cardiovascular disease	8	2	6	0.147
Cerebrovascular disease	13	8	5	0.493
Diabetes	12	3	9	0.043

BMI: body mass index

MMSE: Mini-Mental State Examination

MNA: Mini Nutritional Assessment

ABI: ankle-brachial index

CAVI: cardio-ankle vascular index

GDS: geriatric depression scale

Values are means (95% CIs) for continuous variables.

Table 2 presents the results of the logistic regression analysis for the association between long-time sedentary behavior and high CAVI values after adjusting for possible confounders (age, sex, BMI, ABI, and walking duration in 1 week) in Model 1 (odds ratio [OR] 3.086, 95% CI 1.275–7.467,  $p=0.012$ ). In Model 2, after adjusting for other variables besides those in Model 1, there was a significant association between long-time sedentary behavior and high CAVI values (OR 4.977, 95% CI 1.497–16.554,  $p=0.009$ ).

**Table 2** Logistic regression analysis to explain cardio-ankle vascular index as dependent variables

	Model 1			Model 2		
	Odds	95% CI	<i>p</i>	Odds	95% CI	<i>p</i>
Age	1.128	(1.050–1.211)	<0.001	1.176	(1.055–1.311)	0.003
Gender (female)	0.319	(0.106–0.955)	0.041	0.074	(0.012–0.454)	0.005
BMI	0.917	(0.811–1.036)	0.164	0.723	(0.443–1.178)	0.193
ABI (Right side)	3.384	(1.378–8.307)	0.008	5.149	(1.511–17.547)	0.009
Walking MET-minutes/ week	1.000	(0.999–1.001)	0.969	1.000	(0.999–1.001)	0.549
Long sedentary time	3.086	(1.275–7.467)	0.012	4.977	(1.497–16.554)	0.009
Care     Need Support						
needs     level 1				0.089	(0.016–0.489)	0.005
certificate   Need Support						
level 2				0.040	(0.004–0.371)	0.005
Need Care						
Level 1				0.007	(0.000–0.155)	0.002
Skeletal muscle mass index				1.307	(0.397–4.308)	0.660

Body fat percentage	1.060	(0.894–1.256)	0.501
Grip strength	0.918	(0.817–1.031)	0.148
4m walking time	1.104	(0.822–1.484)	0.511
MMSE	0.919	(0.697–1.212)	0.550
MNA	1.173	(0.948–1.452)	0.141
GDS mild category	3.818	(1.016–14.347)	0.047
severe category	1.049	(0.087–12.660)	0.970
Osteoarthropathy	0.543	(0.165–1.786)	0.315
Cardiovascular disease	1.132	(0.173–7.407)	0.897
Cerebrovascular disease	1.915	(0.217–16.933)	0.559
Diabetes	1.203	(0.146–9.904)	0.864

BMI: body mass index

ABI: ankle-brachial index

MMSE: Mini-Mental State Examination

MNA: Mini Nutritional Assessment

## DISCUSSION

This study revealed that sedentary behavior was independently and significantly indicative of a higher degree of arteriosclerosis. The study participants required supervision or assistance for some of the instrumental activities of daily living.<sup>17</sup> Although this differed from the operational definition by Fried et al<sup>21</sup> and Rockwood et al,<sup>22</sup> these participants were in a transitional state between healthy and disabled conditions and had functional analogies that fulfilled the definition; thus, they were considered as being frail. In a report of the Ministry of Health, Labor and Welfare, Japan in 2017,<sup>23</sup> individuals with frailty accounted for 47.7% of all persons requiring long-term care, and 21.2% had morbidities such as cerebrovascular and heart diseases, which originate from arteriosclerosis.<sup>24</sup> In one study, the prevalence values of arteriosclerosis-related morbidities in frail older adults were 50.8–53.1%, 13.6–25.0%, 12.3%, and 3.8–13.6% for hypertension, diabetes, cerebrovascular disease, and congestive heart failure, respectively,<sup>25</sup> implying that the association between arteriosclerosis and frailty necessitates long-term care. Previous studies on the relationship between arteriosclerosis and physical activity or sedentary behavior have been based on the analysis of either physically independent older people or a mixed population that included older people with limited capacity for activities of daily living. We specifically enrolled frail older adults in this study to evaluate whether the previous findings could be applied to them. The diagnosis of arteriosclerosis relies on noninvasive functional tests and images for measuring arterial stiffness.<sup>18</sup> Pulse-wave velocity has been conventionally used to examine the association of arterial stiffness with physical activity or sedentary behavior; however, it is affected by blood pressure during the measurement.<sup>26</sup> Therefore, in this study, we used the CAVI, wherein arterial stiffness can be assessed without being influenced by blood pressure.<sup>18,27</sup>

Previous studies investigating the relationship between arterial stiffness and physical activity showed that longer sedentary hours may increase the risk of progression of atherosclerosis, independent of physical activity,<sup>15,16,28,29</sup> and that mild to moderate (or above) levels of activity can prevent the progression of arteriosclerosis in older adults. However, as it may be difficult for older people with poor physical function to sustain even mild physical activities, factors other than the increase in physical activity levels need to be considered. In this study, sedentary time

was associated with arterial stiffness after adjusting for possible confounders. This suggests that despite difficulties in maintaining physical activity in frail individuals with functional limitations, simply reducing the sedentary time could contribute to the prevention of arterial stiffness. Reducing the daytime sedentary behavior is not commonly included in standard health guidelines for older people and is therefore not subjected to the usual evaluations or interventions.<sup>3,4,30</sup> However, our findings suggest that improving sedentary behavior should be included in the healthcare management practices for older adults, as it has been done for smoking cessation and physical activity maintenance.

This study had some limitations. A causal relationship between sedentary time and progression of arteriosclerosis could not be demonstrated due to the cross-sectional design. Moreover, as the physical activity levels and sedentary times were evaluated using questionnaires, the results were not based on quantifiable parameters and therefore, lacked objectivity. In recent years, objective evaluation has become available through three-dimensional acceleration sensors, which enable detailed analyses of posture and movement.

The CAVI cannot be measured accurately if the ABI is  $<0.90$ . Accordingly, patients with ABI  $<0.90$  were excluded in this study.<sup>18</sup> In addition, participants with systolic dysfunction, atrial fibrillation/flutter, aortic disease, and/or valvular heart disease may not have been completely excluded. These abovementioned conditions can affect arterial stiffness. Nonetheless, observed significant association of ABI with CAVI suggests a possibility that ABI may serve as a surrogate marker for arterial stiffness at least in individuals who are not suspicious of having arterial occlusions (ABI  $>0.9$ ).

Future investigations should consider a longitudinal study design, use objective measures, implement a confounder-adjusted quasi-randomized study approach, and use propensity scores and manipulable variable methods.

## CONCLUSIONS AND IMPLICATIONS

This study demonstrated an association between long-time sedentary behavior of frail older adults and the degree of arterial stiffness, assessed by CAVI, after adjusting for possible confounders. Interventions in older adults that focus on daily sedentary time to prevent the onset and exacerbation of geriatric syndromes secondary to the progression of arteriosclerosis require further investigation.

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## CONFLICTS OF INTEREST

The authors report no conflicts of interest.



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## UNBLINDED ETHICS STATEMENT

The study protocol was designed and implemented in compliance with the Declaration of Helsinki and was approved by the ethical bodies at both study centers (Ethics Committee of Studies on Human Subjects, Nihon Fukushi University [approval number 17-35] and Ethics Committee of Human Studies, Nagoya University [approval number 14294]).

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