Research Article

Prevalence, Incidence, and Risk Factors for Overall, Physical, and Cognitive Independence Among Those From Exceptionally Long-Lived Families: The Long Life Family Study

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Abstract

Background: The Long Life Family Study (LLFS) enrolled families exhibiting exceptional longevity. The goal of this article was to determine the prevalence and predictors of remaining independent after 7 years in the oldest generation.

Methods: We examined 7-year change in physical (free of activities of daily living difficulty), cognitive (Mini-Mental State Examination score ≥ 24), and overall independence (physically/cognitively independent) in adults aged 90.3 ± 6.3 from LLFS's oldest generation. Potential predictors ($n = 28$) of remaining independent included demographics, diseases, biomarkers, anthropometrics, and physical and cognitive performance tasks and were determined using generalized estimating equations ($\alpha: p < .05$). This was a discovery/exploratory analysis, so no multiple testing correction was employed and the results require independent replication.

Results: At baseline ($n = 1442$), 67.3%, 83.8%, and 79.7% were overall, physically, and cognitively independent, respectively. After 7 years, 66% died, 7.5% were lost to follow-up, and the prevalence of overall independence decreased to 59.1% in survivors (-8.2% , 95% confidence interval: -14.1% , 2.2%). Of those with baseline independence, 156/226 (69.0%) remained independent. Predictors of remaining physically independent included younger age, better Short Physical Performance Battery score and lung function, smaller waist circumference, and lower soluble receptor for advanced glycation end-product levels ($p < .05$). Predictors of remaining cognitively independent included no cancer history, better Digit Symbol Substitution Test performance, and higher body weight ($p < .05$).

Conclusions: The prevalence of independence decreased by only 8.2% after 7 years, demonstrating the close correspondence between disability and mortality. Further, despite a mean baseline age of 90 years, a large proportion of survivors remained independent, suggesting this exceptional subgroup may harbor protective mechanisms.

Keywords: Oldest old, Disability, Dementia, Compression of morbidity

The population of older adults aged 85 years and older is an exceptionally fast-growing segment of the population. For example, the U.S. Census Bureau estimated that the number of citizens aged 85 years and older will increase by over threefold—from 6 million in 2014 to over 20 million by 2060 (1). The rapid aging of the population has enormous public health implications, one of the most essential being physical and cognitive limitations and disability (2). For instance, the Health and Retirement Survey and Medicare Beneficiaries Survey showed that the prevalence of disability in activities of daily living (ADL) among community-dwellers increased from ~9% in those aged 75–84 years to over 20% in those aged 85 years and older (3). The prevalence of dementia also increases with advancing age, with rates increasing from 5% in those aged 70–79 years to 24% in those aged 80–89 years and to 37% in those aged 90 years or older (4). Thus, there is great interest in studying those aged 85 years and older, one primary reason being to understand mechanisms underlying exceptional longevity and health span (living long without limitations or disability) in order to prevent age-related physical and cognitive limitations.

Exceptional health span, or compression of morbidity, is associated with exceptional longevity—that is, disability and mortality are closely linked, even at advanced ages (5,6). Exceptional longevity and health span also cluster in families (7,8). The Long Life Family Study (LLFS) enrolled families selected for longevity (9,10), the oldest generation including many individuals aged 85 years and older, and implemented robust measures of physical and cognitive performance at both the baseline and 7–10 year follow-up visits. LLFS is distinct in that it is equipped to study the basis of exceptional health span in individuals from uniquely long-lived families. The purpose of this article was to determine what proportion of the oldest (proband) generation remained free of physical and/or cognitive limitations 7 years after baseline. Further, participants were also extensively phenotyped, presenting a unique opportunity to investigate potential predictors of preserved physical and cognitive function.

Methods

Study Population

Participants were from the LLFS: a multicenter study that, between 2006 and 2009, recruited and enrolled families from three U.S. field centers (Boston, New York, and Pittsburgh) and one in Denmark. Detailed recruitment/enrollment criteria have been described elsewhere (9). Briefly, family eligibility criteria were based on exceptional familial longevity and were determined using the Family Longevity Selection Score (score ≥ 7 required for enrollment) (11). Baseline phenotyping, and blood collection were performed at in-home visits and, from 2014 to 2017, participants were invited to participate in a follow-up, in-home visit (visit 2). The protocol was approved by the Human Research Protection Office of the coordinating center at Washington University, the Regional Scientific Ethical Committees for Southern Denmark, and the institutional review boards at the University of Pittsburgh, Boston Medical Center, and Columbia University. All participants provided informed consent.

The cohort is primarily white (>99%) and includes two generations: proband (median birth year: 1917) and offspring (median birth year: 1947). These analyses were limited to all those in the proband (oldest) generation with valid data on either physical or cognitive independence.

Physical and Cognitive Status

At both baseline and visit 2, participants were asked how much difficulty they had (none, a little, some, a lot, or unable to do) without help from another person/using special equipment on the ADL tasks: (a) getting in and out of a bed/chair, (b) bathing or showering, or (c) walking across a small room. Physical independence was defined as reporting some or less difficulty, whereas physical limitation was defined as reporting a lot of difficulty or being unable to do one of these tasks (12). Cognitive independence was defined as a Mini-Mental State Examination (MMSE) score greater than or equal to 24 (range 0–30), which has been shown to be a sensitive and specific cutoff for dementia (13,14); those with MMSE scores less than or equal to 23 were referred to as cognitively limited. Trained examiners were asked to rate the validity of MMSE tests. Reasons for invalid MMSE included poor vision, poor hearing, environmental distraction, unable to write, frustration, disinterest/boredom, physical limitation, fatigue, poor effort, or experimenter error. Overall limited was defined as being either cognitively or physically limited (5).

Other Measures

Participants self-reported sex, race, smoking, and education information. Disease history was based on self-reported physician diagnosis. Heart disease was defined as prior myocardial infarction and/or coronary artery bypass surgery, stroke included stroke or transient ischemic attack, and hypertension included presenting with a systolic blood pressure greater than or equal to 140 mm Hg, diastolic blood pressure greater than or equal to 90 mmHg, or history of hypertension confirmed by use of antihypertensive medication. Spirometry was used to determine forced expiratory volume (FEV₁). A standard medication inventory was also collected.

Physical performance was measured using the SPPB (score: 0–12), which includes 3 tests: gait-speed, balance, and 5 repeated chair-rises, each scored 0–4, with 4 being best (15). Gait-speed and time to chair-rises were also treated as continuous variables. Grip strength was measured using a JAMAR hand-held dynamometer (Sammons Preston Rolyan, Bolingbrook, IL). Digit symbol substitution test (DSST) was administered and the number of correct substitutions in 90 seconds was used.

Participants were asked to fast greater than or equal to 8 hours prior to blood draw. Glucose, total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides, creatinine, cystatin C, dehydroepiandrosterone, adiponectin, fasting insulin, fasting glucose, and soluble receptor for advanced glycation end-product (sRAGE) were measured using validated assays by the LLFS central laboratory (University of Minnesota) (16).

Deaths occurring prior to visit 2 were validated via the National Death Index and adjudicated using information from death certificates and/or medical records.

Statistical Methods

Frequency (%) was used to describe the prevalence of independence at baseline and visit 2 in all participants and survivors only, as well as the incidence of remaining independent among those independent at baseline. Baseline age- and sex-adjusted means (standard deviation) and frequencies (%) were compared between those with and without prevalent independence for demographics, disease prevalence, medications, subclinical markers of disease, physical performance, and neuropsychological test performance using generalized estimating equations incorporating an exchangeable

correlation structure to account for relatedness of participants (Supplementary Table 1). To determine potential covariates and predictors of remaining independent, baseline mean (standard deviation) or frequency (%) were compared using *t* and chi-squared tests between those who were independent at baseline and remained independent versus those who developed incident limitations. All baseline measurements that differed at the $p < .15$ level were included as potential predictors in an exploratory/discovery analysis. Recognizing that some potential predictors may have been missed and to improve the robustness of the findings, additional potential predictors were identified using separate forward, backward, and stepwise selection each using $p < .15$, and least absolute shrinkage and selection operator regression. Using the combined set of potential predictors, all subsets were run in multivariable models and ranked by the quasi-likelihood (QIC) criterion, a version of AIC for GEE (17). Age, sex, and field center were forced in all models. The top five QIC models were ranked by number of predictors meeting $p < .05$ among those with all predictors meeting $p < .10$, with the best model based on interpretability, fit, and predictability, selected. Final model results were presented using the odds of remaining independent using GEE with a logit link and exchangeable correlation matrix, and independent variables $p < .05$ were considered to be significant predictors. The same set of descriptive statistics, tests, and sensitivity analyses were also examined for overall, physical, and cognitive independence separately.

Numerous sensitivity analyses were performed. First, to provide a range wherein the “true” prevalence and incident rates of independence lie, we recalculated prevalence and incidence rates using all available (“valid” and “invalid”) MMSE scores. Second, the final model for remaining overall and cognitively independent using only valid MMSE tests was compared to the same model but including all MMSE tests (Supplementary Table 3). Next to account for those lost to follow-up, we examined baseline measures associated with missing visit 2 data (among those who were still alive at the time of visit 2) using multivariable logistic models with a backward stepwise approach ($\alpha p < .15$) to determine final models. The predicted probability of missing visit 2 was obtained from the final model for each participant. Using these probabilities, we adjusted for missing measurements by applying inverse probability weighting (IPW) to the final model of the odds of remaining independent, and independent variables $p < .05$ were considered to be significant predictors. Finally, to determine whether predictors of remaining independent were missed due to the competing risk of death, we determined the predictors of dying prior to visit 2 using the same pipeline for determining the odds of remaining independent as described earlier. We then built multinomial logistic models for the odds of death and incident limitation together (with remaining independent as the referent) consisting of both the final predictors of death and the final predictors of remaining intact.

Results

At baseline, 1442/1500 (96.1%) had either valid cognitive or physical independence data: 58 had low reliability of the MMSE or were missing one or more ADL question(s) and were excluded. At baseline and follow-up, 1373/1500 (91.5%) and 357/394 (90.6%) had available ADL data, respectively. At baseline, 1391/1500 (92.7%) had an MMSE examination; of those 1115 (74.3%) had a valid exam. At visit 2, 309/394 (78.4%) had valid MMSE examinations. A comparison of baseline characteristics between those with complete versus missing visit 2 MMSE data, despite being alive at the

time, versus those who died is presented in supplementary materials (Supplementary Table 2).

At baseline, compared with those who were limited, those with overall independence were younger, more likely to be men, more educated, had lower prevalence of stroke and diabetes history, and had better physical (SPPB) and cognitive (DSST) performance (all $ps < .05$, Supplementary Table 1a). Similarly, those who were physically independent versus limited at baseline were younger, more likely to be men, from a U.S. field center, had a lower prevalence of stroke and diabetes, and had better physical and cognitive performance (all $ps < .05$; Supplementary Table 1b). Finally, those who were cognitively independent versus cognitively limited at baseline were younger, more likely to be men, from a U.S. field center, more educated, and had better physical and cognitive performance (all $ps < .05$, Supplementary Table 1c).

The baseline and follow-up visit prevalence of overall, physical, and cognitive independence can be found in Table 1. Of note, only 7% were both physically and cognitively limited at baseline. The prevalence of independence decreased by very little after 7 years of follow-up (Table 1). Prevalence rates using all MMSE scores are also presented in Table 1. When analyses were limited to survivors, the decrease in the prevalence of independence was much greater (Table 2). Between baseline and follow-up, 958/1442 (66%) died and 98 (7.5%) were lost to follow-up (Table 2). Of those lost to follow-up, 88.3% had overall independence at baseline, compared with 56.3% of those who died (Table 3), indicating that those who were lost to follow-up were not the most disabled at baseline. Of those with valid baseline and follow-up data, as well as baseline overall, physical, and cognitive independence, 156/226 (69.0%), 252/325 (77.5%), and 201/235 (85.5%) remained independent, respectively (Table 4). Incident rates using all MMSE scores for remaining overall and cognitively independent were 180/270 (66.7%) and 245/302 (81.1%), respectively (Supplementary Table 3).

Potential predictors of maintaining independence included all items listed in Supplementary Table 1a–c plus blood biomarkers and lipid-lowering medication use. In final multivariable models, significant predictors of maintaining overall independence included younger age, higher FEV₁, higher SPPB score, and better DSST performance (Table 4, all $ps < .05$). Predictors of maintaining physical independence included younger age, higher SPPB score, higher FEV₁, and lower sRAGE levels. Waist circumference was included in the final model but was nonsignificant (Table 4, $p = .0546$). Field center was also significant in the physical independence model and indicating that the participants from the U.S. field centers were more likely to maintain their independence compared with Denmark. Predictors of maintaining cognitive independence included better DSST performance and higher body weight (quadratic term was $p = .65$ indicating no U-shaped relationship). High-density lipoprotein cholesterol, cancer history, and SPPB score were included in the final model but were nonsignificant (Table 4, $p < .10$). Final model estimates (odds ratios and 95% confidence intervals) for overall and cognitive independence using all valid MMSE scores were similar to estimates using only valid tests (Supplementary Table 3). Finally, to account for loss to follow-up, we determined significant predictors of visit 2 missingness (Supplementary Tables 4–6) and applied IPWs to final models (Supplementary Tables 7–9). Point estimates using IPWs were similar to original estimates. However, lower waist circumference became a significant predictor of maintaining physical independence ($p < .05$), and younger age, female sex, and no history of cancer became significant predictors of maintaining cognitive

Table 1. Prevalence of Independence at Baseline and Visit 2 in All Participants and Survivors

	Number (%) (<i>n</i> for reduced sample)		Difference (95% CI)
	Valid Physical or Valid*/All† Cognitive Data at Baseline (<i>n</i> = 1442/ <i>n</i> = 1496)	Valid Physical or Valid/All Cognitive Data at Visit 2 (<i>n</i> = 384/ <i>n</i> = 391)	
Overall independent (valid)*	771 (67.3%) (<i>n</i> = 1146)	195 (59.1%) (<i>n</i> = 330)‡	-8.2% (-14.1; -2.2)
Overall independent (all)†	866 (66.4%) (<i>n</i> = 1304)	213 (59.7%) (<i>n</i> = 357)	-6.7% (-12.4; -1.0)
Physically independent	1151 (83.8%) (<i>n</i> = 1373)	264 (74.0%) (<i>n</i> = 357)	-9.9% (-14.8; -4.9)
Cognitively independent (valid)	889 (79.7%) (<i>n</i> = 1115)	246 (79.6%) (<i>n</i> = 309)	-0.1% (-5.2; 5.0)
Cognitively Independent (all)	1036 (74.5%) (<i>n</i> = 1391)	273 (74.8%) (<i>n</i> = 365)	0.3% (-4.7; 5.3)

Note: MMSE = Mini-Mental State Examination.

*Valid refers to using only valid MMSE exams.

†All refers to using all MMSE exams.

‡These *n*'s do not match those in Table 2. due to some participants having valid data at visit 2 but not at visit 1.

Table 2. Prevalence of Independence at Visit 2 in Survivors.

Visit 2 Prevalence in Survivors	Valid Data and Survived to Visit 2	Difference in Prevalence of Independence from Baseline to Visit 2 in Survivors (95% CI)
Status at follow-up:		
Overall independent (valid)	159 (61.6%) (<i>n</i> = 258)‡	-26.0% (-33.1; -18.8)
Overall independent (all)	183 (59.6%) (<i>n</i> = 307)	-26.7% (-33.4; -20.0)
Physically independent	253 (74.9%) (<i>n</i> = 338)	-21.3% (-26.4; -16.2)
Cognitively independent (valid)	204 (81.6%) (<i>n</i> = 250)	-12.4% (-18.0; -6.8)
Cognitively independent (all)	249 (75.0%) (<i>n</i> = 332)	-16.0% (-21.6; -10.4)

Note: MMSE = Mini-Mental State Examination.

*Valid refers to using only valid MMSE exams.

†All refers to using all MMSE exams.

‡These *n*'s do not match those in Table 1. due to some participants having valid data at visit 2 but not at visit 1.

Table 3. Prevalence of Visit 2 Independence, Number of Deaths and Lost to Follow Up by Baseline Independence Status

Baseline Prevalence in Survivors	Valid Data at Baseline and Survived to Visit 2	Died Before Follow-up	Lost to Follow-up
Baseline status:			
Overall independent (valid)	226 (87.6%) (<i>n</i> = 258)‡	427 (56.3%) (<i>n</i> = 758)	68 (88.3%) (<i>n</i> = 77)
Overall independent (all)	265 (86.3%) (<i>n</i> = 307)	490 (55.9%) (<i>n</i> = 876)	75 (88.2%) (<i>n</i> = 85)
Physically independent	325 (96.2%) (<i>n</i> = 338)	700 (77.2%) (<i>n</i> = 907)	90 (97.8%) (<i>n</i> = 92)
Cognitively independent (valid)	235 (94.0%) (<i>n</i> = 250)	522 (72.9%) (<i>n</i> = 716)	74 (91.4%) (<i>n</i> = 81)
Cognitively independent (all)	302 (91.0%) (<i>n</i> = 332)	626 (66.7%) (<i>n</i> = 939)	85 (91.4%) (<i>n</i> = 92)

Note: MMSE = Mini-Mental State Examination.

*Valid refers to using only valid MMSE exams.

†All refers to using all MMSE exams.

‡These *n*'s do not match those in Table 1. due to some participants having valid data at visit 2 but not at visit 1.

independence ($p < .05$) when IPWs were applied—these predictors were between $p = .05$ – 0.15 in original models (Table 4).

To determine whether predictors of remaining independent were missed due to the competing risk of death, we determined predictors of dying before visit 2 and modeled these together with final predictors of maintaining independence using multinomial models with remaining independent as the referent (Supplementary Tables 8–10). Importantly, in models predicting death, no additional potential predictors beyond those for maintaining independence were identified at the $p < .15$ level. However, higher adiponectin levels and diastolic blood pressure levels (U-shaped relationship) were included in the final (best) mortality model, but were not included in any final (best) incident independence model (Table 4). In multinomial models, neither adiponectin nor

diastolic blood pressure were predictive of any type of limitation (Supplementary Tables 8–10).

Discussion

In this family-based study of older adults with an average baseline age of 90.3 years, we found that the prevalence of overall, physical, and cognitive independence decreased by very little after 7 years. Further, despite having a baseline age of 90 years, a remarkably large proportion (69%) of survivors with overall independence at baseline remained independent 7 years later. The stable prevalence of overall independence appeared to be primarily attributable to high mortality among those who were limited at baseline. This hypothesis was supported by the fact that the decrease in the

Table 4. Predictors of Remaining Independent

Parameter	Odds ratio (95% CI)*
Maintain overall independence (<i>n</i> = 156/226, 69.0%)	
Age, years	0.88 (0.82, 0.95)
Sex, male	0.78 (0.37–1.63)
Field center	Overall trend: <i>p</i> = .43
Forced expiratory volume ₁ , L [†]	1.53 (1.03, 2.27)
SPPB Score, 0–12	1.16 (1.02, 1.32)
Digit symbol substitution test, number of correct responses	1.05 (1.01, 1.09)
Maintain physical independence (<i>n</i> = 252/325, 77.5%)	
Age, years	0.84 (0.77–0.91)
Sex, male	1.13 (0.49–2.63)
Field center	Overall trend <i>p</i> = .04
SPPB, 0–12	1.32 (1.12, 1.56)
Forced expiratory volume ₁ , L [†]	1.56 (1.02–2.38)
Waist circumference, cm ²	0.97 (0.94–1.00), <i>p</i> = .0546
sRAGE [‡]	0.67 (0.47–0.94)
Maintain cognitive independence (<i>n</i> = 201/235, 85.5%)	
Age, years	0.94 (0.85–1.03)
Sex, male	0.47 (0.19–1.16)
Field center	Overall Trend: <i>p</i> = .14
Cancer, yes [‡]	0.48 (0.19, 1.24), <i>p</i> = .13
Digit symbol substitution test, # correct	1.10 (1.04–1.16)
Body weight, kg	1.05 (1.00, 1.10)
HDL cholesterol, mL/dL	1.03 (1.00, 1.06), <i>p</i> = .06
Total SPPB Score, 0–12	1.14 (0.98, 1.33), <i>p</i> = .09

Notes: CI = confidence interval; HDL = high-density lipoprotein; SPPB = Short Physical Performance Battery; sRAGE = soluble receptor for advanced glycation end-product. *p* values are shown for items *p* > .05. *p* values are given for variables not forced-in and non-significant using an α < 0.05. All ORs are expressed per unit increase except sRAGE and forced expiratory volume₁, which were expressed per standard deviation increase.

*Modeled using generalized estimating equations adjusting for relatedness of participants.

[†]Expressed per sex-specific standard deviation.

[‡]Cancer excluding nonmelanoma skin cancers.

prevalence of independence was much greater when analyses were limited to survivors.

In the oldest LLFS generation, the baseline prevalence of physical limitation was 16%. This is lower than what has been reported by nationally representative samples in similar age groups, using similar definitions. For example, National Health and Nutrition Examination Survey reported 25% of those aged 80 years and older had some or greater difficulty with an ADL task (3). In those aged 85 years and older, ADL disability prevalence rates were 21%, 19%, 17%, and 20% in the Health and Retirement Survey, Medicare Beneficiary Survey, National Health Interview Survey, and National Long Term Care Survey, respectively (3). The 90+ Study observed ADL difficulty prevalence rates of 71% in those aged 90–94 years, with rates increasing to 89% in those aged 95–99 years (18). In the older LLFS generation, the prevalence of those with MMSE scores less than or equal to 23 (which is indicative of dementia) ranged from 20%, using only valid MMSEs, to 25%, using all MMSEs. This is also generally lower than the general population, as estimates of dementia in population studies of those aged 85 years and older are between 18%–38%, with an average prevalence of 29% (19) and 37% in those aged 90 years and older (4). The low prevalence of physical and cognitive limitation, coupled with the

remarkably large number who remained independent in LLFS, warrants further investigation of these exceptional individuals.

Although LLFS participants were recruited for being from families with exceptional longevity, the 8% decrease in prevalence of independence after 7 years in the oldest generation was strikingly similar to a study by Christensen and colleagues of the entire Danish 1905 birth cohort, in which the prevalence of overall independence (also defined using ADL and MMSE) decreased by only 7% from 1998 (aged 93 years) to 2005 (aged 100 years). Thus, the small change in prevalence over time in the oldest LLFS generation may be generalizable to similarly aged populations. Further, just as in LLFS, the small decrease in the prevalence of independence in the 1905 Danish birth cohort was mostly attributable to high mortality among those who were limited at baseline, and also similar to LLFS, the decrease in the prevalence of independence was much greater (37%) when the sample was limited to survivors (note only seven in these analyses were Danes born in 1905). Thus, the individual risk of developing incident limitations is much higher than the change in prevalence over time at the population level. Other studies have also shown that exceptional longevity does not lead to excessive levels of disability at the population level, and that although the individual rates of disability and dementia remain high at advanced ages, they are lower for more recent birth cohorts (6,20–22). Finally, these studies and our results demonstrate that health span approximates life span, even at advanced ages and in those from exceptionally long-lived families.

Our study contributes novel data describing predictors of remaining overall and physically and cognitively independent among those aged 85 years and older. Few studies have large or healthy enough baseline samples of extensively phenotyped individuals with a mean baseline age of 85 years and older to investigate predictors of remaining physically or cognitively independent (5,6,21,23) separately. Interestingly, higher SPPB score was predictive of both overall and physical limitations. This is likely due to the fact that lower physical performance is the manifestation of many adverse health effects, and as a result, is a good indicator of overall health. Other predictors of remaining free of physical limitations included younger age, better lung function (FEV₁), smaller waist circumference (in IPW model), and lower sRAGE levels. Compromised lung function and abdominal obesity have well-established relationships with disability and worse physical performance (24,25). Advanced glycation end products (AGEs) and its receptor, sRAGE, are associated with increased inflammation, hyperglycemia, and reactive oxygen species production; thus, the AGEs/sRAGE axis is thought to play a role in the pathology of many diseases including, cardiovascular disease, inflammatory diseases, diabetes, and kidney disease, among others (26). Higher sRAGE levels are also known to be associated with advancing disease severity and complications including disability and mortality (27,28) and was a significant contributor to a biomarker signature of aging discovered in LLFS (29). sRAGE's use as a biomarker of physical function needs to be replicated and warrants further investigation. Participants from U.S. field centers were also more likely to maintain physical independence compared with Denmark; however, this is explained by the fact that the Danish site had considerably less lost to follow-up (5% vs. 35%, 32%, and 28%, [Supplementary Table 2](#), column 3) and those lost to follow-up would be more likely to have limitations at visit 2. Significant predictors of remaining cognitively independent included better DSST performance, no history of cancer (IPW

model), and higher body weight. The DSST measures processing speed and is a well-established marker of overall cognitive function (30). The association between higher body weight and cognition corroborates previous work showing that higher body mass index in late-life is protective against cognitive decline (31), which is reviewed in detail here (32). No history of cancer was associated with maintaining cognitive independence, which supports previous evidence showing chemotherapy/radiation treatment has neurotoxic effects (33). These results require independent replication.

This study has several strengths including the large number of oldest old enrolled at baseline, the relatively long follow-up time of 7 years, and the extensive characterization of the LLFS cohort. Further, we examined physical and cognitive limitations in aggregate, which provides greater insights, compared with studying each separately, into the burden of limitations. We addressed the “healthy cohort effect” that plagues prospective cohort studies of aging via IPW based on predictors of being alive but missing visit 2; however, as is the case with all prospective studies, the missingness due to death was likely not random. To address this, we determined the predictors of dying before visit 2 and built multinomial, competing risk models. This study also has several limitations. First, we do not have time to event data to pinpoint the exact time physical or cognitive limitations occurred. Second, the predictors of remaining independent analyses were designed to take advantage of the extensive phenotyping performed in LLFS and to be hypothesis generating; thus, we did not adjust for multiple comparisons. Had a Bonferroni correction been applied, $p < .0017$ would have been the significance threshold and the following predictors would no longer have been considered significant—overall independence: FEV₁, SPPB, and DSST scores; physical independence: field center, sRAGE, waist circumference, and FEV₁; and cognitive independence: age, sex, and body weight. However, this is a conservative threshold for sample sizes of 226, 325, and 235, respectively, but it is important that these results are independently replicated. Third, due to the discovery/exploratory approach of these analyses, we did not consider mediation or “over-adjustment”—eg, lower SPPB may be in the pathway between heart disease and physical dependence; thus, including SPPB would attenuate any observed effect of heart disease on dependence. Finally, due to the design of LLFS, we were unable to examine birth cohort effects.

In conclusion, due to high mortality among those physically and/or cognitively limited at baseline, the prevalence of independence remained relatively stable at the population level. Thus, the increase in limitations/disability associated with population aging, and the resulting societal burden, may not be as severe as originally theorized. Further, we observed lower than expected prevalence rates in the oldest LLFS generation, and despite having an average baseline age of 90 years, a remarkably large proportion (69%) remained independent after 7 years. This subgroup who survived with neither physical nor cognitive limitations have demonstrated they are exceptional beyond the initial, highly selective LLFS enrollment criteria, and this subgroup should be further investigated as they likely harbor mechanisms underlying preserved function at very advanced ages.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

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