Table 1 Inclusion/exclusion characteristics of 2378 participants in the third wave examination of the National Institute for Longevity Sciences-Longitudinal Study of Aging (NILS-LSA), 2002–2004

Characteristics	Men	Women
Inclusion ($n = 2006$)		
Total (n (%))	1017 (50.7)	989 (49.3)
Age group (n (%))†		
40s	250 (12.5)	279 (13.9)
50s	302 (15.1)	265 (13.2)
60s	250 (12.5)	242 (12.1)
≥70	215 (10.7)	203 (10.1)
Exclusion ($n = 372$)		
Total (n (%))	187 (50.3)	185 (49.7)
Prevalence of disease (n (%))		
Stroke	42 (22.5)	23 (12.4)
Ischemic heart disease	41 (21.9)	41 (22.2)
Chronic bronchitis	7 (3.7)	3 (1.6)
Arthritis	26 (13.9)	56 (30.3)
Fracture	5 (2.7)	6 (3.2)
Dementia	–	1 (0.5)
Parkinson's disease	3 (1.6)	–
Walking difficulties in ADL (n (%))	50 (26.7)	54 (29.2)
Not completed walking test (n (%))	55 (29.4)	53 (28.6)

$^†\chi^2$-Test test examines significance among each age group and sex. Values are numbers (% of total at each inclusion/exclusion category) of samples. ADL, activities of daily living.

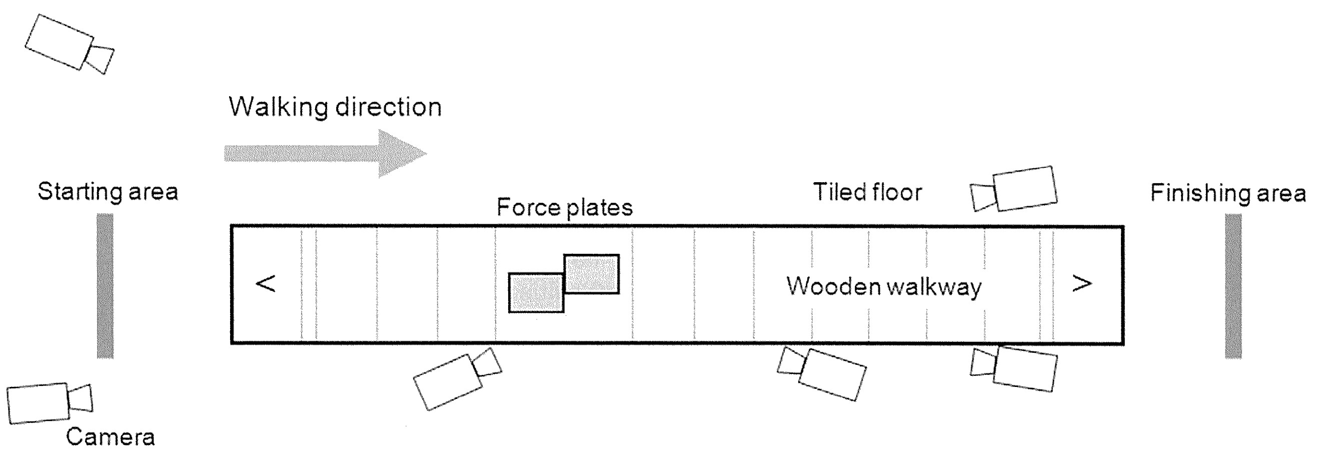

Figure 1 Setup of 3-D gait system: the 10-m walkway consisted of a wooden walkway. Six cameras were placed at various positions and two force platforms were embedded in the center of the walkway. Double support time in pre-swing phase of right foot was measured in this setting.

superior iliac spines and the acromions.[34] The subjects walked on a 10-m walkway at two speeds: (i) at a self-selected pace (comfortable walking); and (ii) as fast as possible without running (brisk walking). Each pace was repeated approximately twice on average. The walkway consisted of a tiled floor and a wooden walkway along the corridor (Fig. 1). The surface of the wooden walkway was covered with gray-colored, thin, stiff rubber, which measured 0.036 m in height from the tile floor surface of the corridor. Force platforms (0.6 m × 0.4 m) (9286; Kistler Instrumente AG, Winterthur, Switzerland), with surface colors similar to those of the walkways, were embedded in the center of the wooden walkway. The starting point for each trial was

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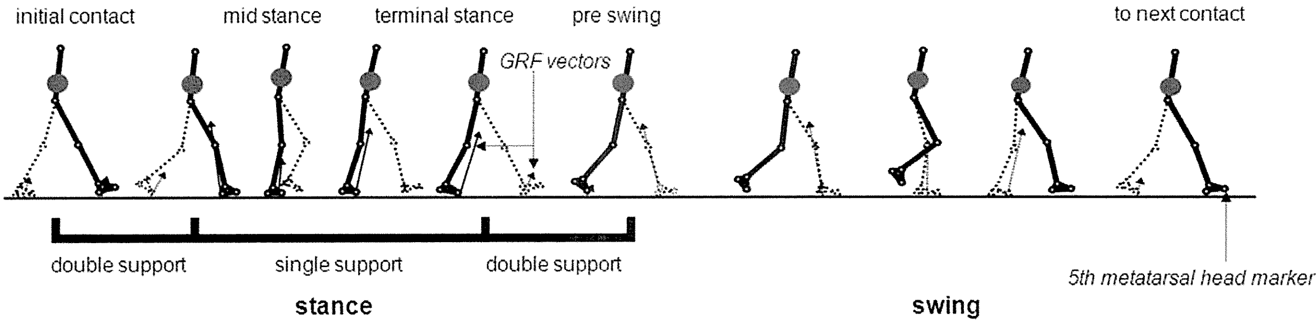

Figure 2 Definition of gait cycle using ground reaction force (GRF) and the fifth metatarsal head marker.

selected in relation to the foot contacts on the force platforms. The distance from each starting and departure point to the force platforms was approximately 3.5–4.5 m. One trial each of comfortable and brisk walking was used in the data analysis. The trials used were those that lacked the least data.

The Vicon 370 system (Oxford Metrics Ltd, Oxford, UK), which consisted of six cameras, was used to obtain the 3-D coordinates of the trunk, thighs, shins and feet. The calibration residual at each camera was set below 1.0 mm. The data were processed using a custom routine that was programmed by the Clinical Gait Analysis Forum of Japan.[34] The raw coordinate data at 60 Hz were digitally filtered with a fourth-order, zero-lag, Butterworth filter[22] with a cut-off at 5 Hz, and the raw ground reaction force data at 1200 Hz were digitally filtered with a cut-off at 10 Hz. The force data were interpolated to correspond with the coordinate data to synchronize the datasets. Smoothed coordinates of the lower extremities were used to construct a rigid link-segment model.[22] Segment masses and inertial properties were determined using previously reports[35] and the participants' mass and height, which were used for calculating COM.

Gait cycle and walking variable calculation

SAS ver. 9.1.3.[36] was used to automatically identify gait event times and each phase of the gait cycle based on kinematic and kinetic gait data. The divisions of the gait cycle are shown in Figure 2.[30] The gait event times for initial contacts and toe off were determined using vertical force data and the vertical motion of the optical marker on the fifth metatarsal head. The period from the first right initial contact to ipsilateral second initial contact was one gait cycle.[30]

Both the right and left leg motions were captured, and primarily the right stride was analyzed. Left leg motion was used for calculating the step length and double support times. The mean COM velocities, step lengths, step frequencies and double support times during a gait cycle were also automatically computed by SAS. The double support time was defined as the duration of time during which each foot was on the ground in the pre-swing phase. The mean COM velocity, step length, and step frequency were normalized as proposed by Hof[37] as follows:

Normalized COM velocity, $\hat{v} = \dfrac{v}{\sqrt{gl_0}}$,

Normalized step length, $\hat{l} = \dfrac{l}{l_0}$,

Normalized step frequency, $\hat{f} = \dfrac{f}{\sqrt{g/l_0}}$,

where v is actual mean COM velocity, l_0 is the leg length of each subject, l is the actual step length, f is the actual step frequency and g is the acceleration due to gravity (9.81 m/s^2). Leg length was measured from the ground to the greater trochanter during quiet standing. Patients with arthritis and fracture were excluded (Table 1), and no case of limited knee extension was observed in the present study. The double support time was also normalized by each subject's cycle duration, from right initial contact to next right initial contact (over one gait cycle).

For the calculation of walking variables, technical difficulties sometimes caused missing data due to the effect of occlusion while capturing motion. Thus, for example, the mean COM velocity over the gait cycle was calculated using data from 1716 men and women (85.5% of the total sample) during comfortable walking and using data from 1614 men and women during brisk walking (80.4%). To demonstrate the lack (or presence) of bias with respect to velocity data loss, the Student's t-test was used to compare the velocity between the group with all available data and that with data available only in the velocity category. The results showed that the velocities were not significantly different between the two groups, and this was confirmed for all walking variables.

Statistical analyses

All analyses were performed using SAS ver. 9.1.3. Sex differences were examined using the Student's t-test. For analysis of age differences, participants were divided

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into eight groups based on sex and age (40–49, 50–59, 60–69 and 70–84 years for each sex). Trends in differences across all age groups in the walking variables were tested using the General Linear Model (GLM), and differences by age group were tested using the Tukey–Kramer method for each sex. $P < 0.05$ was considered statistically significant.

Results

The proportion of the sample drawn from each age group and each sex group was the same (χ^2-test, $P > 0.05$). The mean ± standard deviation age was 58.1 ± 11.4 years in men and 58.7 ± 11.4 years in women, which was not significant ($P > 0.05$).

The results of the GLM and Tukey–Kramer tests revealed age-related changes in each age and sex group. Descriptive statistics for all values are shown in Tables 2 and 3 and Figure 3. Mean COM velocities during comfortable and brisk walking significantly decreased with age in both sexes ($P < 0.001$). Age-related changes in the comfortable COM velocity were marked in the 70–84-year group compared with other age groups. Similar changes were found in the brisk COM velocity. The step lengths and frequencies followed these COM velocity patterns in both sexes during both comfortable and brisk walking.

These age-related changes occurred earlier in the middle-aged group. Earlier patterns involving brisk gait parameters were more apparent in women: for example, the brisk COM velocity decreased at 60–69 years in men and at 50–59 years in women, then the decrease accelerated at 70–84 years (Tables 2,3, Fig. 3). The step length and frequency followed these COM velocity patterns. The double support time during pre-swing was significantly increased with age only at the women's comfortable walking pace; it was significantly longer in the 70–84-year group compared to other age groups (Table 3, Fig. 3). The men's double support times showed no significant age-related differences among age groups (P for trend >0.05, Fig. 3).

Descriptive statistics and the results of sex differences for gait parameters are depicted in Table 4. The results of mean COM velocity differed according to walking pace: the comfortable COM velocity was significantly faster in women than in men ($P < 0.001$), and the brisk COM velocity was significantly faster in men than in women. Step length pattern was similar to COM velocity pattern: the brisk step length was longer in men than in women ($P < 0.001$), but the comfortable step length was not significantly different. On the other hand, women had a higher step frequency during both walking paces ($P < 0.001$). The results of the pre-swing double support time were equal to the step frequency.

Discussion

Mobility is essential for independence in the elderly. A better understanding of age-related changes in gait provides useful information for appropriate intervention programs targeting specific age groups.[8] The present cross-sectional, descriptive study showed spatiotemporal components of gait over one gait cycle among community-living middle-aged and elderly Japanese subjects. The sample of 1017 men and 989 women was large enough to allow analysis by age group,[17] and, to the best of our knowledge, the sample size is the largest to be published in which gait characteristics have been analyzed using a 3-D gait system. There was no disproportionate lack of gait data caused by difficulties in capturing the 3-D coordinates.

Mean COM velocities decreased with age, which is in almost complete agreement with previous results, despite the use of different measurement equipment and instrumentation.[16–21,25,29] The age-related decreases in the normalized COM velocities accelerated at 70 years and over were noted at a relatively later age compared with the previous reports: they showed the accelerated decline occurred in 50–59- and 60–69-year age groups,[17] at 62 years,[19] between 60- and 70-year age groups,[20] and at 65 years and in the 67–73-year age group.[18] The differences in age of accelerated decline among the previous and the present findings were likely due to the differences in method and data characteristics.

The brisk COM velocity decreases advancing with age were earlier compared with the comfortable walking. Some previous studies showed the age-related decrease was independent of walking pace,[18–20] while another reported that the decrease depended on the pace.[7] In a report by Bohannon on the comfortable and maximum walking speeds of adults aged 20–79 years,[7] walking speed was found to be influenced by the interaction of pace and age. This result matched our present findings that the age-related decrease was clearer during brisk walking than during comfortable walking. Moreover, these earlier age-related declines in the brisk COM velocities were apparent in women. Some studies reported that the critical age for marked velocity decrease did not differ by sex,[16,19] while another found the critical age to be earlier in men.[17] However, Callisaya *et al.*[8] showed women's walking velocity to be an earlier age-related change compared to men's parameters during the preferred speed of walking among the subjects aged 60 years and older. These results are in agreement with our own, though our data was particularly strong in the brisk parameters across middle-aged and elderly persons. The brisk walking task required greater forward momentum and increased demands in muscle activity[24,38–40] and aerobic capacity[33,41] might alter the spatiotemporal gait parameters accompanying aging.

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Table 2 Men's normalized mean COM velocities, step lengths and frequencies and double support times during comfortable and brisk walking in each age group

Men: walking parameters by age group	Mean COM velocity				Step length				Step frequency				Double support times (pre-swing)			
	N	Mean	SD	95% CI	N	Mean	SD	95% CI	N	Mean	SD	95% CI	N	Mean	SD	95% CI
Comfortable walking																
40s	211	0.524	0.053	0.517–0.531	240	0.892	0.065	0.884–0.900	207	0.587	0.043	0.582–0.593	208	14.8	1.5	14.6–15.0
50s	266	0.527	0.059	0.520–0.534	289	0.897	0.076	0.888–0.906	259	0.590	0.042	0.585–0.595	249	14.8	1.5	14.6–14.9
60s	218	0.523	0.067	0.514–0.532	240	0.901	0.089	0.890–0.913	215	0.583	0.046	0.577–0.589	205	14.5	1.6	14.3–14.7
70–	186	0.485	0.070	0.475–0.495	213	0.859	0.096	0.846–0.872	185	0.569	0.047	0.562–0.576	177	15.2	2.0	14.9–15.5
P for trend†	<0.001				<0.001				<0.001				NS			
(Tukey–Kramer test)‡	40s, 50s, 60s >70–				40s, 50s, 60s >70–				40s, 50s, 60s >70–				NA			
Brisk walking																
40s	190	0.705	0.078	0.694–0.716	229	0.998	0.074	0.989–1.008	180	0.707	0.070	0.696–0.717	173	13.3	6.0	12.4–14.2
50s	235	0.699	0.082	0.688–0.709	272	0.998	0.088	0.987–1.008	214	0.697	0.064	0.688–0.705	209	13.3	5.6	12.6–14.1
60s	191	0.678	0.079	0.667–0.690	237	1.000	0.094	0.988–1.012	185	0.685	0.066	0.676–0.695	180	13.4	5.0	12.6–14.1
70–	182	0.618	0.092	0.605–0.631	203	0.946	0.100	0.932–0.960	177	0.657	0.066	0.647–0.667	169	14.1	2.1	13.8–14.4
P for trend†	<0.001				<0.001				<0.001				NS			
(Tukey–Kramer test)‡	40s > 60s > 70–., 50s > 70–				40s, 50s, 60s >70–				40s > 60s > 70–., 50s > 70–				NA			

†Trend tests examine main effects of age in each gait parameter. ‡Tukey–Kramer tests examine the significant difference among each age group. '>' indicates the significant difference between the age groups, with *P*-value is less than 0.5. Values are numbers of samples (N), means (Mean), standard deviations (SD) and 95% confidence intervals (95% CI) at each variable. Age group: 40s, 40–49 years age group; 50s, 50–59 years age group; 60s, 60–69 years age group; 70–, 70–84 years age group. COM, center of mass; NS, not significant; NA, not applicable.

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Table 3 Women's normalized mean COM velocities, step lengths and frequencies and double support times during comfortable and brisk walking in each age group

Women: walking parameters by age group	Mean COM velocity				Step length				Step frequency				Double support times (pre-swing)			
	N	Mean	SD	95% CI	N	Mean	SD	95% CI	N	Mean	SD	95% CI	N	Mean	SD	95% CI
Comfortable walking																
40s	228	0.542	0.060	0.535–0.550	267	0.905	0.072	0.896–0.913	223	0.602	0.044	0.596–0.608	212	14.9	1.7	14.7–15.2
50s	224	0.547	0.066	0.538–0.556	252	0.902	0.082	0.891–0.912	219	0.607	0.051	0.600–0.614	214	14.9	1.7	14.7–15.1
60s	210	0.536	0.064	0.527–0.544	236	0.890	0.079	0.880–0.900	207	0.602	0.045	0.596–0.608	189	15.0	1.9	14.8–15.3
70–	173	0.472	0.071	0.461–0.483	189	0.833	0.093	0.820–0.847	169	0.570	0.051	0.562–0.578	148	15.8	1.9	15.5–16.1
P for trend†	<0.001				<0.001				<0.001				<0.001			
(Tukey–Kramer test)‡	40s, 50s, 60s >70–				40s, 50s, 60s >70–				40s, 50s, 60s >70–				70– > 60s, 50s, 40s			
Brisk walking																
40s	216	0.702	0.072	0.692–0.711	269	0.972	0.070	0.963–0.980	210	0.728	0.071	0.719–0.738	201	13.9	1.6	13.7–14.2
50s	215	0.675	0.080	0.665–0.686	252	0.960	0.087	0.950–0.971	212	0.706	0.073	0.696–0.715	209	14.2	1.7	13.9–14.4
60s	212	0.653	0.072	0.643–0.662	230	0.941	0.085	0.929–0.952	209	0.696	0.072	0.687–0.706	199	14.2	1.8	14.0–14.5
70–	173	0.577	0.084	0.565–0.590	187	0.890	0.109	0.875–0.906	163	0.651	0.064	0.562–0.578	157	14.3	8.8	12.9–15.7
P for trend†	<0.001				<0.001				<0.001				NS			
(Tukey–Kramer test)‡	40s > 50s > 60s > 70–				40s > 60s > 70–., 50s > 70–				40s > 50s, 60s > 70–				NA			

†Trend tests examine main effects of age in each gait parameter. ‡Tukey–Kramer tests examine the significant difference among each age group. '>' indicates the significant difference between the age groups, with $P < 0.05$. Values are numbers of samples (N), means, standard deviations (SD) and 95% confidence intervals (95% CI) at each variable. Age group: 40s, 40–49 years age group; 50s, 50–59 years age group; 60s, 60–69 years age group; 70–, 70–84 years age group. COM, center of mass; NS, not significant; NA, not applicable.

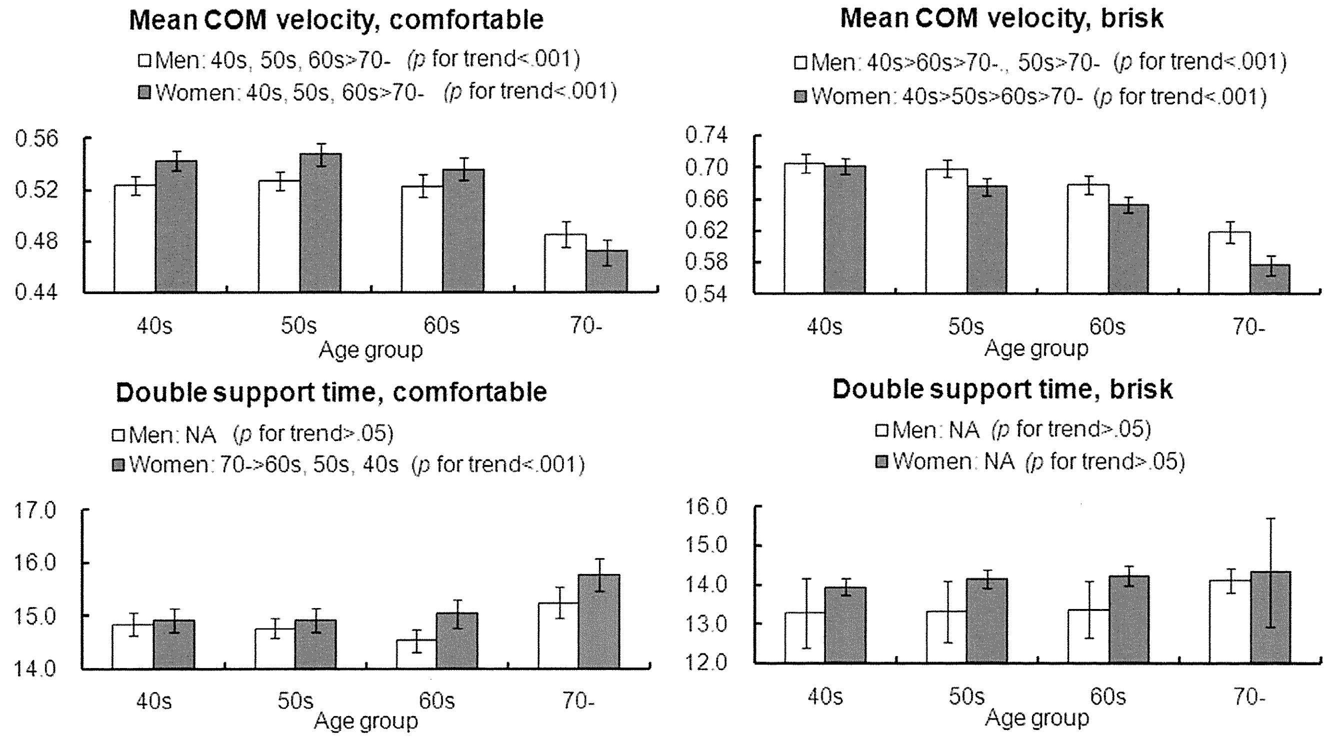

Figure 3 Age-related differences (trend tests and Tukey–Kramer tests); means and 95% confidence intervals of normalized mean center of mass (COM) velocities ($(\mathrm{m/sec})/\sqrt{((\mathrm{m/sec^2})\times \mathrm{m})}$) and double support times (s/s) during comfortable and brisk walking in men and women. Significant differences by age group in men and women are noted on the upper side of each figure. '>' indicates the significant difference between the age groups, with *P*-values of ≤0.05.

Table 4 Normalized mean COM velocities, step lengths and frequencies and double support times during comfortable and brisk walking among men and women

Walking parameters	Men				Women				*P*-value†
	N	Mean	SD	95% CI	N	Mean	SD	95% CI	
Comfortable walking									
Mean COM velocity	881	0.516	0.064	0.512–0.521	835	0.527	0.071	0.523–0.532	<0.001
Step length	982	0.889	0.083	0.883–0.894	944	0.886	0.085	0.881–0.891	NS
Step frequency	866	0.583	0.069	0.580–0.586	818	0.597	0.045	0.593–0.600	<0.001
Double support time (pre-swing)	839	14.8	1.7	14.7–14.9	763	15.1	1.8	15.0–15.2	<0.001
Brisk walking									
Mean COM velocity	798	0.677	0.089	0.671–0.683	816	0.656	0.089	0.650–0.662	<0.001
Step length	941	0.987	0.092	0.981–0.993	938	0.945	0.092	0.939–0.951	<0.001
Step frequency	756	0.687	0.075	0.682–0.692	794	0.698	0.049	0.693–0.703	<0.001
Double support time (pre-swing)	731	13.5	5.0	13.2–13.9	766	14.2	4.3	13.9–14.5	<0.01

†Student *t*-tests examine the sex differences. Values are numbers of samples (N), means, standard deviations (SD) and 95% confidence intervals (95% CI) at each variable. COM, center of mass; NS, not significant.

Further investigation should have discussed the difference between comfortable and brisk walking parameters.[38,42,43]

Age-related step length decreases during comfortable and brisk walking were almost concomitant with the COM velocity decreases, which was similar to the previous findings.[16,20] In brisk walking, however, age-related reduction in the step length seemed to be smaller than that in the step frequency compared with comfortable walking. For example, women's brisk step length decrease was 8.4% across middle-aged and elderly groups compared with their step frequency decrease of 10.7% (Table 3). This was observed also in men's. This may suggest that ambulatory ability observed in the COM velocity may be caused more by the step length during comfortable walking and the step frequency

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during brisk walking in the elderly. This was also apparent in middle-aged women. The interpretation was limited qualitatively and should be further explored.

Step frequencies also decreased with age and this decrease was found even in middle-aged women during brisk walking. Previous studies in step frequency reported no age-related changes,[16,17,21] age-related decrease[8,18–20,25] and age-related increase.[26] Moreover, the current age- and sex-related decrease depending on required walking pace was not previously reported.[16,17] One explanation of these conflicts was that degree of the age-related reduction in step frequency was relatively less than that in other gait parameters such as velocity or step length.[8,17,19,20] Therefore, sample size, subject characteristics and measuring instruments may affect the age-related decrease in the step frequency.[16,25] Double support times in the present study did not increase with age, with the exception of women's comfortable data. On the other hand, exploratory analyses of actual values of double support times showed age-related increases in both sexes during both walking paces (data not shown, P for trend <0.001, <0.022). This shows that the double support as a percentage of one gait cycle remained almost constant in middle-aged and elderly subjects. Ferrandez *et al.*[32] found that double support time increased as velocity decreased, and that prolonged double support time was affected more by walking velocity than age.

The present study found brisk COM velocity and step length to be greater in men than in women. By contrast, step frequencies and double support times were greater in women than in men. This is characteristic of sex differences and is supported by previous findings.[8,17,21] Although the comfortable COM velocity was faster in women than in men, this is believed to be a result of the difference in body size as the actual comfortable COM velocity was significantly faster in men than in women (men, 1.46 ± 0.18 m/s; women, 1.43 ± 0.20 m/s; $P < 0.001$). The comfortable step length did not differ significantly between either sex group, perhaps because of the slower men's COM velocity.

The present gait data may give some insight into gait assessment and preventive walking exercise programs for older persons as previously reported.[42,44,45] The values for the gait parameters during one gait cycle may be useful to clinicians judging the ambulatory ability of patients from a short indoor walk.[7,42] Patients whose gait parameters are lower than that of their appropriate age group are at increased risk of ADL difficulties.[8,11] Comfortable and brisk walking velocities are predictive of adverse outcomes such as loss of physical function, requirement of caregivers, hospitalization and increased mortality in elderly persons.[8,10–12] Decreased step length and prolonged double support time are correlated with fear of falling and/or future fall risk.[4,5,9] Also, the other gait parameters such as gait velocity,[9,11] stride-to-stride variability[4] and lateral sway[3,5,6,46] are associated with the falling events. We did not directly ascertain whether the participants had a history of falls and/or a fear of falling in our gait parameters. Further work should confirm which gait measure is the best independent predictor for future fall risk in a large sample.

A moderate workload prescription in walking exercise programs should be given by controlling both step length and step frequency during comfortable walking in the elderly. Brisk walking, which is recommended for moderately vigorous endurance training and has a high impact compared to comfortable pace walking, might be considered for middle-aged women and the elderly to improve physical functions such as muscle strength[7,40,43] and/or cardiovascular fitness.[33,41]

This study has some limitations. Some previous gait investigations used the results of several trials or mean values of gait, while we used gait data from one trial of each participant. This was done because of technical difficulties in the automatically computed 3-D gait parameters. Next, the conjunction of our excluding criteria with the potential diseases might overestimate gait disorders: the elderly subjects were more likely to be healthy and physically fit. Moreover, patients with dementia were considered to be less in the present sample. The general comparability of the present gait variables with previously reported data is limited because of the lack of data for young adults in their 20s and 30s. Furthermore, our cross-sectional analysis approach could not demonstrate a cause-and-effect relationship from aging. We are planning longitudinal studies to further determine the effects of aging on gait. The present study included regional limitations such as race, culture, lifestyle, genetics and socioeconomic status which also may be important. However, the findings did permit age- and sex-related differences in gait to be clarified in the elderly.

In conclusion, age- and sex-related gait alterations were apparent in one gait cycle of walking in a large sample of community-dwelling, middle-aged and elderly Japanese men and women, when analyzed by a 3-D gait system. There were marked age-related gait differences in subjects aged 70 years and over compared to subjects aged 40–69 years during comfortable walking, and subtle differences were also observed in subjects aged 40–69 years during brisk walking. The earlier age-related changes were clearer in women than in men. These results may guide the assessment of gait patterns attributed to usual aging and to develop moderate exercise programs for the elderly.

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運動器疾患の長期縦断疫学研究

Longitudinal epidemiological study on locomotive organ disease

下方浩史(写真)　**安藤富士子**
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◎運動器症候群の予防方法を解明するためには，その危険因子を明らかにすることが必要である．一般住民を対象とした長期縦断疫学研究により，運動器疾患罹患の実態を明らかにするとともに，栄養や運動，疾病罹患，飲酒や喫煙などの生活習慣，遺伝的素因などと加齢にかかわる運動器疾患の発症との関連を解明することができる．国立長寿医療研究センターでは無作為抽出された一般地域住民を対象に，老化・老年病に関する基礎データの収集のための長期にわたる集団の大規模な縦断研究「老化に関する長期縦断疫学研究(NILS-LSA)」を平成 9 年度(1997)より行っている．NILS-LSA での調査から，日本人全体で骨粗鬆症は 1,000 万人，変形性膝関節症は 3,000 万人を超える患者がいると推計された．現在，遺伝子や生活習慣，体力，栄養などさまざまな要因についての縦断的な解析から高齢者の運動器疾患のリスク要因を明らかにし，予防方法を開発するための研究を行っている．

Key word：長期縦断疫学，老化，骨粗鬆症，変形性関節症

運動器症候群(ロコモティブシンドローム)とは，運動器の障害により要介護になるリスクの高い状態になることである．実際に要介護となる要因として関節疾患，転倒・骨折が大きな割合を占めている．高齢者における関節疾患のほとんどは変形性関節症であり，また高齢者の骨折は骨粗鬆症がおもな要因となっている．変形性関節症と骨粗鬆症に限っても，運動器症候群の推計患者数は 4,700 万人(男性 2,100 万人，女性 2,600 万人)に達するという[1]．日本社会の高齢化に伴って，今後さらに急速にこれらの患者数は増大していくものと推定されている．また，運動器症候群は認知症の要因となるとも考えられており，運動器症候群の予防に関する研究は，日本において今後の進展が強く望まれる分野である[2]．

運動器症候群の予防方法を解明するためには，その危険因子を明らかにすることが必要である．無作為抽出された一般住民を対象とした長期にわたる観察研究は，一般住民の間での運動器疾患罹患の実態を明らかにするとともに，栄養や運動，疾病罹患，飲酒や喫煙などの生活習慣，遺伝的素因などと加齢にかかわる運動器疾患の発症との関連を解明するために不可欠である．こうした研究により，どのような素因をもち生活を送っている人が，どのような確率で運動器疾患に罹患していくのか，どのように対策を取れば，どのくらいの確率で予防できるのかを明らかにすることができる[2]．

長期縦断疫学研究

国立長寿医療研究センターでは老化・老年病に関する基礎データの収集のために長期にわたる集団の大規模な縦断研究「老化に関する長期縦断疫学研究(NILS-LSA)」を平成 9 年度(1997)より行っている(図 1)[3-7]．対象は地域住民から年齢・性別に層化し無作為抽出された，観察開始年齢が 40～79 歳の男女である．抽出によって選定された人を説明会に招いて，検査の目的や方法などを十分に説明し，インフォームドコンセントを得たうえで検査を実施している．追跡中のドロップアウ

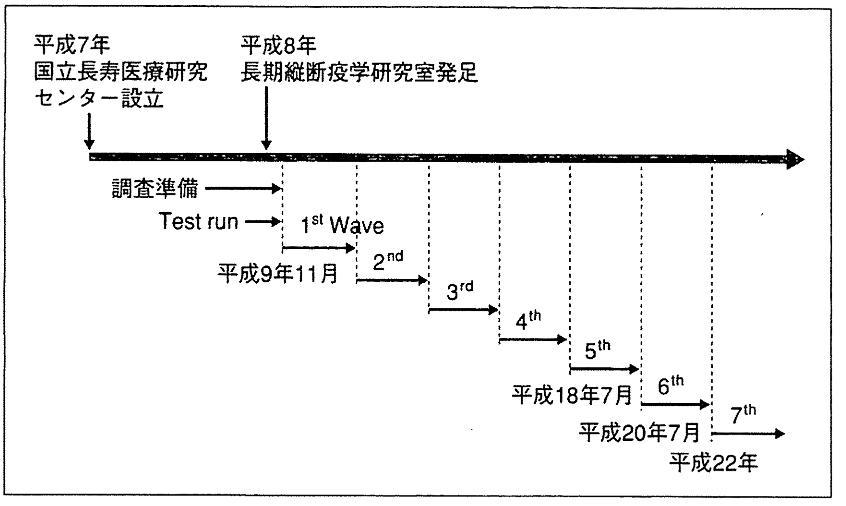

図 1　国立長寿医療研究センター・老化に関する長期縦断疫学研究(NILS-LSA)の経緯
NILS-LSA では地域在住の中高年者約 2,400 人の 10 年以上にわたるデータが蓄積されている．

トは，同じ人数のあらたな補充を行い，定常状態として約 2,400 人のダイナミックコホートをめざしている．

施設内に設けられた専用の検査センターで朝 9 時から夕方 4 時までの間に分刻みでスケジュールを組んで，1 日 7 名，週 4 日，年間を通して詳細な老化に関連する検査を行っている．平成 12 年(2000)4 月に 2,267 名の基礎集団が完成し，以後は 2 年ごとに検査を繰り返し行っており，現在は第 7 次調査を行っている．調査項目は頭部 MRI や超音波断層，骨密度測定，腹部 CT など最新の機器を利用した医学検査のみならず，詳細な生活調査，栄養調査，運動機能調査，心理検査など広汎で精度の高い内容である(図 2)．運動器疾患に関連した検査としては，DXA 法による全身骨，腰椎，左右大腿骨頸部の 4 スキャンでの骨密度測定，末梢骨定量 CT 検査法(pQCT)による橈骨 16 スキャン，左右膝 X 線撮影，胸椎腰椎 X 線撮影，膝関節機能検査，転倒調査，膝痛調査，腰痛調査，骨折調査，骨代謝マーカー検査などを実施している．調査開始当初より，調査参加者のほぼ全員からの血液サンプルを用いて DNA を蓄積している．これほど背景因子が詳細に検討されている一般住民の DNA 試料の蓄積は，国内外でもほかにはほとんどないと思われる[8,9]．

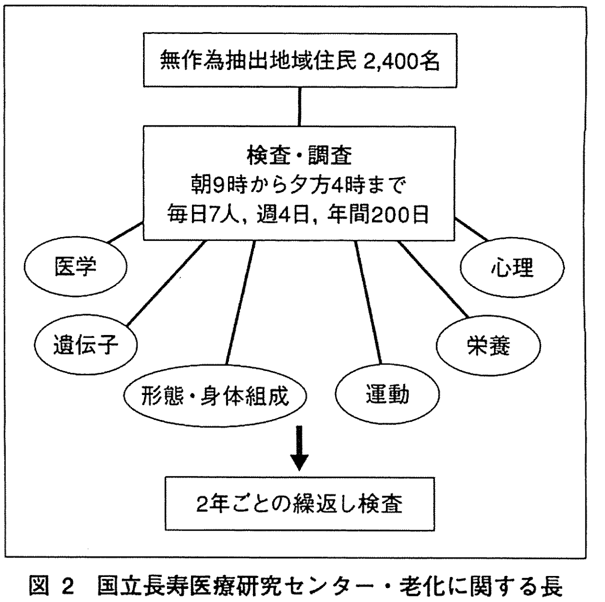

図 2　国立長寿医療研究センター・老化に関する長期縦断疫学研究(NILS-LSA)の概要

加齢に伴う運動器疾患罹患の実態

NILS-LSA の第 5 次調査に参加した 40〜88 歳の男性 1,200 名，女性 1,219 名の合計 2,419 名を対象として，立位で両膝の X 線写真を撮影し，Kellgren-Lawrence 分類(KL 分類)[10]にて変形性膝関節症を grade 0 から grade Ⅳ までに分類し，grade Ⅱ以上を変形性膝関節症と診断した．また，grade Ⅲ以上を膝関節高度変形として，10 歳ごとの年齢別および性別に有病率を算定した．図 3 に示すように，変形性膝関節症は男性よりも女性に多く，年

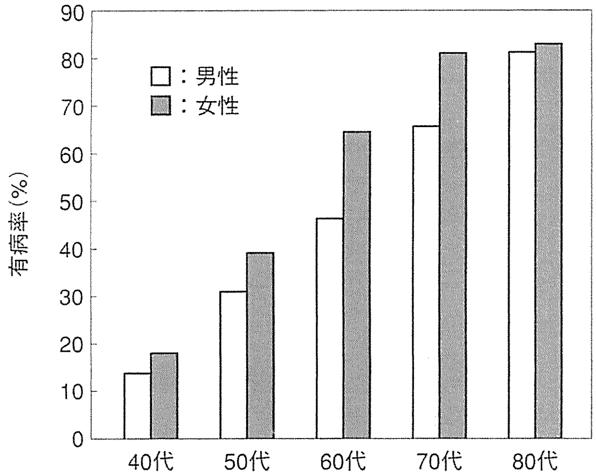

図 3　年代別，性別の膝変形性関節症の有病率
(Kellgren-Lawrence 分類 grade II 以上)

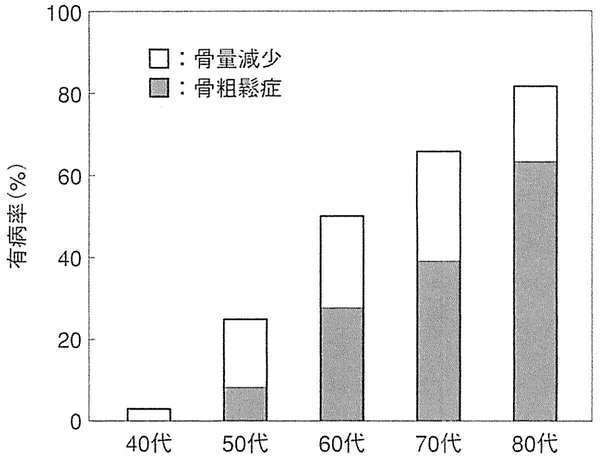

図 4　女性の年代別の骨粗鬆症および骨量減少の有病率(日本骨代謝学会診断基準による腰椎骨密度からの判定)

齢とともに有病率は上昇する．40 歳以上の女性全体での有病率は 52.3%，男性で 43.5%であった．また，KL 分類 grade III 以上の膝高度変形保有率は女性のほうが男性よりも 2 倍以上多く，また女性では年齢とともにその率は大きく上昇していた．上記の有病率を用いて日本人全体の人口構成から有病率を計算すると，男性 1,278 万人，女性 1,950 万人の合計 3,228 万人と推定された．

日本骨代謝学会の診断基準[11]を用いて，DXA 法で計測した腰椎骨密度(第 2，3，4 腰椎の平均骨密度)および右大腿骨頸部骨密度により，性別，年齢別に骨粗鬆症の有病率を算定した(図 4)．50 歳以上の女性の有病率は，腰椎 BMD の判定の場合 26.1%，大腿骨頸部 BMD 判定の場合 21.3%であった．骨粗鬆症・骨量減少の年代別有病率は，どちらの部位の判定でも加齢で高くなり，とくに 60 歳代で急に高くなった．腰椎に比べ，大腿骨頸部判定の場合，50, 60 歳代での有病率は低かった．50 歳以上の男性の骨粗鬆症有病率は，腰椎 BMD の判定の場合 7.6%，大腿骨頸部 BMD 判定の場合 10.3%であった．骨粗鬆症・骨量減少の年代別有病率は，大腿骨頸部の判定において 60 歳代以降，男性でも加齢で高くなっていた．この結果をもとに，今回得られた骨粗鬆症有病率から見積もられる骨粗鬆症患者数は，腰椎骨密度による有病率を用いると 50 歳以上の女性で約 811 万人，50 歳以上の男性で 189 万人と推計され，大腿骨頸部では女性 685 万人，男性 250 万人となる．男女合計で骨粗鬆症患者数は 900 万～1,000 万人と推定された．

骨粗鬆症疾患ゲノム研究

骨粗鬆症は生活習慣病であり，カルシウム摂取の不足ややせ，運動不足などの危険因子が指摘されている[2]．一方で，骨粗鬆症の危険因子として家族歴がある．他の多くの生活習慣病や老年病と同じように，骨粗鬆症は遺伝的素因と生活習慣や加齢などが複雑に影響しあって発症する多因子疾患であると考えられている．疾患によって遺伝的要因の影響の強さは異なる．人種差や環境，生活習慣による違いはあろうが，アメリカの Framingham スタディの報告では，骨密度の遺伝率(heritability)は約 60%と推定されており，遺伝的な要因は比較的大きいと思われる[12]．NILS-LSA では，これまでに骨密度と有意な関連のあった 31 種類の遺伝子多型についてあらたに発見，あるいは確認の報告を行っている(表 1)[7]．

骨粗鬆症や骨密度への遺伝子多型の影響は，直接的な影響よりもむしろ生活習慣や環境因子による骨への影響を遺伝子多型が修飾する部分が大きい可能性がある．図 5 は著者らの調査の解析結果である．閉経女性の DXA 法による骨密度と除脂肪体重との関係へのエストロゲン受容体(ERα)遺伝子 *Xba* I 多型の影響について検討した[13]．除脂肪体重として求めた筋量が多ければ骨密度は高いが，その影響は AA 型よりも AG/GG 型のほうが

表 1　NILS-LSAにおいて骨密度との関連をあらたに発見または確認した遺伝子多型

略号	遺伝子多型	骨密度への影響
カルシウム向性ホルモンおよび受容体		
VDR	vitamin D receptor (A-3731G)	男性の CC 型で大腿骨頸部の骨密度が高い
ESR1	estrogen receptor α (PP/pp)	高齢女性の CC 型で骨密度が低い
ESR1	estrogen receptor α (XX/xx)	高齢女性の GG 型で骨密度が低い
OST	osteocalcin (C298T)	閉経女性の TT 型で骨密度が低い
ADR	androgen receptor (CAG repeat)	未閉経女性の CAG リピートが多いと骨密度が低い
CYP17A1	cytochrome P450, family 17, subfamily A, polypeptide 1 (T-34C)	閉経女性の CC 型で骨密度が低い
サイトカイン，成長ホルモンおよび受容体		
IL-6	interleukin-6 (C-634G)	閉経女性の GG 型で橈骨遠位の骨密度が低い
TGF-β	transforming growth factor-β1 (T29C)	高齢女性の TT/TC 型で橈骨の骨密度が低い
OPG	osteoprotegerin (T950C)	未閉経女性の CC 型で橈骨近位の骨密度が低い
OPG	osteoprotegerin (T245G)	閉経女性の GG 型で大腿骨頸部骨密度が低い
CCR	chemokine receptor 2 (G190A)	若年男性と閉経女性の GG/GA で骨密度が低い
骨基質関連蛋白		
MMP1	matrix metalloproteinase-1 (1G/2G at-1607)	閉経女性の GG/GG 型で橈骨遠位骨密度が低い
MMP9	matrix metalloproteinase-9 (C-1562T)	男性の CT/TT 型で骨密度が低い
COL	collagen type 1 (G-1997T)	閉経女性の GG 型で骨密度が低い
ICAM-1	intercellular adhesion molecule-1 (Lys469Glu)	閉経女性の AA 型で骨密度が低い
PLOD1	procollagen-lysine 2-oxyglutarate 5-dioxygenase (Ala99Thr)	未閉経・閉経女性の GA/AA 型で骨密度が低い
CX37	connexin 37 (Pro319Ser)	男性の TT 型で骨密度が低い
その他		
KLOT	klotho (G-395A)	閉経・未閉経女性の GG 型で骨密度が低い
MTP	microsomal triglyceride transfer protein (G-493T)	未閉経女性の TT 型で骨密度が高い
VLDLR	VLDL receptor (triplet repeat)	男性の CGG リピート 8 以上で骨密度が高い
ALAP	adipocyte-derived leucine aminopeptidase (Lys528Arg)	未閉経女性の GA/AA 型で骨密度が低い
LIPC	hepatic lipase (C-514T)	閉経女性の TT 型で骨密度が低い
CNR2	cannabinoid receptor 2 gene (A/G, rs2501431)	未閉経・閉経女性の AA/AG 型で骨密度が低い
PON1	paraoxonase-1 (Gln192Arg)	閉経女性の GG 型で骨密度が低い
PON1	paraoxonase-1 (Met55Leu)	閉経女性の TT 型で骨密度が低い
PON2	paraoxonase-2 (Cys311Ser)	閉経女性の CC 型で骨密度が低い
DRD4	dopamine D4 receptor (C-521T)	男性の CC 型で骨密度が低い
FOXC2	forkhead box C2 (C-512T)	男女ともに T アリルで骨密度が低い
PLN	perilipin (C1243T)	男性の C アリルで骨密度が低い
MAOA	monoamine oxidase A (uVNTR)	未閉経・閉経女性のリピート 4 未満で骨密度低い
SH2B1	Src-homology-2-B (Ala484Thr)	未閉経・閉経女性の A アリルで骨密度が低い

強い．AG/GG 型の多型をもつ人は筋量を増やすことが，AA 型の人よりも骨粗鬆症の予防には効果的であることがわかる．筋量が少ない集団では AA 型のほうが骨密度は高いが，筋量が多い集団では AG/GG 型のほうが骨密度は高いという逆転が生じており，このため対象集団の筋量が異なれば，遺伝子多型の骨密度との関係はまったく逆になってしまう．遺伝子以外の個体差が十分に検討されていないことが，ゲノム研究での再現性が乏しいことの要因のひとつになっている可能性がある．

感受性遺伝子多型をもっていても発症しない人もいる．その要因を探るというアプローチもある．感受性遺伝子多型をもっていて発症した人，発症していない人について生活習慣などの要因を詳細に比較検討することで，感受性遺伝子をもっていても骨粗鬆症をどうすれば予防できるかを明らかにすることができる．さらに生活習慣などの修飾可能な危険要因については，その縦断的変化についての検討も必要である．特定の遺伝子多型をもつ人が，たとえば身体活動量を 2 倍にしたとき骨密度はどう変化するのか，遺伝子多型によってその効果にどのような差があるのかを明らかにする

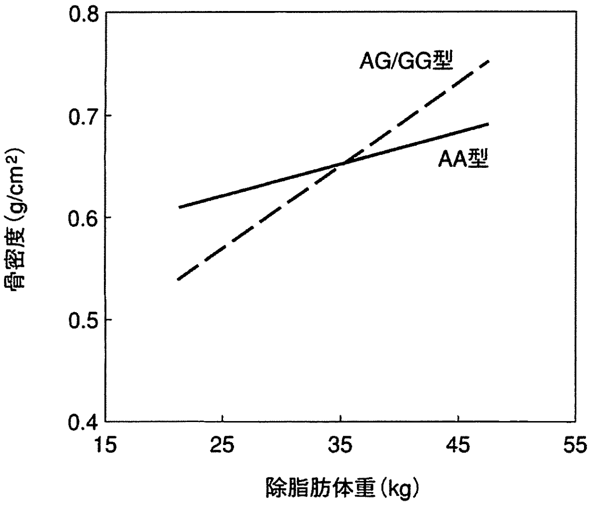

図 5　閉経女性のDXA法による骨密度と除脂肪体重との関係へのエストロゲン受容体(ERα)遺伝子 *Xba I* 多型の影響[13)]

除脂肪体重，すなわち筋量が多ければ骨密度は高いが，その影響はAA型よりもAG/GG型のほうが強い．

ことが，遺伝子多型を利用した実際の予防指導の際には重要である．こうしたデータを蓄積するためには，多数の集団で長期にわたった詳細な生活習慣や環境要因の調査が必要である(「サイドメモ」参照)．

運動器疾患のリスク予想と予防

骨代謝マーカー測定によって骨粗鬆症や骨量減少の予測ができるかをNILS-LSAで検討した．骨代謝マーカーとしてオステオカルシン(OC)，骨型アルカリホスファターゼ(BAP)，尿中I型コラーゲン架橋N-ペプチド(NTx)，デオキシピリジノリン(DPD)を測定したところ，女性の腰椎でOC，BAP，NTxが，女性の大腿骨頸部でDPD，BAP，NTxが，男性の大腿骨頸部でBAPが6年後の骨粗鬆症や骨量減少の発症に有意に関連しており，これらのマーカーから将来の骨粗鬆症や骨量減少の発症を予測できる可能性が示された[14)]．

NILS-LSAでは，生活習慣や環境要因との相互関係を考慮した骨粗鬆症の遺伝要因の検討も順次進めている．DXA法による骨粗鬆症診断結果と，握力，脚筋力など運動・体力に関する要因，カルシウム，ビタミンDなど栄養に関する要因，BMI，除脂肪体重など体格・体型に関する要因，そのほか嗜好，閉経，骨代謝マーカーを含む血液尿検査結果などの項目の追跡による縦断的なデータについて網羅的に検討を行うことで，それぞれ骨粗鬆症と関連の強い要因を抽出する．抽出された要因と遺伝子多型との相互作用を網羅的に検討し，その結果から最終的に骨粗鬆症と関連する生活習慣要因，遺伝子多型，生活習慣要因と遺伝子多型の交互作用を抽出し，骨粗鬆症の予測を行う総合的なシステムの構築を行っている．長期縦断研究によりこうしたシステムが完成すれば，骨粗鬆症の医療や予防の実用化へ一歩前進するものと期待される．

おわりに

高齢化が急速に進む日本の社会において，高齢者の健康維持・増進はきわめて重要な課題である．高齢者が健康に長生きできることは国民の共通の願いであり，これを実現することが急務である．高齢者の運動器疾患は直接の死因とはならない場合がほとんどではあるが，高齢者のQOLを阻害し，寝たきりや廃用症候群を引き起こし，認知症や肺炎の要因ともなる．高齢者の運動器疾患の予防と治療は高齢者の健康長寿を考える場合には欠かすことができない．そのためのエビデンスを集積する研究として，疾患そのものだけでなく，

サイドメモ

縦断研究

加齢による変化を検討する方法には大きく分けて，横断的方法と縦断的方法の2つがある．縦断的研究は同一の個人を継続して観察し，加齢による実際の心身の変化，加齢に関連する要因，発育，発達，老化，寿命などをとらえようとするものである[1-4)]．一方，さまざまな年齢を含む集団を設定して種々の検査を一度に実施し，1歳ごとの，あるいは5歳，10歳ごとの年齢群で検査値がどのように異なるのかを検討し，その差を加齢変化とする方法が横断的研究である．一度の調査で終了してしまう横断研究に比べて経時的な追跡を行う縦断研究は，結論が出るまでに一般に数年から10年以上もの期間を要し，調査を継続するための費用や人材の確保も必要である．しかし，加齢変化の観察を行うためには横断的観察のみでは加齢による変化を正確にとらえることができない．

遺伝子や栄養，運動までを含めた学際的な長期縦断疫学研究の進展が望まれる．

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Impact of Caregiver Burden on Adverse Health Outcomes in Community-Dwelling Dependent Older Care Recipients

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Objective: *To determine whether caregiver burden is associated with subsequent all-cause mortality or hospitalization among dependent community-dwelling older care recipients.* **Methods:** *A prospective cohort study of 1,067 pairs of community-dwelling 65-year-old or older care recipients and their informal caregivers was conducted. The 1,067 pairs completed the baseline assessment including caregiver burden assessed by the Zarit Burden Interview and a 3-year follow-up for all-cause mortality and hospitalization.* **Results:** *During the 3-year follow-up, 268 recipients died and 455 were admitted to hospitals. The multivariate Cox proportional hazards model revealed that the recipients with caregivers with a baseline ZBI score in the highest quartile were 1.54 and 1.51 times more likely to show increased risks of all-cause mortality and hospitalization, respectively, in comparison with those with caregivers in the lowest quartile after adjustment for potential confounders. The highest quartile of caregiver burden was associated with all-cause mortality and hospitalization within nonusers of respite services including day-care services, home-help services, and nursing-home respite stay services. No apparent association was observed within the users of these services except for day-care services, for which users showed a statistically significant association between the highest quartile and the risk of hospitalization.* **Conclusions:** *Heavy caregiver burden is associated with mortality and hospitalization among community-dwelling dependent older adults, even after adjusting for potential confounders. The reduction of caregiver burden and improvement of caregiver well-being may not only prevent the deterioration of caregiver health but also reduce adverse health outcomes for care recipients.* (Am J Geriatr Psychiatry 2011; 19:382–391)

Key Words: Caregiver burden, mortlity, hospitalization, adverse health outcomes of care recipient

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The current trend toward a community-based healthcare system means that when older people require care, much of it is provided at home. Thus, family members are providing care for ill or disabled older relatives. Family caregiving has been intensively studied in the past decade, particularly the impact on caregivers of providing home care to a family member. Caregiver burden has been defined as a negative reaction to the impact of providing care on the caregiver's social, occupational, and personal roles.[1–3] It is well documented that informal care for the disabled elderly places heavy burdens on family caregivers.[1–3] Previous studies demonstrated that caregiver burden is associated with the substantial care needs of seriously ill patients, which are in turn associated with the presence of dementia, behavioral problems, poorer physical functioning, and factors that are not readily modifiable.[4–7] Caregiver burden can lead to a chronic stress response that can worsen caregiver health, contribute to psychiatric morbidity in the form of increased depression,[8] contribute to the risk of health problems such as wound healing impairment, elevated blood pressure, and coronary heart disease risk and immune function impairment,[9–11] and is an independent risk factor for mortality.[12]

Thus, most of the previous studies on caregiver burden have focused on examining its cause(s) and extensively examining caregiver health. However, conversely, much less attention has been paid to the impact of caregiver burden or distress on the health of the partner, the care recipient. In fact, it remains uncertain whether caregiver burden or distress has any influence on the health-related outcomes of care recipients, although the association of caregiver burden with long-term care placement has been well demonstrated.[13,14] In this study, we investigated whether caregiver burden is associated with adverse health outcomes of the care recipients, including all-cause mortality and hospitalization for acute illness, during a 3-year study period. In addition, we examined the effect of community-based respite care services, including day-care, home-help, and nursing-home respite stay services on the adverse outcomes of care recipients.

METHODS

Study Setting and Cohort Participants

In this study, we employed baseline data on the care recipient and caregiver pairs in the Nagoya Longitudinal Study for Frail Elderly (NLS-FE) and data on the mortality and hospitalization of the care recipients during the 3-year follow-up period. Japan introduced a universal-coverage long-term care insurance (LTCI) program in 2000. Under the LTCI program, each applicant's care levels are determined according to eligibility criteria. Eligibility status is classified into six levels ("needs support" and care levels 1–5) by the estimation of care needs based on an assessment of the current physical and mental status of the patient and their use of medical procedures.[15] The NLS-FE was designed to compare the outcomes of different uses of community-based care services provided by the LTCI program.[16,17] The study sample consisted of 1,875 community-dwelling elderly (632 men and 1,243 women, age 65 years or older) with some degree of physical or mental disability. They were eligible for the LTCI program, lived in Nagoya City, Japan, and received various kinds of community-based services from the Nagoya City Health Care Service Foundation for Older People, which has 17 visiting nursing stations associated with care-managing centers. These 1,875 NLS-FE participants and 1,502 caregivers (373 of the 1,875 participants lacked a primary caregiver), who were enrolled between December 1, 2003, and January 31, 2004, were scheduled to undergo comprehensive in-home assessments by trained nurses at the baseline and at 6, 12, and 24 months. At 3-month intervals, data were collected about any important events in the lives of the participants, including mortality and admission to the hospital for acute illness during the 3-year follow-up. Written informed consent for participation was obtained from the participants, care recipients, and caregivers, or, for those with substantial cognitive impairment, from a surrogate (usually the closest relative or legal guardian), according to procedures approved by the Institutional Review Board of Nagoya University Graduate School of Medicine.

Data Collection

The data were collected at the clients' homes through structured interviews with care recipients or surrogates and caregivers and from care-managing center records taken by trained nurses. The data included each participant's demographic characteristics, general socioeconomic status, living arrangements, subjective economic status, use of medical services, and the utilization of a total of seven community-based services available under LTCI programs, including the day-care service, visiting nurse service, home-help service, visiting bathing service, visiting rehabilitation, assistive device leasing, and nursing-home respite stay (overnight respite, temporary stays at nursing facilities). The data also included depressive symptoms as assessed by the 15-item Geriatric Depression Scale (GDS-15) (range: 0–15, with higher values indicating more depressive symptoms)[18] and a rating for eight basic activities of daily living (bADL) using summary scores ranging from 0 (total disability) to 20 (no disability). The information on the following physician-diagnosed chronic conditions was obtained from care-managing center records: ischemic heart disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, dementia, chronic obstructive pulmonary disease, cancer, hypertension, and other diseases comprising the Charlson Comorbidity Index,[19] which represents a sum of weighted indexes that takes into account the number and seriousness of preexisting comorbid conditions (range: 0–19, with a higher value indicating higher comorbidity).

Data were also obtained from caregivers concerning their own personal demographic characteristics including caregiver relationship to care recipient (spouse or not), and the presence of behavioral disturbance of the care recipient according to the primary assessment dataset of the public LTCI, including wandering, hallucinations, physically aggressive behaviors, verbal aggression, delusions, altered sleep-wake cycles, sexually disinhibited behaviors, aberrant behaviors, abnormal eating behaviors, and resistance to care. Depressive symptoms were assessed by the GDS-15, and the caregiver's subjective burden was assessed by the Japanese version of the Zarit Burden Interview (ZBI), which is a 22-item self-report inventory that examines the burden associated with functional behavioral impairments in the home care situation (range: 0–88, with higher values indicating a greater burden). The primary caregivers were also asked to rate their current overall health in three categories of subjective health status (poor, fair, and good to excellent).

Subjects for the Analysis

Among the original 1,502 pairs at baseline, 276 caregivers could not complete or refused to assess the ZBI, and the data on comorbidity condition or sociodemographic characteristics were lacking for 159 participants. The study sample, therefore, consisted of 1,067 community-dwelling disabled elderly (387 men, 680 women, age range: 65–104 years) and paired caregivers (256 men, 811 women, age range: 31–90 years). There were no statistical differences in mortality and hospitalization rates during the follow-up period between participants with and without caregiver ZBI measurements among the 1,502 participants. Of these 1,067 pairs, 259 care recipients could not complete the GDS-15 because of severe cognitive impairment or communication impairment, and 101 caregivers because of refusal to do the assessment.

Statistical Analysis

The ZBI score was categorized into quartiles (quartile 1: score, 0–15, N = 284; quartile 2: 16–26, N = 253; quartile 3: 27–39, N = 269; quartile 4: 40–84, N = 261). Baseline characteristics of the study participants, including both care recipients and caregivers, were examined using the Jonckheere–Terpstra test or the General Linear Models for trends across the quartiles of the ZBI score. Analysis of variance for multiple comparisons was used to determine differences among the quartiles of the ZBI score for continuous variables, and the Pearson χ^2 test was used to test categorical variables. The end point of this study was defined as the time to all-cause death or hospitalization because of acute illness, whichever occurred first, during follow-up. Cox proportional hazard models and the Kaplan–Meier method (differences between strata of the ZBI score levels determined using log-rank tests) were used to assess the association of quartiles of the ZBI score with those adverse outcomes after enrollment during a 3-year period (3-month intervals). To create an ideal model for a multivariate Cox proportional hazards model, we first evaluated the association between each covariate and all-cause death or hospitalization, using the univariate Cox proportional hazards model. Covariates included, for the recipient, sociodemographic characteristics, the presence or absence of regular medical checkups, the number of community-based services, economic status, bADL score, the Charlson comorbidity index, and the presence or absence of selected major comorbidities and behavioral problems. Covariates also included, for the caregiver, sociodemographic characteristics, subjective health status, and categorized ZBI score. In the multivariate analysis, the covariates included were variables associated with each event with $p < 0.05$ in univariate analysis. In models considering the quartiles of the caregiver ZBI score, we compared hazard ratios (HRs) with a corresponding 95% confidence interval (CI) in the second, third, and fourth quartiles with those in the first quartile (referent).

Additional analyses stratified by the use or nonuse of community-based respite care services including day-care, home-help, and nursing-home respite stay services were also performed using a consistent set of covariates to examine the data for possible interactions of these variables with the adverse health outcomes of care recipients. Student's *t*-test and analysis of covariance (ANCOVA) were used to compare the caregiver ZBI score according to the service use and nonuse groups. Covariates of ANCOVA included recipient gender, age, bADL score, the Charlson comorbidity index, the presence or absence of dementia and behavior problems, caregiver gender, and caregiver age.

The data were analyzed using the SAS, Release 9.13. Probability value of <0.05 was considered significant.

RESULTS

The baseline distribution of the sociodemographic characteristics of the care recipients and caregivers according to the quartiles of the ZBI score is shown in Table 1. We used analysis of variance or Pearson χ^2 test to evaluate differences among the quartiles of the ZBI score. The bADL score decreased, and the number of community-based services used, the Charlson comorbidity index, and recipient GDS-15 score increased as the level of the ZBI quartile increased. The care recipients whose caregivers' ZBI scores were in higher quartiles were more likely to show a higher prevalence of dementia (χ^2 test: $\chi^2 = 61.09$, degrees of freedom [*df*] = 3, $p < 0.001$; Jonckheere-Terpstra test: *z* statistics, Z value = 7.51, N = 1,067, $p < 0.001$), behavioral problems ($\chi^2 = 14.75$, $df = 3$, $p = 0.002$; Jonckheere-Terpstra test, Z value = 8.58, N = 1,067, $p < 0.001$) and a history of cerebrovascular disease ($\chi^2 = 10.31$, $df = 3$, $p = 0.016$; Jonckheere-Terpstra test, Z value = 2.37, N = 1,067, $p = 0.018$). The caregiver's GDS-15 score increased (General Linear Model, *F* value = 313.48, $df = 1{,}964$, $p < 0.001$), and the prevalence of good to excellent subjective health status of the caregiver decreased with increasing quartiles of the ZBI score (Jonckheere-Terpstra test, Z value = 5.37, N = 1,067, $p < 0.001$). There were no differences in the rate of regular medical checkups (χ^2 test, $\chi^2 = 5.66$, $df = 3$, $p = 0.130$), living arrangements (living alone or with one person versus living with two or more, $\chi^2 = 1.46$, $df = 3$, $p = 0.692$), and three categories of economic status ($\chi^2 = 6.70$, $df = 3$, $p = 0.349$) among the quartiles of the ZBI score.

During the 3-year period, 268 care recipients died and 455 were admitted to hospitals (Table 2). The participants whose caregivers' ZBI scores were in the higher quartiles were more likely to die and be hospitalized during the follow-up period than those whose caregivers' scores were in the lower quartile categories (χ^2 test, $\chi^2 = 9.78$, $df = 3$, $p = 0.020$; $\chi^2 = 11.09$, $df = 3$, $p = 0.007$, respectively).

Kaplan–Meier curves of survival and the cumulative incidence of hospitalization during the 3-year period among care recipients according to the quartile of the caregivers' ZBI scores demonstrated that all-cause mortality and hospitalization increased with higher quartiles of caregiver ZBI at baseline (log-rank χ^2 test, mortality: $\chi^2 = 17.29$, $df = 3$, $p < 0.001$; hospitalization: $\chi^2 = 23.61$, $df = 3$, $p < 0.001$; Fig. 1).

The univariate Cox proportional hazards model revealed that the recipients whose caregivers' ZBI scores were in the highest quartile were 1.93 times and 1.86 times more likely to suffer all-cause mortality and hospitalization, respectively, during the 3-year period than those in the lowest quartile (95% CI: 1.38–2.71, Wald χ^2 test, $\chi^2 = 14.80$, $df = 1$, $p < 0.001$; 95% CI: 1.43–2.42, Wald $\chi^2 = 21.16$, $df = 1$, $p < 0.001$). The GDS-15 score of the care recipients and caregivers was not associated with mortality and hospitalization in univariate analysis (mortality: HR: 1.03; 95% CI: 0.98–1.07, Wald χ^2

TABLE 1. Baseline Characteristics of Study Participants According to ZBI Score Quartile of Caregivers

	Quartile Group of Caregiver ZBI Score					
	1st, Score: 0–15, n = 284	2nd, Score: 16–26, n = 253	3rd, Score: 27–39, n = 269	4th, Score: 40–84, n = 261	*F*	p
Care recipients (n = 1067)						
Men/women, N (% of men)	89/195 (31.3)	88/165 (34.8)	100/169 (37.2)	110/151 (42.1)		0.065
Age, M (SD), year[a]	81.0 (7.1)	81.1 (7.7)	81.2 (7.8)	80.8 (8.5)	0.10	0.962
Basic ADL (rage: 0-20), *M* (SD)[a]	14.2 (6.1)	12.5 (6.2)	11.0 (6.5)	10.4 (6.3)	20.07	<0.001
Charlson comorbidity index, *M* (SD)[a]	1.8 (1.5)	2.2 (1.5)	2.3 (1.5)	2.4 (1.7)	7.06	<0.001
GDS-15 (range: 0-15), *M* (SD)[a,b]	5.4 (3.4)	6.2 (3.2)	6.6 (3.4)	8.1 (3.7)	21.19	<0.001
No. of service uses (range: 0-7), *M* (SD)[a]	2.0 (1.1)	2.2 (1.2)	2.4 (1.3)	2.5 (1.3)	8.97	<0.001
Presence of chronic disease, no. (%)						
Ischemic heart disease	36 (12.7)	31 (12.3)	36 (13.4)	29 (11.1)		0.882
Congestive heart failure	17 (6.0)	20 (7.9)	22 (8.2)	27 (10.3)		0.321
Cerebrovascular disease	93 (32.7)	110 (43.5)	120 (44.6)	111 (42.5)		0.016
COPD	11 (3.9)	11 (4.3)	14 (5.2)	18 (6.9)		0.400
Dementia	66 (23.2)	92 (36.4)	135 (50.2)	135 (51.7)		<0.001
Cancer	29 (10.2)	22 (8.7)	14 (5.2)	28 (10.7)		0.098
Presence of behavioral problems, no. (%)	8 (2.8)	11 (4.3)	21 (7.8)	26 (10.0)		0.002
Caregiver variables (n = 1067)						
Men/women, no. (% of men)	71/213 (25.0)	69/184 (27.3)	56/213 (20.3)	60/201 (23.0)		0.350
Age, *M* (SD), year[a]	64.1 (13.0)	65.4 (12.2)	63.5 (12.6)	65.8 (11.3)	2.05	0.106
GDS-15 (range: 0-15), *M* (SD)[a,c]	3.4 (3.0)	4.7 (3.2)	5.8 (3.5)	8.5 (3.4)	107.98	<0.001
Relationship to care recipient, no. (%)						
Spouse	115 (40.5)	119 (47.0)	106 (39.4)	128 (49.0)		0.061
Nonspouse	169 (59.5)	134 (53.0)	163 (60.6)	133 (51.0)		
Health status, no. (%)						
Good to excellent	150 (52.8)	101 (39.9)	98 (36.4)	80 (26.2)		<0.001
Fair	103 (36.3)	127 (50.2)	148 (55.0)	169 (55.4)		
Poor	31 (10.9)	25 (9.9)	23 (8.6)	56 (18.4)		
ZBI score (range: 0-88), *M* (SD)[a]	9.4 (4.7)	21.0 (3.1)	32.6 (4.0)	52.5 (9.8)	2553.05	<0.001

Notes: *M*: mean; SD: standard deviation; COPD: chronic obstructive pulmonary diseasee.
[a]Analysis of variance for multiple comparisons was used to determine differences among the quartiles of the ZBI score for continuous variables ($df = 3{,}1063$ except for recipient GDS-15 [$df = 3, 804$] and caregiver GDS-15 [$df = 3{,}962$]), and the Pearson χ^2 test was used to test categorical variables ($df = 3$).
[b]n = 808.
[c]n = 966.

TABLE 2. Adverse Events During 3-year Period According to the Quartile Group of ZBI Score

	Quartile Group of ZBI Score					
	1st, n = 284	2nd, n = 253	3rd, n = 269	4th, n = 261	Total, n = 1,067	p[a]
Adverse outcomes, no. (% of each quartile)						
All-cause death	58 (20.4)	63 (24.9)	64 (23.8)	83 (31.8)	268 (25.1)	0.020
Hospitalization	98 (34.5)	111 (43.9)	119 (44.2)	127 (48.7)	455 (42.6)	0.007

[a]Pearson χ^2 test. Degree of freedom is equal to 3.

test, $\chi^2 = 1.52$, $df = 1$, $p = 0.218$, and HR: 1.02; 95% CI: 0.98–1.05, Wald $\chi^2 = 1.072$, $df = 1$, $p = 0.301$, respectively; hospitalization: HR: 1.02; 95% CI: 0.99–1.05; Wald χ^2 test, $\chi^2 = 1.54$, $df = 1$, $p = 0.215$, and HR: 1.01; 95% CI: 0.99–1.04; Wald $\chi^2 = 0.81$, $df = 1$, $p = 0.369$, respectively).

As shown in Table 3, multivariate adjustment for confounders, including recipient gender and age, bADL score, number of community-based services used, the Charlson comorbidity index, caregiver gender and age, presence or absence of behavioral problems (only for all-cause mortality analysis), and the subjective health status of the caregiver (only for hospitalization analysis), showed that the highest quartile of caregivers' ZBI scores (compared with the lowest quartile) was associated with a 1.54-fold risk