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Research Article

Association of Family History of Exceptional Longevity With Decline in Physical Function in Aging

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Abstract

Background: Although many genetic and nongenetic factors interact to determine an individual's physical phenotype, there has been limited examination of the contribution of family history of exceptional parental longevity on decline in physical function in aging.

Methods: The LonGenity study recruited a relatively genetically homogenous cohort of Ashkenazi Jewish adults age 65 and older, who were defined as either offspring of parents with exceptional longevity ([OPEL]: having at least one parent who lived to age 95 or older) or offspring of parents with usual survival ([OPUS]: neither parent survived to age 95). Decline in performance on objective measures of strength (grip strength), balance (unipedal stance), and mobility (gait speed) as well as a composite physical function measure, the Short physical performance battery (SPPB), were compared between the two groups over a median follow-up of 3.2 years, accounting for age, sex, education, and comorbidities.

Results: Of the 984 LonGenity participants (mean age 76, 55% women), 448 were OPEL and 536 were OPUS. Compared to OPUS, OPEL had slower decline on measures of unipedal stance (–0.03 log-units/year, $p = .026$), repeated chair rise (0.13 s/year, $p = .020$) and SPPB (–0.11 points/year, $p = .002$). OPEL women had slower decline on chair rise and SPPB scores compared to OPUS women, although OPEL men had slower decline on unipedal stance compared to OPUS men.

Conclusion: Our findings provide evidence that variation in late-life decline in physical function is associated with familial longevity, and may vary for men and women.

Keywords: Successful aging—Genotypes—Phenotypes—Physical function

Maintenance of physical function is a key component of most definitions of successful aging (1,2), and is considered among the most highly rated attributes of successful aging in surveys of the general elderly population (1,3). Recent research has suggested that individuals with exceptional longevity, defined as living to age 95 or more, experience a delayed onset of major age-related diseases and disabilities (4). Individuals with exceptional longevity have been shown to be similar to the general population in lifestyle factors such as obesity, smoking, and physical inactivity, suggesting that they are protected from the harmful effects of these choices by longevity-enhancing genes (5). Studies of twins have shown a strong influence of genetic factors on physical function performance in older adults (6,7), providing further evidence of the genetic benefits of longevity traits. Similarly, offspring of centenarians have a lower prevalence of many age-related diseases, remain healthier longer and enjoy better physical function compared to age matched controls (8,9). Previous studies have shown that offspring of parents with exceptional longevity (OPEL) are more likely to carry longevity associated genotypes, and age more successfully than offspring of parents with usual survival (OPUS) (10,11).

The LonGenity study recruited a cohort of Ashkenazi Jewish (AJ) adults age 65 and older, who were either OPEL, defined as having at least one parent who lived to age 95 or older, or OPUS, which was defined as having neither parent survive to age 95. Exceptional longevity associated genotypes are over represented in OPEL (10,11). We have previously reported that OPEL have a healthier phenotype than OPUS, with lower prevalence of chronic illnesses such as hypertension, diabetes mellitus, heart attacks, and strokes (8). Recently, we also showed that OPEL performed better than OPUS on objective and subjective measures of physical function in a cross-sectional

analysis in the same cohort (12). Based on these findings, we hypothesized that OPEL may possess genetic "protection" that allows them to have a slower rate of decline in physical function compared to OPUS. Hence, we examined the association of familial history of exceptional longevity with decline in four key individual physical function measures (grip strength, gait speed, unipedal stance, and repeated chair rise) as well as one composite physical function measure, Short Physical Performance Battery (SPPB) in the LonGenity study cohort.

Methods

The LonGenity study was established in 2007. The primary aim of the study is to identify genotypes associated with longevity and their association with successful aging. Participants in the LonGenity study were recruited using public records such as voter registration lists and through contacts at synagogues, community organizations, and advertisements in Jewish newspapers (13). Potential participants were contacted by telephone to assess interest and eligibility. AJ adults age 65 and above were invited to our research center for participation and returned for follow-up assessment visits every 12–18 months. Exclusion criteria included diagnosis of dementia (previous physician diagnosed dementia, impairment on the Memory Impairment Screen (14) conducted during the initial telephone interview or diagnosed at consensus case conference after review of all available clinical, neuropsychological, and medical information as previously reported (14)) as well as severe visual or hearing impairments. The total eligible sample for this analysis included 984 participants who received a clinical evaluation at our research center between October 2004 and January 2016 and completed at least one of the five selected physical function assessments at their visit. Only two participants who attended a visit during the designated study period (n = 986) but did not receive any one of the five assessments were excluded.

A subset of AJ individuals who were cross-enrolled from the Einstein Aging Study (EAS) (n = 87), described previously (15), and met all inclusion criteria for the LonGenity study were included in this sample. EAS participants were recruited through voter registration lists of Bronx county residents, and physical function assessments were introduced into the in-person baseline and annual follow-up EAS visits in 2004 (15).

Physical Function

Physical function measures were implemented in the LonGenity cohort to provide a broad overview of overall physical function, and were selected based on previous studies from our group and others to examine physical decline, frailty, and disability in older adults (15–18). The five established objective physical function assessments selected for our analyses include measures of upper extremity strength (grip strength), lower extremity strength (repeated chair rise), balance (unipedal stance), and mobility (gait speed) as well as a composite physical function measure, the SPPB. Gait speed is considered a geriatric vital sign, and predicts multiple adverse outcomes in older adults (15). As previously described (15), research assistants measured gait speed using an 8.5 meter long computerized walkway (GAITRite; CIR Systems, PA). The GAITRite system is widely used in clinical and research settings, and excellent reliability has been reported in our and other centers (15,19). Participants were asked to walk on the walkway at their normal pace in a quiet well-lit room wearing comfortable footwear and without any attached monitors. Start and stop points were marked on the floor and included four feet from the walkway edge for initial acceleration and terminal deceleration. Based on footfalls recorded on the walkway, the software automatically computes quantitative gait parameters. For this study, we examined normal pace gait speed (cm/s). The unipedal stance (seconds) measures the ability to stand on one foot (maximum 30 seconds), and is a clinical test of balance that is a good predictor of falls (20). Time (seconds) to get up five times from a chair unassisted is a predictor of disability (16) and falls (21) and was evaluated as a measure of lower extremity strength (22). Research assistants measured grip strength (kg), an established clinical measure for assessing risk of functional decline and disability (23), as the maximum voluntary contraction in the dominant hand with a Jamar Dynamometer over three trials, and the highest value was recorded. Lastly, the SPPB which includes tests of balance, gait speed, and chair rise was used to assess overall lower extremity function, and has been shown to be associated with loss of independence, disability, and mortality (16,24). Tests of balance included tandem, semi-tandem, and side-by-side stands. Participants were given points for each test held for 10 seconds or more, and a categorical score of 0–4 was assigned. Gait speed was assessed as described above and a categorical score (0–4) was assigned to each participant corresponding to quartiles of gait speed with faster speed yielding more points. Chair rise was also assessed as described above and participants were assigned a categorical score (0–4) based on quartiles of completion time with fewer seconds corresponding to more points. A summary SPPB score was determined (0–12, higher better) based on the categorical scores of 0–4 from each of the three areas (24).

Covariates

Covariates were selected based on results from our cross-sectional analysis (12). Presence of depression, diabetes, heart failure, hypertension, myocardial infarction, angina, strokes, Parkinson's disease, chronic obstructive lung disease, and arthritis was used to calculate a global health summary (GHS) as previously described (15). Body mass index (BMI, kg/m^2) was calculated based on height and weight.

Statistical Analysis

Subject characteristics at baseline were summarized with descriptive statistics for the entire sample in Table 1. To determine the longitudinal association of familial history of longevity (OPEL vs. OPUS status) with risk of physical decline, linear mixed-effects models were applied. Model 1 is adjusted for age and gender and Model 2 is additionally adjusted for years of education and GHS. Analyses reported in the text are from Model 2. Data were inspected descriptively and graphically, and model assumptions were formally tested. The distribution of the unipedal stance variable was skewed to the right, and was log-transformed for all analyses. Results are reported as parameter estimates with 95% confidence intervals (CI). The linear mixed effects model can accommodate unbalanced data resulting from missing data points, unequal numbers of follow-up visits, and unequal intervals between visits (25). The approach that we used was based on the assumption that the data were missing at random, that is, the missing data process does not depend on the unobserved data given the observed data. A random intercept was included in the model to allow entry point to vary across individuals. "Time" represents average rate of change in performance on the physical function variable over follow-up. An interaction between individual longevity status and time was included to model the effect of familial longevity status (OPEL vs. OPUS) on rate of change in each physical function measure. All analyses were performed using SAS, version 9.3 (SAS Institute, Inc., Cary, NC).

Table 1. Baseline Characteristics of Overall Study Population and OPUS Versus OPEL

Description	Overall (n = 984)	OPEL (n = 448)	OPUS (n = 536)	p-value
Age, mean (1st–3rd quartile)	76.07 (70.61–80.53)	74.84 (70.17–78.32)	77.09 (70.88–81.68)	<.001
Sex (% female), n (%)	545 (55.4)	269 (60.0)	276 (51.8)	.008
Education (years), mean ± *SD*	17.28 ± 2.97	17.57 ± 2.90	17.03 ± 3.01	.005
Body Mass Index, mean ± *SD*	27.84 ± 6.53	28.37 ± 8.24	27.40 ± 4.59	.021
Blessed-Information-Memory Concentration test, mean ± *SD* (range 0–32)	1.13 ± 1.44	0.95 ± 1.29	1.27 ± 1.53	.001
Gait speed (cm/s), mean ± *SD*	108.93 ± 20.18	112.12 ± 18.81	106.30 ± 20.89	<.001
Repeated chair rise time (s), mean ± *SD*	10.63 ± 3.64	10.32 ± 3.44	11.30 ± 3.77	<.001
Unipedal stance time (s), mean ± *SD*	15.90 ± 12.07	17.12 ± 10.65	13.21 ± 10.55	<.001
SPPB[a] score, mean ± *SD*	8.58 ± 2.30	9.00 ± 2.21	8.21 ± 2.31	<.001
Grip strength (kg), mean ± *SD*	12.42 ± 11.28	12.02 ± 10.98	12.76 ± 11.52	.307
Global health summary, mean ± *SD*	1.30 ± 1.08	1.19 ± 1.07	1.39 ± 1.08	.003
Depression, n (%)	181 (18.4)	83 (18.8)	98 (18.5)	.934
Diabetes, n (%)	90 (9.1)	33 (7.4)	57 (10.7)	.095
Heart Failure, n (%)	11 (1.1)	3 (0.7)	8 (1.5)	.362
Hypertension, n (%)	433 (44.0)	164 (39.6)	269 (52.6)	<.001
Myocardial Infarction, n (%)	60 (6.1)	21 (4.7)	39 (7.3)	.108
Angina, n (%)	32 (3.3)	16 (3.7)	16 (3.1)	.587
Stroke, n (%)	38 (3.9)	7 (1.6)	31 (5.8)	.001
Parkinson's Disease, n (%)	14 (1.4)	5 (1.1)	9 (1.7)	.592
Chronic Obstructive Lung Disease, n (%)	34 (3.5)	13 (2.9)	21 (3.9)	.484
Arthritis, n (%)	377 (38.3)	181 (41.0)	196 (36.8)	.187

Notes: OPUS = offspring of parents with usual survival; OPEL = offspring of parents with exceptional longevity.
[a]Short Physical Performance Battery.

Results

Table 1 shows subject characteristics at baseline overall and by longevity status. Of the 984 participants included at baseline, 753 (77%) completed at least one follow-up assessment. Of the 231 participants who did not return for follow-up 133 (58%) were OPEL and 98 (42%) were OPUS. Among the 753 participants with at least one follow-up visit 315 (42%) were OPEL and 438 (58%) were OPUS. The mean inter-visit follow-up time was 1.3 ± 0.5 years. The median follow-up time overall was 3.2 years (range 0–10) with a mean number of visits per person of 3.4 and 3,137 person-years follow-up. The mean overall follow-up time for OPEL was 2.8 years and for OPUS was 3.5 years with an average number of visits per person of 3.0 for OPEL and 3.7 for OPUS.

Participants who did not return for a follow-up visit were slightly older at baseline (76.8 vs. 75.8, p = .051), and had significantly worse cognitive function measured by the Blessed Orientation-Memory-Concentration test (26) (1.6 vs. 1.0, p < .001), an assessment of general mental status, compared to those who did return for at least one follow-up visit. The groups did not differ in gender or education years. Baseline physical performance measures of gait speed, unipedal stance, SPPB, and grip strength were not significantly different between participants who did and did not return for at least one follow-up visit. Participants who did not return for at least one follow-up visit performed significantly better on the repeated chair rise assessment compared to those who did return for at least one follow-up visit (10.2 vs. 11.0, p = .024). OPEL who did not return for at least one follow-up visit were significantly younger (75.3 vs. 78.8, p < .001), the majority were female (66% vs. 51%, p = .020), and they performed significantly better physical function measures of gait speed, unipedal stance, SPPB, and chair rise than OPUS who did not return for at least one follow-up visit.

Of the 984 eligible participants 545 (55%) were female and the mean age at baseline was 76.1 ± 6.7. The 448 (46%) OPEL were younger than the 536 (55%) OPUS at baseline (74.8 vs. 77.1 years, p < .001), and included a higher proportion of women (60 vs. 52%, p = .008). Education years were statistically higher in OPEL, though the absolute difference was only a half year. At baseline, OPEL had a higher BMI than OPUS (28.4 vs. 27.4 kg/m^2, p = .021). OPEL reported lower medical illness burden than OPUS (GHS 1.19 vs. 1.39, p = .003). Among individual illnesses, OPUS had a higher prevalence of hypertension and strokes.

OPEL performed better on all physical function measures at baseline compared to OPUS except for grip strength. However, the group difference in grip strength was not statistically significant and is probably due to the higher percentage of women in the OPEL group.

Table 2 shows that after controlling for age, sex, education and GHS, OPUS had worse physical function performance at baseline compared to OPEL with slower gait speed (group difference –2.92 cm/s, p = .014), shorter unipedal stance time (group difference –0.14 log-units, p = .007), longer chair rise time (group difference 0.70 s, p = .002) and lower SPPB scores (group difference –0.38 points, p = .006). Average rate of decline in gait speed was significant for both OPEL (–1.82 cm/s/year) and OPUS (–2.10 cm/s/year, 95% CI 2.44 to –1.76, p < .001). Decline on unipedal stance was also significant for both OPEL (–0.03 log-units/year) and OPUS (–0.06 log-units/year 95% CI –0.07 to –0.04, p < .001). Rate of decline on SPPB scores was only significant for OPUS with a rate of –0.16 points per year (95% CI –0.20 to –0.11, p < .001). Mean repeated chair rise performance for OPEL changed –0.27 seconds per year, indicating improvement in performance over time. OPUS showed a similar trend, indicating a change of –0.14 seconds per year (95% CI –0.21 to –0.07, p < .001). Sensitivity analyses restricted to cases within 1.5 standard deviations of the mean (to exclude outliers) did not change the results. Further analyses stratified by age indicated that the improvement in chair rise was only significant for OPELs in the youngest age groups (<75 years)

Table 2. Linear Mixed Effects Model of Longevity Status With Physical Function Performance

	Model 1 Adjusted estimate (95% CI), *p*-value[a]	Model 2 Adjusted estimate (95% CI), *p*-value[b]
Gait speed		
Longevity status	−3.44 (−5.82 to −1.06), .005	−2.92 (−5.25 to −0.59), .014
Time	−1.83 (−2.26 to −1.41), <.001	−1.82 (−2.24 to −1.40), <.001
Longevity status × Time	−0.26 (−0.80 to 0.29), .351	−0.28 (−0.82 to 0.26), .307
Unipedal stance		
Longevity status	−0.17 (−0.27 to −0.06), .002	−0.14 (−0.24 to −0.04), .007
Time	−0.03 (−0.05 to −0.01), .004	−0.03 (−0.05 to −0.01), .004
Longevity status × Time	−0.03 (−0.05 to −0.00), .035	−0.03 (−0.05 to −0.00), .026
Repeated chair rise		
Longevity status	0.81 (0.38 to 1.25), <.001	0.70 (0.27 to 1.13), .002
Time	−0.27 (−0.36 to −0.19), <.001	−0.27 (−0.36 to −0.19), <.001
Longevity status × Time	0.12 (0.01 to 0.23), .029	0.13 (0.02 to 0.24), .020
SPPB[c]		
Longevity status	−0.44 (−0.73 to −0.17), .002	−0.38 (−0.65 to −0.11), .006
Time	−0.05 (−0.10 to 0.01), .107	−0.05 (−0.10 to 0.01), .109
Longevity status × Time	−0.11 (−0.18 to −0.04), .003	−0.11 (−0.18 to −0.04), .002
Grip strength		
Longevity status	0.58 (−0.62 to 1.79), .342	0.52 (−0.68 to 1.72), .392
Time	−0.27 (−0.56 to 0.02), .070	−0.26 (−0.55 to 0.03), .076
Longevity status × Time	−0.23 (−0.60 to 0.13), .208	−0.17 (−0.54 to 0.19), .354

Note: CI = confidence interval.

[a]Adjusted for age and sex. [b]Adjusted for age, sex, education and global health summary. [c]Short Physical Performance Battery, which is a composite score that includes measures of repeated chair rise and gait speed.

at baseline. A detailed analysis of these findings indicated that the younger age group also reported fewer illnesses (lower GHS) and performed better on tests of cognitive abilities such as the Blessed Orientation-Memory-Concentration test (26).

Familial longevity status (two-way interaction term in Table 2) was a predictor of longitudinal change in unipedal stance (−0.03 log-units/year, p = .026), repeated chair rise (0.13 s/year, p = .020), and SPPB scores (−0.11 points/year, p = .002) over follow-up, showing that compared to OPUS, OPEL had slower decline in performance on these three measures after adjusting for age, sex, education, and comorbidities. Familial longevity status did not predict change in gait speed and grip strength. After additionally adjusting for BMI, familial longevity status remained a predictor of longitudinal change in unipedal stance (−0.03 log-units/year, p = .031), repeated chair rise (0.13 s/year, p = .019), and SPPB scores (−0.11 points/year, p = .003).

Table 3 shows the effect of gender on the associations between familial longevity status and decline on the physical function measures. OPEL women had slower decline on the repeated chair rise (0.23 s/year, p = .001) and SPPB (−0.17 points/year, p = .001) compared to OPUS women. Gait speed reached borderline significance indicating that OPEL women had slower decline in gait speed (−0.71 cm/s/year, p = .054) compared to OPUS women. Conversely, OPEL men had a slower rate of decline on unipedal stance (−0.04 log-units/year, p = .022) compared to OPUS men. Although, different measures of physical function were significant for men and women, there was no significant difference between men and women in decline on any of the physical function measures. We examined further the influence mothers' longevity compared with fathers' longevity on decline in physical function in OPELs whose parental age at death was available. Those with both parents who survived to 95 or more (n = 29) were excluded from this analysis. Results showed that OPELs' mothers who lived to be at least 95 had significantly slower decline on chair rise performance (0.25 s/year 95% CI 0.04–0.46, p = .020) compared to OPELs with fathers who lived to be 95 or more. There was no significant difference in decline on any of the other measures of physical function.

Sensitivity analyses adjusting for baseline performance on the physical function measures did not affect the association of familial longevity with repeated chair rise (0.18 s/year, p = .019) and SPPB (−0.15 points/year, p = .002); however, familial longevity was no longer a significant predictor of unipedal stance. A similar effect was found after stratifying by gender. After adjusting for baseline performance on the selected measure, OPEL women showed a significantly slower decline on SPPB (−0.22 points/year, p = .001) and chair rise (0.26 s/year, p = .010) compared to OPUS women. However, familial longevity status was no longer a significant predictor of unipedal stance in men after adjusting for baseline performance.

Discussion

Results of our study show that OPEL had slower physical function decline compared to those with usual survival (OPUS). Specifically, OPEL had reduced decline in unipedal stance, repeated chair rise, and SPPB scores over the study follow-up. The strongest association was seen on the SPPB, which is a more comprehensive measure of physical function than the individual measures, and may be more sensitive to detecting early physical function decline in high functioning adults (16). These results are consistent with our hypothesis that persons with long-lived parents may enjoy not only a longer life but one with slower declines in physical function.

Our findings are supported by other studies indicating that parental life span accounted for a substantial portion of variation in physical function in their adult offspring (27). Support for the influence of familial longevity in maintaining physical function in aging is seen in studies that report that long-lived individuals experience a delayed onset of many age-related diseases, and are relatively protected against developing disability (4,9). A study which examined several different physical performance measures showed that a

Table 3. The Effect of Gender on Association of Longevity Status and Physical Function Decline

	Females (n = 545) Adjusted estimate (95% CI), p-value[a]	Males (n = 439) Adjusted estimate (95% CI), p-value[a]
Gait speed		
Longevity status	−1.59 (−4.70 to 1.53), .318	−4.34 (−7.91 to −0.78), .017
Time	−1.46 (−2.01 to −0.91), <.001	−2.32 (−2.98 to −1.66), <.001
Longevity status × Time	−0.71 (−1.42 to 0.01), .054	0.28 (−0.55 to 1.10), .507
Unipedal stance		
Longevity status	−0.13 (−0.26 to 0.01), .069	−0.16 (−0.31 to 0.00), .055
Time	−0.04 (−0.06 to −0.01), .002	−0.01 (−0.04 to 0.02), .402
Longevity status × Time	−0.02 (−0.05 to 0.02), .320	−0.04 (−0.08 to −0.01), .022
Repeated chair rise		
Longevity status	0.26 (−0.31 to 0.83), .366	1.21 (0.56 to 1.87), <.001
Time	−0.35 (−0.45 to −0.24), <.001	−0.17 (−0.31 to −0.02), .022
Longevity status × Time	0.23 (0.09 to 0.37), .002	0.00 (−0.17 to 0.18), .966
SPPB[b]		
Longevity status	−0.21 (−0.58 to 0.16), .273	−0.57 (−0.97 to −0.17), .006
Time	0.01 (−0.07 to 0.08), .898	−0.12 (−0.20 to −0.03), .009
Longevity status × Time	−0.17 (−0.27 to −0.07), .001	−0.03 (−0.14 to 0.07), .539
Grip strength		
Longevity status	−0.20 (−1.61 to 1.22), .782	1.13 (−0.90 to 3.16), .273
Time	−0.44 (−0.79 to −0.09), .015	−0.02 (−0.49 to 0.45), .935
Longevity status × Time	−0.08 (−0.54 to 0.38), .723	−0.34 (−0.92 to 0.24), .250

Note: CI = confidence interval.

[a]Adjusted for age, education and global health summary. [b]Short Physical Performance Battery.

significant portion of the variance in decline on these measures over a 7-year period was attributable to heredity (28). Several previous studies that examine longevity and physical function decline focused on muscle strength as a proxy for overall physical capacity and found variable results (17,27). Our results showing that the SPPB, which includes measures of mobility, strength and balance, had the strongest association with familial longevity indicate the complexity of physical function decline in aging.

Physical function decline in older adults is attributable to both genetic and nongenetic factors such as environment and disease, and may be linked with specific genotypes via the effect of genes on muscles, nerves, and vasculature. Previous studies have linked specific gene polymorphisms to physical function, frailty, and disability in aging (29–32). Gene polymorphisms, such as catechol-O-methyltransferase and apolipoprotein E (APOE), are linked to gait speed and disability older adults (32,33). Elevated inflammation levels of Interleukin-6 and C-reactive protein are also associated with increased risk of gait speed decline, frailty, and disability in aging (34–36), suggesting that genetic and biological factors may interact to determine the rate of physical decline on measures gait, balance, and strength of older adults.

Our results indicated an interesting gender effect; familial longevity status was associated with decline on different measures of physical function for men and women, although the difference between men and women was not significant. OPEL women showed slower decline compared to OPUS women in lower extremity strength and function measured by repeated chair rise and SPPB. On the other hand, OPEL men showed slower decline in balance measured by unipedal stance compared to OPUS men. Previous results have been inconsistent with some studies indicating that despite worse initial physical function performance at baseline women show a slower rate of decline over follow-up (37,38), although others show a faster rate of decline in physical function in older women compared to men (39,40). Based on our findings, the slower rate of physical decline among women may be explained by a subgroup of women with longevity genotypes or other favorable genotypes that influence maintenance of physical function in aging. Several studies have shown significant gender differences in genotypes linked to physical function (32,41,42). The ACTN3 genotype was reported to have a greater effect on muscle strength in women compared to men (41). Another study of community dwelling older adults showed that women but not men with the APOE E4 allele had an increased risk of functional decline and disability (42). These findings support our results that men and women may experience decline in different areas of physical function.

There are several potential limitations of our study. Results from this study come from a convenience sample of AJ older adults, and need to be validated in other populations, although recent evidence indicates that AJ individuals demonstrate similar patterns of disease onset as more diverse groups (4). The LonGenity cohort includes a non-disabled, ambulatory, community-dwelling sample with excellent overall health and a relatively short follow-up period, which might have minimized the difference in rates of declines between our study groups. Hence, the differences seen between the OPEL and OPUS might be indicating early and mild signs of physical function decline, and longer follow-up is needed. Additionally, the unequal follow-up time and baseline difference in physical function between OPEL and OPUS must be noted as a limitation of our analysis. Results from this study should be interpreted cautiously and validated in future studies of cohorts with more similar baseline function and follow-up times. However, although there was a significant age and physical function difference between OPEL and OPUS at baseline; all of our analyses were adjusted for age and additionally accounting for baseline performance on each of the measures did not have a major impact on the findings. Inflammatory markers have been associated with physical function changes (34,35), may mediate physical decline but were not available. The role of these and other biological factors as well as previously identified longevity associated genotypes (10,11) on physical function decline in OPUS and OPEL, and on their differential effect for men and women, should be further studied.

Our findings suggest that variation in physical function decline is attributable at least in part to genetic factors (as indicated by familial longevity status), and that the influence of these genetic longevity traits may vary by gender and become increasingly important with aging. The

present study can guide future research in exploring the mediating effect of health behaviors and biological factors, as well as the role of specific genotypes, on physical function decline, frailty, and disability in aging.

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