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# Physical Independence and Mortality at the Extreme Limit of Life Span: Supercentenarians Study in Japan

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***Background.*** Prevention of disability is a major challenge in aging populations; however, the extent to which physical independence can be maintained toward the limit of human life span remains to be determined.

***Methods.*** We examined the health and functional status of 642 centenarians: 207 younger centenarians (age: 100–104 years), 351 semi-supercentenarians (age: 105–109 years), and 84 supercentenarians (age: >110 years). All-cause mortality was followed by means of an annual telephone or mailed survey.

***Results.*** Age-specific disability patterns revealed that the older the age group, the higher the proportion of those manifesting independence in activities of daily living at any given age of entry. Multiple logistic regression analysis identified male gender and better cognitive function as consistent determinants of physical independence across all age categories. In a longitudinal analysis, better physical function was significantly associated with survival advantage until the age of 110. However, mortality beyond that age was predicted neither by functional status nor biomedical measurements, indicating alternative trajectories of mortality at the highest ages.

***Conclusions.*** These findings suggest that maintaining physical independence is a key feature of survival into extreme old age. Future studies illuminating genetic and environmental underpinnings of supercentenarians' phenotypes will provide invaluable opportunities not only to improve preventive strategies but also to test the central hypotheses of human aging.

***Key Words:*** Physical function—Centenarians—Longevity—Epidemiology.

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ON the basis of improvements in survival into advanced age, centenarians (those who reach the age of 100 years) have emerged as the fastest growing segment of populations in postindustrialized countries (1,2). Consequently, the number of centenarian studies has appreciably increased during the recent two decades, expanding our knowledge of longevity traits of humans. Centenarians are generally characterized by delayed onset of age-related diseases or disabilities into their 90s; however, upon reaching the age of 100 years, substantial evidence has demonstrated that frailty (3,4), multimorbidity (5,6), and a high rate of hospitalization (7) are commonplace. These observations raise an essential question regarding whether extended longevity will be accompanied by elongation of disabling processes or by a marked compression of disability.

A few studies have addressed this important question by focusing on supercentenarians, individuals who have reached their 110th birthday. The number of validated supercentenarians worldwide has been monitored in an international collaborative effort involving the International Database on Longevity: the database includes a total of 12 supercentenarians in Sweden, 2 in Denmark, 49 in France, 78 in Japan, and 341 in the United States (8). Among the 1895 birth cohort in Japan, the ratio of individuals who reached 100 years old in 1995 was 239 per 100,000 births, and the ratio of those who reached 110 years old in 2005 was 0.96 per 100,000 births. Indeed only 0.4% of those who reached 100 years old then survived to 110 years old (9). Because of the extraordinarily low probability of reaching that age even in current low-mortality countries, epidemiological observations of supercentenarians are sparse and conflicting (10,11). A precise description of what happens to individuals' health and independence at the tail end of the human survival curve has assumed an important role in

estimating future disability trends and health care demands; such knowledge has enormous social, economic, and medical implications in our aging societies.

In this context, Japan represents a unique opportunity for explicating supercentenarians' phenotypes because (i) it has one of the world's highest longevity rates and a relatively large population (approximately 127 million in 2012) and (ii) it implemented a national family registration system (Jin-Shin Koseki) as early as 1872, making high-quality data on the number of births available (12,13). These conditions allowed us to conduct a nationwide survey of supercentenarians involving direct examination using a standardized procedure. We hypothesized that maintaining independence and delayed onset of disability would be the key determinant of extended longevity, beyond 100 years of age, because functional capability might correlate highly with mortality even at the extreme limit of life span. To test our hypothesis, we explored the health and functional status of 642 centenarians, including 84 supercentenarians, in connection with mortality beyond 100 years of age.

## Methods

### *Subjects*

This study was based on two prospective cohorts of the Tokyo Centenarians Study (TCS) and the Japanese Semi-supercentenarians Study (JSS). Details of the population-based recruitment of the TCS have been described previously (3,5,14). Briefly, we identified 1,194 eligible centenarians (individuals aged 100 years or older) from the basic residential register at the administrative institution of each of 23 wards of the Tokyo metropolitan area and sent all of them an invitation letter to our study. Consequently, 514 centenarians participated in our mailed survey, of which 304 (age: 100–108 years; mean age: 101.1 ± 1.7 years; 65 men and 239 women) agreed to participate in our visiting survey. The male-to-female ratio in our participant group was 1:3.6, which was similar to the ratio in the total centenarian population in this area (1:3.8). The baseline assessment was performed at the participants' residences between July 2000 and May 2002. Of the 304 participants, 297 with complete baseline data on the Barthel Index and mortality follow-up until the end of June 2012 were included in the analysis.

The JSS is a nationwide longitudinal survey that involves mainly individuals aged 105 years or older. Since 1963, a list of centenarians has been compiled annually by the Ministry of Health, Welfare and Labor, and this list has been linked with the resident registration system and the periodic census (12). According to the list, 849 semi-supercentenarians were living in Japan in 2002, including 23 supercentenarians aged 110 years and older. They had been successively recorded on the annual centenarians list since 1997 or earlier. We identified the names and addresses of 543 individuals (82 males and 461 females) among the 849 semi-supercentenarians listed and sent all of them an invitation letter for a home visit examination. As a result, 135 (115 females and 20 males) agreed to participate in our visiting survey. Because the list was discontinued in 2002, our subsequent recruitment strategy has relied on responses to local governments and nursing homes in the whole country, and direct inquires by our research team. Consequently, in total, 429 centenarians (90.2% older than 105 years) were enrolled in the JSS by the end of November 2011. Of them, 13 were excluded because they lacked baseline assessment of the Barthel Index or dropped out from the follow-up survey, and 71 were excluded because they were recently recruited and remained alive between 105 and 109 years of age at the time of analysis (potential candidates for supercentenarians); thus, 345 were included in the analysis. Dates of birth of all participants in the JSS were certified by the national health insurance or long-term care insurance systems, both of which are linked to the basic residential registration.

Written informed consent to participate was obtained either from the participants or by proxy when individuals lacked the capacity to consent. The TCS and JSS were approved by the Ethical Committee of the Keio University School of Medicine.

### *Data Collection*

TCS assessment procedures have been reported elsewhere (3,5). All participants in the TCS and JSS were visited by our research team, including geriatricians, at their residence. To assess physical functional status, a geriatrician interviewed both centenarians and proxy/care givers, and verified their activities of daily living (ADL) status by physical examination. Basic ADL were assessed using the Barthel Index. Cognitive function was evaluated according to the Mini-Mental State Examination. Because approximately 20% of centenarians could not complete the Mini-Mental State Examination due to visual/hearing impairment or an inability to communicate, they were simultaneously evaluated using the Clinical Dementia Rating scale (15). Information regarding past medical history was obtained from personal interviews with the care giver/proxy, available documentation, including discharge summary and medication list, and medical examinations conducted by geriatricians for both the TCS and JSS (5). We defined diabetes as follows: (i) self-reported diagnosis, (ii) administration of insulin or other oral hypoglycemic medications, (iii) random plasma glucose level ≥200 mg/dL, or (iv) hemoglobin A1c level ≥6.5%. Hemoglobin A1c (%) values were estimated as National Glycohemoglobin Standardization Program-equivalent values (%). The classification of self-reported medical conditions was based on the International Classification of Diseases, 10th Revision categories.

Nonfasting blood samples were obtained at baseline, and the plasma concentrations of albumin, C-reactive protein, total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured by standard automated methods (SRL Limited, Tokyo, Japan).

For both the TCS and JSS cohorts, all-cause mortality was ascertained by telephone contact or mail survey conducted every 12 months until June 30, 2012 with a 285,392 person-day (median period: 740 days; range: 3–4,036 days) follow-up for the TCS (16) and a 180,759 person-day (median period: 409 days; range: 1–2,561 days) follow-up for the JSS. Follow-ups of centenarians were completed by confirming either the date of death or survival at the end of the observation period.

### *Statistical Analysis*

For cross-sectional analyses of the association between functional status and extended longevity, 642 centenarians were classified into three age categories based on their age at death:

- Younger centenarians: individuals who died between 100 and 104 years of age.
- Semi-supercentenarians: individuals who died between 105 and 109 years of age.
- Supercentenarians: individuals who survived beyond 110 years of age.

For all participants, except 35 semi-supercentenarians and 3 supercentenarians, we assessed their physical functional status at entry only. To compare ADL status between the three centenarian age groups, we created disability patterns at synchronized entry age, in which physical function was classified into five categories based on the Barthel Index: "independent," score of 80–100; "minimal assistance," score of 60–79; "partially dependent," score of 40–59; "very dependent," score of 20–39; and "totally dependent," score of 0–19 (3,10). We then used multiple logistic regression models to determine the possible mediators of physical independence for each centenarian age category. Continuous variables with a skewed distribution are described as medians (interquartile ranges) and were logarithmically transformed for statistical analyses.

For longitudinal analysis of age-specific survival probability beyond the age of 100 years in connection with physical function, we plotted Kaplan–Meier survival curves according to functional status and albumin levels. A prognostically significant result was defined as log-rank $p < .05$.

All analyses were performed using SPSS ver. 18.0 (SPSS, Chicago, IL). Results were considered statistically significant at a $p$ value of <.05, and two-sided tests were used.

## Results

Baseline characteristics of the centenarian age groups are presented in Table 1. The median age at enrollment was significantly higher in the order of younger centenarians (100.4 years), semi-supercentenarians (106.1 years), and supercentenarians (108.8 years). The proportions of females as well as institutionalized persons increased in the same order. The mean Barthel Index and Mini-Mental State Examination scores of younger centenarians were significantly higher than those of the other two groups. The prevalence of any single disease or multimorbidity did not differ among the centenarian age groups except for a higher prevalence of fragility fractures in supercentenarians ($p = .011$).

To examine cross-sectional associations between physical function and extended longevity beyond the age of 100 years, we compared disability patterns at entry among the centenarian age groups (Figure 1). In 84 supercentenarians who survived beyond 110 years of age (Figure 1A), 5 were enrolled at ages 100–104 years, 58 were enrolled between 105 and 109 years, and 21 were enrolled at 110 years or older. At entry ages 100–104 years, the percentage of physically independent participants was 80%, and it declined to 14% at entry age between 105 and 109, and 0% at entry age of 110 or older. In contrast, the percentages of totally dependent were 0%, 43%, and 76%, respectively. In semi-supercentenarians (Figure 1B), the percentages of physically independent were 26% at entry ages 100–104 and 7% at 105–109 years, whereas those of totally dependent were 25% and 59%, respectively. Above the entry age of 110 years, supercentenarians exhibited a strongly positively skewed pattern, with a very high percentage of totally dependent individuals; this pattern was similar to that exhibited by semi-supercentenarians at entry ages of 105–109 years, suggesting that supercentenarians postponed disabling processes towards the last years of their extremely long lives. Supplementary Figure 1 demonstrates the mean Barthel Index scores at various entry ages across the three centenarian age groups, showing significantly higher physical function of supercentenarians compared with semi-supercentenarians or younger centenarians at any given age.

In the multivariate logistic regression analyses, male gender and better cognitive function were consistently associated with physical independence across all centenarian categories, although the small population size of supercentenarians resulted in a wide 95% confidence interval (Table 2). Serum albumin levels were significantly associated with physical independence in younger centenarians and semi-supercentenarians but not in supercentenarians. No chronic diseases, with the exception of a borderline significance of multimorbidity (odds ratio: 0.59; 95% confidence interval: 0.35–1.01; $p = .052$), or blood chemistry measurements were associated with physical independence in each centenarian age group (data not shown).

To determine whether baseline functional status is predictive of mortality beyond 100 years of age, we constructed age-specific Kaplan–Meier survival plots according to three categories of Barthel Index scores (Figure 2). At any given

Table 1. Baseline Characteristics of the Three Centenarians Age Groups

| | Younger Centenarians (died between ages 100 and 104) | Semi-supercentenarians (died between ages 105 and 109) | Supercentenarians (survived beyond age 110) | *p* |
|---|---|---|---|---|
| *N* (male, female) | 207 (51, 156) | 351 (44, 307) | 84 (7, 77) | |
| Age at enrollment (IQR) | 100.4 (100.1–101.4) | 106.1 (105.0–107.1) | 108.8 (107.1–110.0) | |
| Institutionalized (%) | 36.7 | 57.8 | 71.1 | <.001 |
| High school graduate (%) | 20.8 | 12.7 | 7.9 | .007 |
| Past or current smoking (%) | 18.8 | 12.3 | 14.8 | .146 |
| Past or current drinking (%) | 33.5 | 33.7 | 39.3 | .674 |
| Barthel Index (mean) | 40.4 ± 34.4 | 30.8 ± 32.0 | 32.1 ± 32.6 | .001* |
| Barthel Index category (range) (%) | | | | |
| Independent (80–100) | 22.2 | 12.0 | 14.3 | |
| Minimal assistance (60–79) | 11.1 | 11.7 | 10.7 | |
| Partially dependent (40–59) | 12.1 | 11.7 | 10.7 | .093 |
| Very dependent (20–39) | 16.4 | 14.5 | 15.4 | |
| Totally dependent (0–19) | 38.2 | 50.1 | 48.8 | |
| MMSE (mean) | 11.4 ± 8.7 | 9.0 ± 8.3 | 7.4 ± 8.0 | .003* |
| MMSE, category (%) | | | | |
| ≥21 | 17.4 | 9.1 | 8.3 | |
| 11–20 | 27.1 | 24.2 | 16.7 | .001 |
| 0–10 | 44.4 | 44.7 | 56.0 | |
| Not scored | 11.1 | 21.9 | 19.0 | |
| Poor eyesight (%) | 64.1 | 70.0 | 70.7 | .307 |
| Hearing impairment (%) | 74.9 | 85.8 | 86.7 | .003 |
| Past medical history (%) | | | | |
| Stroke | 18.1 | 20.2 | 14.3 | .431 |
| Coronary heart disease | 16.2 | 14.3 | 13.1 | .586 |
| Hypertension | 33.3 | 37.7 | 34.5 | .559 |
| Diabetes mellitus | 8.2 | 6.3 | 3.5 | .333 |
| Hyperlipidemia | 11.1 | 12.4 | 17.9 | .193 |
| Respiratory disease | 19.4 | 26.4 | 25.6 | .277 |
| Fragility fracture | 42.6 | 54.9 | 57.1 | .011 |
| Cataract | 43.1 | 50.3 | 52.3 | .193 |
| Cancer other than skin | 10.8 | 11.7 | 12.0 | .914 |
| Number of diseases (%) | | | | |
| 0 | 17.4 | 10.5 | 13.1 | |
| 1 | 35.7 | 29.3 | 27.3 | |
| Multimorbidity (2 or more) | 46.8 | 60.1 | 59.5 | .058 |
| Laboratory data, mean | | | | |
| WBC (/μL) | 5400 ± 1500 | 5400 ± 1600 | 5800 ± 2300 | .135 |
| RBC ($\times 10^6$/μL) | 3.58 ± 0.52 | 3.56 ± 0.55 | 3.80 ± 0.50 | .001 |
| Hemoglobin (g/dL) | 11.3 ± 1.7 | 11.1 ± 1.6 | 11.6 ± 1.6 | .029 |
| Platelets ($\times 10^4$/μL) | 18.8 ± 6.1 | 19.2 ± 6.9 | 19.5 ± 6.3 | .660 |
| Total cholesterol (mg/dL) | 169 ± 35 | 166 ± 36 | 168 ± 34 | .766 |
| HDL cholesterol (mg/dL) | 52 ± 12 | 47 ± 14 | 48 ± 12 | <.001 |
| Albumin (g/dL) | 3.6 ± 0.4 | 3.4 ± 0.5 | 3.4 ± 0.4 | <.001 |
| Hemoglobin A1c (%) | 5.7 ± 0.7 | 5.5 ± 0.6 | 5.5 ± 0.5 | <.001 |
| CRP (mg/dL) | 0.73 ± 1.76 | 0.79 ± 1.51 | 0.94 ± 2.10 | .120† |
| Creatinine (mg/dL) | 0.90 ± 0.49 | 0.86 ± 0.44 | 0.80 ± 0.32 | .192 |

*Notes* : CRP = C-reactive protein; HDL = high-density lipoprotein; IQR = interquartile range; MMSE = Mini-Mental State Examination; RBC = red blood cells; WBC = white blood cells. *p* Values were calculated for categorical covariates using chi-square test, whereas *p* values for continuous variables were calculated using one way analysis of variance (ANOVA) unless otherwise indicated.

*$p$ Values were calculated using nonparametric Kruskal–Wallis test.

†$p$ Values were calculated using ANOVA after logarithmic transformation.

age below 110 years, ADL levels were a significant predictor of all-cause mortality; the most dependent fraction of individuals declined first, and those maintaining better physical function lived longer (Figure 2A and B). However, functional status failed to depict mortality trajectories beyond the age of 110 years (Figure 2C). Dichotomization of individuals aged 110 years or older by the median Barthel Index confirmed that the survival advantage for better physical function was cancelled in this population (Figure 2D). When we split the participants into narrower age ranges (100–101, 102–104, 105–106, 107–109, and 110 or older), the association between functional status and mortality remained robust except in those aged 107 or older (Supplementary Figure 2).

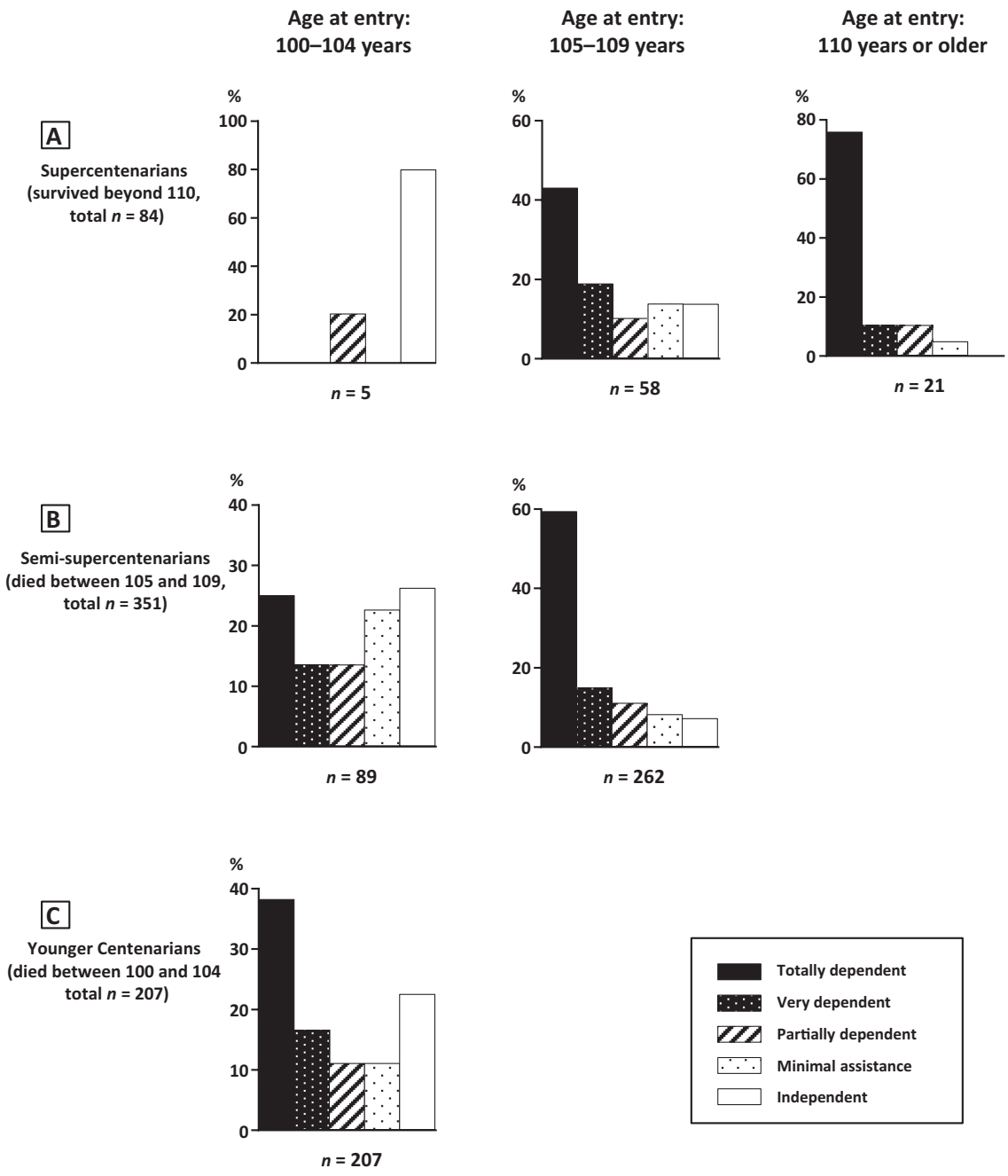


Figure 1. Cross-sectional comparison of disability pattern at entry among three centenarian age groups. Disability patterns at the age of examination (100–104, 105–109, and 110 years or older) were compared cross-sectionally among supercentenarians (**A**), semi-supercentenarians (**B**), and younger centenarians (**C**). Physical functional categories are defined by the Barthel Index, as described in Table 1.

Next, we assessed the predictive power of albumin levels, the most well-documented predictor of health outcomes in older adults, on mortality beyond the age of 100 years (Figure 3). Tertiles of albumin levels were significantly associated with all-cause mortality below the age of 110 years (Figure 3A and B); however, albumin levels failed to explain mortality beyond that age (Figure 3C and D). We also examined age-specific survival probability in relation to cognitive function, number of comorbidities, and levels of C-reactive protein, hemoglobin A1c, and hemoglobin; however, none of those parameters explained mortality beyond the age of 110 years (data not shown).

## Discussion

According to direct clinical examinations and complete mortality follow-ups of 642 centenarians, including 84 supercentenarians and 351 semi-supercentenarians, we herein provide two realistic pictures of what happens to an

Table 2. Multivariate Logistic Regression Analysis of Factors Associated With Physical Independence in Each Centenarians Age Group

| | Younger Centenarians | | Semi-supercentenarians | | Supercentenarians | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* |
| Age | 0.75 (0.43–1.30) | .304 | 0.93 (0.76–1.14) | .482 | 0.64 (0.36–1.01) | .055 |
| Gender (male) | 3.49 (1.11–11.02) | .032 | 5.55 (1.73–17.8) | .004 | 9.89 (0.74–131.7) | .083 |
| MMSE (per 1 *SD*) | 3.37 (1.78–6.38) | <.001 | 3.01 (1.54–5.89) | .001 | 3.70 (0.89–15.44) | .073 |
| Visual impairment | 0.26 (0.09–0.71) | .008 | 0.59 (0.20–1.57) | .287 | 0.27 (0.03–2.51) | .249 |
| Multimorbidity | 1.07 (0.66–1.73) | .781 | 0.59 (0.35–1.01) | .052 | 0.70 (0.22–2.25) | .546 |
| Albumin (per 1 *SD*) | 2.88 (1.39–5.94) | .004 | 4.23 (1.77–10.07) | .001 | 0.97 (0.18–5.33) | .972 |
| Log CRP (per 1 *SD*) | 0.80 (0.43–1.50) | .489 | 0.76 (0.41–1.41) | .383 | 0.31 (0.06–1.57) | .306 |

*Notes*: CI = confidence interval; MMSE = Mini-Mental State Examination; OR = odds ratio. Univariate analysis was used to select independent variables.

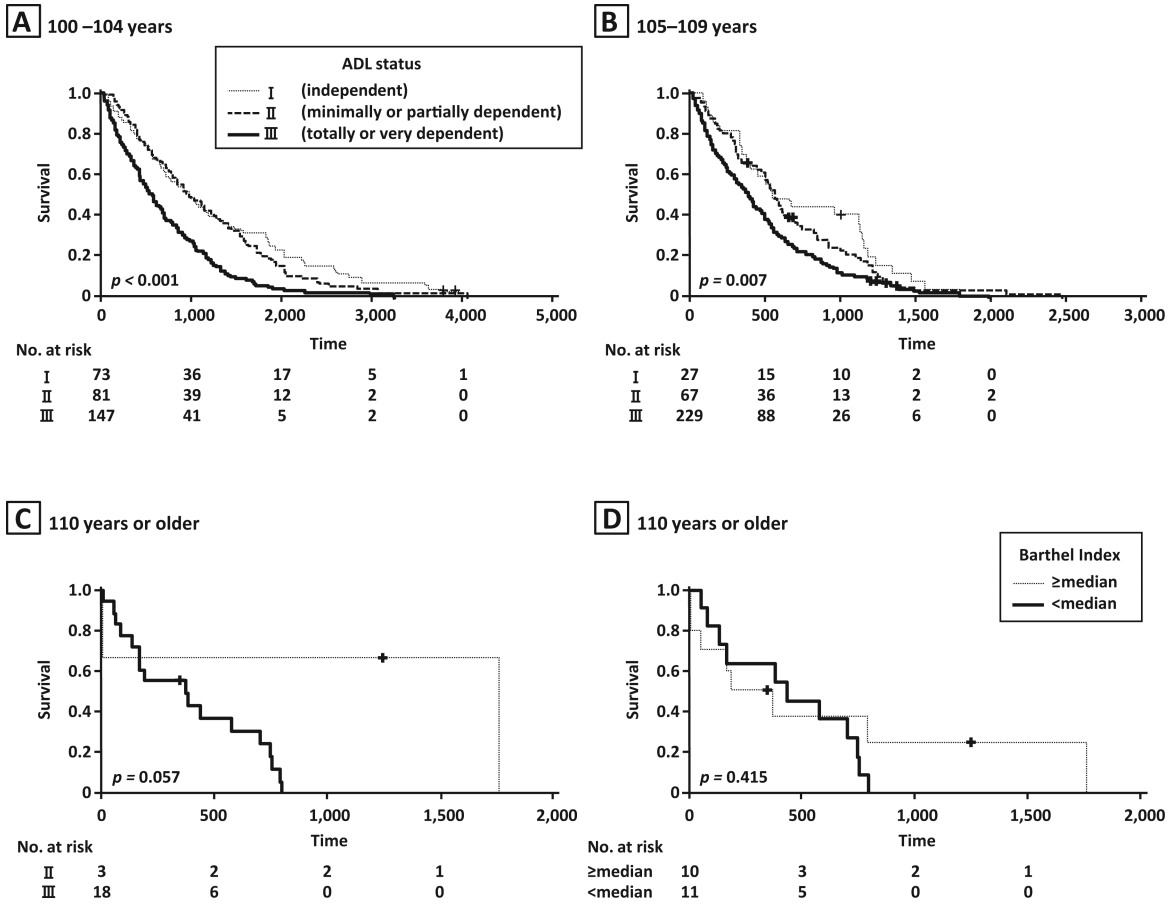


Figure 2. Age-specific Kaplan–Meier survival estimates according to physical functional status. Physical functional status was defined by Barthel Index categories, as follows: I, independent; II, minimally or partially dependent; and III, totally or very dependent (**A**–**C**). Status was dichotomized by the median Barthel Index (**D**). The *p* value was calculated from log-rank statistics. The '+' symbols indicate censored data.

individual's health and function at the tail end of the human survival curve. First, supercentenarians are virtually characterized by marked postponement of the age-related debilitating process and maintenance of physical independence for an extraordinarily long period. Second, as observed in elderly populations, functional capability correlates significantly with mortality even beyond 100 years of age; the most dependent fraction of individuals die first, and those with better fitness remain alive. However, a unique finding is that mortality beyond the age of 110 years is predicted neither by this golden rule nor other well-known predictors of death (eg, serum albumin, cognitive impairment, or multimorbidity), offering alternative trajectories of mortality at the highest ages.

Previous studies of physical function in relation to extended longevity above the age of 100 years are very limited. A recent report of the New England Centenarian Study demonstrated a clear relationship between delayed onset of

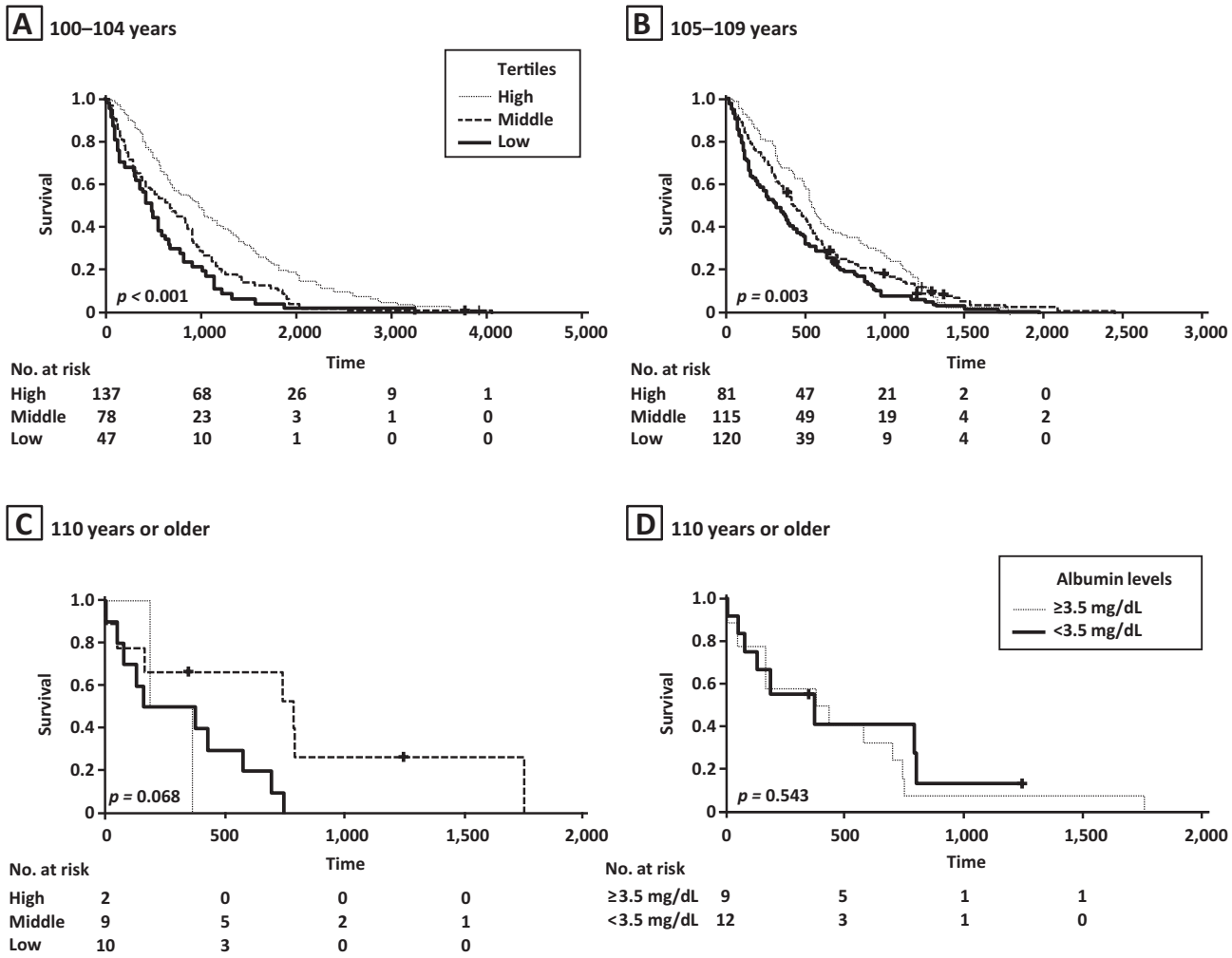


Figure 3. Age-specific Kaplan–Meier survival estimates according to albumin level. Participants in each age strata were classified into groups according to tertiles of albumin levels (**A**–**C**). Albumin levels were dichotomized by the median (**D**). The '+' symbols indicate censored data.

physical disability and extended life span, based on a longitudinal analysis of the Barthel Index obtained from 794 centenarians (100–104 years), 394 semi-supercentenarians, and 102 supercentenarians (17). Our results are consistent with their findings, demonstrating that maintaining functional capability and delayed onset of disability is the key feature of survival into extreme old age through a direct geriatric examination.

Although we obtained a complete dataset of functional status and mortality follow-up from substantial numbers of the oldest centenarians, our findings should be interpreted with caution in view of the following limitations. First, population-based sampling of centenarians, particularly of the oldest ones, has enormous practical challenges, so many centenarian studies, especially those that are cross-sectional in nature, are susceptible to healthy-volunteer bias such that highly functional centenarians are most likely to participate. The early phase of the New England Centenarian Study, in which 32 supercentenarians were recruited from media reports, internet, or family volunteering, found that 41% (13 of 32) of these supercentenarians required minimal or no assistance in performing basic ADL (10). In contrast, a population-based study of Okinawan centenarians reported that the majority of 12 age-validated supercentenarians were physically independent at the age of 100 years; however, they rapidly lost functionality between ages 105 and 109 years, and consequently none was independent in basic ADL at the age of 110 years (11). These findings were consistent with disability patterns of supercentenarians in our sample. In the current study, participants in the TCS and approximately one third of the JSS represented population-based sampling; however, the rest of the recruitment relied on responses from local government and nursing homes, with the result that our sample is not population-based as a whole. This may have led to selection bias toward the relatively well-functioning fraction of the population (eg, male participants). Nonetheless, our samples exhibited a comparable male-to-female ratio (1:6.97 and 1:11 for 105–109 and 110+ years, respectively) to those reported in the annual vital statistics in Japan in 2005 (ratios of 1:7.19 and 1:10 for

105–109 and 110+ years, respectively). Moreover, when we compared ADL status between 105+ participants recruited from a population-based scheme and those from convenience sampling, the former exhibited a higher percentage of physically independent individuals than their counterparts (12.6% vs 5.4%, respectively, $p = .019$), possibly because a significant part of the latter consisted of nursing home residents or hospitalized individuals (65% vs 74%, respectively, $p = .055$). Thus, part of our recruitment might bias against healthy voluntary effects.

Second, although our participants were examined and interviewed directly by geriatricians, the assessment lacked objective measures of physical performance, such as walking speed or chair standing. This may lead to overestimation of the functional status of the centenarians in this study. In the Georgia Centenarian Study, a population-based study with a 67.2% response rate, 73.0% and 86.0% of male and female centenarians were categorized as having severe disabilities when assessed using the Short Physical Performance Battery (18), although only 4% of participants in the study were aged 105 years or older (19). When recruiting a large number of the oldest centenarians, these methodological issues are difficult to overcome; accordingly, our findings must be taken in the context of these limitations. However, in comparisons of physical functional status between different centenarian age groups, this issue is less likely to result in bias, because all participants were assessed using the same protocol and by the same geriatricians.

In a longitudinal analysis of age-specific mortality, our study provides empirical evidence that disability or decline in physical function is the major driving force behind mortality in the oldest humans. The findings are consistent with a series of epidemiological data in the very old (20,21), including the Danish 1905 cohort survey, which reported that disability and poor physical and cognitive function, but not sociodemographic factors or self-reported diseases, were the determinants of mortality among 2,249 nonagenarians (21). Collectively, these results confirm that functional capacity correlates highly with survival into extreme old age. Our results, however, identified a unique phenomenon, that mortality trajectories at the highest ages are not shaped by functional status or any other clinical measure. Although our sample size of supercentenarians does not allow us to provide conclusions regarding determinants of exceptional human longevity, mortality beyond the age of 110 years is a long-standing subject in aging research and deserves discussion. First, the unique mortality pattern at the highest ages could be explained by the biodemographic concept of heterogeneity in frailty (22), which suggests that the frailer fraction within a cohort at any given time dies first, leaving a select subset to survive. Consequently, at the ultimate stage of longevity, relatively homogeneous residuals are composed of the most robust individuals, causing a distinct trajectory in mortality. In this context, supercentenarians are likely to harbor a set of longevity-assuring genes or physiological bases, which regulates somatic maintenance and repair functions to counteract age-related molecular damage (eg, oxidative stress, DNA instability, and telomere attrition) and postpone senescence (23,24). Preliminary studies provided some promising findings supporting this notion. Complete genome sequences of two supercentenarians (a man and a woman, both aged 114 years or older) were described, showing that rates of disease-associated variants were comparable to those in samples of much younger subjects; however, the older individuals' DNA sequences were enriched for coding variants near longevity-associated variants (25). Proteomics analyses of plasma proteins in 10 semi-supercentenarians revealed that a series of antioxidative proteins including paraoxonase 1 were associated with exceptional longevity (26). Although promising, empirical evidence supporting the hypothesis remains limited. Future research with an expanded sample size is needed to provide insight into the biological resilience of supercentenarians, which will contribute to a better understanding of the protective mechanisms and help to identify new preventative interventions.

Second, although supercentenarians maintain physical independence for an extraordinarily long period, at the age of 110 years or above, 76% of them were totally dependent (Barthel Index < 19), and none of them were physically independent; only one man was minimally assisted at best. The result suggested that frailty or diminution of organ reserve is a hallmark of living at the extreme limit of life span. Under these circumstances, the Barthel Index may not be sensitive in predicting mortality, and biomarkers that precisely reflect the degree of reduced organ reserve or robustness of intrinsic homeostasis may be good candidates for predicting these unique mortality trajectories. Alternatively, environmental variation (eg, quality of care or even climatic variation) may explain their mortality, because frail people are supposed to exhibit little resistance to environmental hazards (27). Further explanations of the oddities of supercentenarians and their mortality attributes will provide invaluable opportunities to test the central hypotheses of the aging process: whether stochasticity (28), genetic homogeneity (22), or environmental variation (29) can explain the trajectories of mortality in those approaching the limit of the human life span.

Our study had several limitations. First, we demonstrated that neither the number of diseases nor any single disease hampered physical independence or predicted mortality beyond the age of 100 years. However, our assessment of comorbidities was based on self self- and/or proxy-reported-reports, and the severity and duration of disease were not taken into account. Additionally, musculoskeletal conditions including arthritis, which are frequently underreported in the very old (30), were not included in our list of chronic diseases. This may have resulted in an underestimation of the impact of comorbidities on functional status. Second, follow-up with respect to functional status was lacking for most of our subjects, and this may limit our study's ability to capture the trajectories of disability beyond 100 years of age. However, in a

subset of semi-supercentenarians ($n = 35$) in whom ADL status was assessed on multiple occasions at an average interval of 3.6 years, longitudinal declines in functional status were similar to the corresponding disability pattern obtained from cross-sectional observations (Supplementary Figure 3).

## Conclusions

As has been demonstrated in previous studies, we confirmed that supercentenarians have a unique trait, characterized by postponement of functional decline and maintenance of physical independence until very late in life. Explication of the biological and genetic architecture underpinning this phenotype will further our understanding of the ultimate aging process, which has assumed a central position in terms of refining preventive intervention and health promotion at advanced ages. Finally, our results highlight the potential of our longitudinal database of centenarians and supercentenarians to provide invaluable opportunities to test the central hypotheses of human aging.

### Supplementary Material

Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/

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