THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2017, Vol. 00, No. 00, 1–6
doi:10.1093/gerona/glx034
Advance Access publication March 10, 2017

OXFORD

Research Article

Age-Related Biomarkers in LLFS Families With Exceptional Cognitive Abilities

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Received September 13, 2016; Editorial Decision Date February 20, 2017

Decision Editor: Stephen Kritchevsky, PhD

Abstract

Background: We previously demonstrated familial aggregation of memory performance within the Long Life Family Study (LLFS), suggesting that exceptional cognition (EC) may contribute to their exceptional longevity. Here, we investigated whether LLFS families with EC may also exhibit more favorable profiles of other age-related biomarkers.

Methods: Nondemented offspring of the LLFS probands scoring 1.5 *SD* above the mean in a cognitive phenotype were classified as participants with EC. Families were categorized into EC (n = 28) and non-EC families (n = 433) based on having at least two EC offspring. Adjusted general estimating equations were used to investigate whether EC families had a better longevity and age-related biomarker profiles than non-EC families.

Results: EC families exhibited higher scores on familial longevity than non-EC families (average Family Longevity Selection Score of 12 ± 7 vs 9 ± 8, $p = 2.5 \times 10^{-14}$). EC families showed a better a metabolic profile ($\beta = -0.63$, $SE = 0.23$, $p = .006$) than non-EC families. The healthier metabolic profile is related to obesity in an age-dependent fashion. The prevalence of obesity in EC families is significantly lower compared with non-EC families (38% vs 51%, $p = .015$) among family members less than 80 years of age; however, among EC family members 80 years of age and older, the prevalence of obesity is higher (40% vs 38%, $p = .011$). EC families also showed better physical/pulmonary function than non-EC families ($\beta = 0.51$, $SE = 0.25$, $p = .042$).

Conclusions: Long-live families with EC are characterized by a healthier metabolic profile which is related to the prevalence of obesity in the older family members. Our results suggest that familial exceptional longevity may be achieved through heterogeneous yet correlated pathways.

Keywords: Exceptional cognition—Age-related biomarkers—Exceptional longevity

As the proportion of elderly adults in the population grows, predictors of exceptional longevity (EL) become increasingly important. Understanding the mechanisms underlying EL will allow the development of approaches to promote healthy aging. Studies in diverse elderly populations have consistently reported that age-related cognitive impairment is associated with higher risk of mortality, even after adjustment for a variety of health conditions, lifestyle factors, and socio-demographic characteristics. This strong association between cognition and EL has also been reported for cognitive abilities in childhood (1), early adulthood, and middle-aged adults (2). Findings from elderly nondemented cohorts also reported significant association between the rate of decline in cognitive and functional skills and risk of mortality (3,4). In addition, impairment of cognitive abilities has been also related to the presence of concomitant diseases such as cardiovascular events (5), diabetes (6), lung disease (7), or age-related eye diseases (8).

Studies have also demonstrated a strong familial component to EL. We previously reported (9) that offspring of probands from the Long Life Family Study (LLFS) showed better cognitive performance on multiple cognitive tasks compared with individuals without a family history of longevity. Also in the LLFS cohort, we demonstrated that exceptional episodic memory performance strongly aggregates in the LLFS families (10) and that might be genetically modulated (11). To better characterize the successful longevity of the LLFS family cohort, we have previously developed five heritable age-related biomarker constructs strongly associated with mortality (12). These age-related biomarkers were constructed using factor analysis on data on 28 measures from LLFS participants that represented five age-related domains (cognition, cardiovascular, metabolic, physical activity, and pulmonary). When similar age-related biomarker constructs were derived using data from the Health, Aging and Body Composition cohort (Health ABC), the most dominant biomarkers for both cohorts, reflecting physical activity and pulmonary domains, were significantly associated with decreased mortality in both cohorts (12). In this study, we investigated the relation of exceptional cognition (EC families) to longevity and to specific age-related biomarker constructs in LLFS families. We hypothesize that EC families will show a more favorable profile of age-related biomarkers compared with non-EC families.

Methods

LLFS

The LLFS cohort consists of multigenerational families selected for exceptional longevity in the United States and Denmark. Long-lived individuals, their siblings, and their offspring were recruited for an examination that characterized key intermediate phenotypes of longevity, including major chronic diseases, risk factors, and physical and cognitive function. Dementia status was defined as cognitive impairment characteristic of Alzheimer's disease based on a diagnostic algorithm (13), which included demographic factors that have been associated with this disease (age, sex, and education) and the cognitive abilities that are known to be affected in this disease (Logical Memory II). Detailed characteristics of the LLFS cohort have been described elsewhere (9,14). The LLFS cohort consists of 4,472 participants from 574 families (1,292 members in the LLFS's proband generation and 3,180 members in the LLFS's offspring generation).

The Institutional Review Boards at all of the Field Centers and the Data Management and Coordinating Center (Washington University, St. Louis) in the United States reviewed and approved this project and the regional Institutional Review Board in Denmark reviewed and approved this project.

LLFS Age-Related Biomarkers

We used the age-related biomarker constructs previously described in the LLFS cohort (12). In that study, factor analytic methods were applied to LLFS' participant's phenotypic data for 28 traits from 5 health-related domains (cognitive, cardiovascular, metabolic, physical, and pulmonary). Eigenvalues and eigenvectors for the first five LLFS factors (LFs: LF1 to LF5) revealed five different age-related biomarker constructs (Supplementary Table 1): LF1 (~14% of the variation) was dominated by physical activity (grip strength and gait speed) and pulmonary function measures (forced expiratory volumes), LF2 (~11% of the variation) was loaded with metabolic measures (body mass index [BMI], waist circumference), LF3 (~9%) consisted of predominantly cognitive traits (immediate and delayed memory), LF4 (9%) reflected blood pressure related traits (pulse pressure, systolic/diastolic), and LF5 (~8%) was largely comprised of cardiovascular traits (total cholesterol, LDL cholesterol). Moreover, the LF1 representing physical activity was significantly associated with decreased mortality, and its association with mortality was validated using the Health, Aging and Body Composition Study (Health ABC).

Family Longevity Selection Score (FLoSS)

In order to rank LLFS families according to their longevity (based on sex and birth-year cohort survival probabilities of the LLFS's proband and their siblings), we developed the FLoSS (15). The FLoSS measures the average excess observed life span over that expected based upon lifetables, while adding a bonus term for still-living individuals. The initial study eligibility criteria require families with FLoSS score equal or greater than 7. To assess whether EC families may have exhibited a higher degree of familial longevity, we investigated whether FLoSS scores were significantly different between the two types of LLFS families (EC vs non-EC families).

Exceptional Cognitive Performance (EC)

To define exceptional cognitive performance, we have used the previously derived LLFS factor LF3 that, as described earlier, consisted of predominantly cognitive traits (immediate and delayed memory). To derive a threshold for EC, we used the entire offspring generation of the LLFS cohort (offspring of the LLFS probands and their spouses, n = 2,140), after excluding family members classified as demented based on a previously derived diagnostic algorithm (13). Among the nondemented LLFS family members in the offspring generation, the distribution of the LF3 factor had a mean value of 0.12 (SD = 2.49), ranging from a minimum score of –9.38 to a maximum score of 9.34. Using as a threshold cognitive phenotype LF3 factor scores greater than 1.5 SD above the mean in the nondemented offspring sample, we classified family members in the entire LLFS cohort as EC and non-EC subjects (cognitive scores = 3.86 and < 3.86, respectively). After retaining families with at least four family members, 461 LLFS families (4,470 subjects) were then classified as EC or non-EC LLFS families based on the number of offspring with EC: 28 EC families (families with at least two EC family members in the offspring generation, n = 568) and 433 non-EC families (families with one or none EC family members in the offspring generation, n = 3,902).

Statistical Analysis

To assess differences in the levels of the age-related biomarkers (metabolic, cardiovascular, and physical/pulmonary function) between the EC and non-EC families, we used General Linear Models in Generalized Estimating Equations (GEE) to adjust for differences in family size and relatedness among LLFS participants. Family members meeting criteria for cognitive impairment were excluded from the analysis. In the four different GEE analyses performed, each of the age-related biomarkers was modeled as the dependent variable and EC versus non-EC membership as the independent variable. All analyses were adjusted for sex, age, and education. The Apolipoprotein E (*APOE*) e4 allele has consistently emerged as a determinant of both dementia (16) and mortality (17). To further investigate whether results might be influenced by *APOE* locus (18), we stratified the sample based on the presence or absence of *APOE*-e4 allele. After excluding heterozygous individuals' e2e4 (n = 79), the genotypes at the *APOE* locus were recoded into the

following two categories: (i) having no *APOE*-e4 allele and (ii) having at least one copy of the *APOE*-e4 allele). LLFS participants were classified into four different weight categories according to their BMI measures (Supplementary Table 3): underweight (BMI < 18.5), normal (BMI 18.5–24.9), overweight (BMI 25–29.9), and obese (BMI = 30). Using binary logistic GEE models, adjusted for sex, age, and waist circumference, we investigated whether the prevalence of BMI categories was significantly different between EC and non-EC families. We tested EC and non-EC families within two different group comparisons: (i) the proportion of obese versus normal and (ii) the proportion of overweight versus normal. The analysis was carried out in three different age groups: (i) the non-age stratified sample, (ii) the subset of LLFS subjects younger than 80 years of age, and (iii) the subset of LLFS subjects older than 80 years of age.

Age and sex adjusted GEE models were also used to assess the differences between EC and non-EC families based on their FLoSS. All statistical analyses were performed using SPSS 22 statistical software.

Results

The demographic characteristics of the LLFS families are provided in Table 1. Compared with non-EC families, LLFS members from EC families appear to be an average of 3 years younger (63 ± 14 vs 66 ± 14). There were no statistically significant differences in the proportion of females (~55%), the educational level (average of 12 years of education) or distribution of the APOE-e4 allele (=20%) between EC and non-EC families. EC families showed significantly higher estimated family exceptional longevity when compared to non-EC families as measured by FLoSS scores (12 ± 7 vs 9 ± 8, $p = 2.5 \times 10^{-14}$).

As summarized in Table 2, our results show that LLFS participants from EC families had a significantly better metabolic/cardiovascular profile than those of LLFS participants from non-EC families (average scores of −0.53 ± 3.9 vs 0.10 ± 3.8 respectively, $p = .006$). BMI and waist circumference measures (Supplementary Table 2), adapted from Singh and colleagues (12) had the higher factor loadings (=0.74) within the metabolic/cardiovascular profile. BMI was used to classify LLFS participants into four different weight categories: underweight, normal weight, overweight, and obese (Supplementary Table 3). When differences in the proportion of subjects within BMI categories between EC and non-EC families were tested in an adjusted (sex, age, and waist circumference) binary logistic GEE model (Table 3), results showed a statistical trend of lower prevalence of obesity in EC family families compared with non-EC families (38% vs 49%, $p = .062$). We tested whether the differences in obesity prevalence might be age-dependent. When the sample was restricted to LLFS family members 80 years old or younger, we observed a statistically significant lower prevalence of obesity among subjects from EC families (38% vs 51%, respectively, $p = .015$). However, if analysis was restricted to the oldest LLFS family members (age > 80), we observed a significantly higher prevalence of obese subjects within EC families compared to non-EC families (40% vs 38% respectively, $p = .011$).

Table 1. Demographic Characteristics of the EC and Non-EC Families

	EC (28 fams, $n = 400$)	Non-EC (433 fams, $n = 2{,}508$)	p Value
Age, mean ± *SD*	63 ± 14	66 ± 14	<.001
Education, mean ± *SD*	12 ± 3	12 ± 3	NS
% Females	56	57	NS
APOE-E4 carriers, *N* (%)	74 (19)	473 (20)	NS
FLoSS score, mean ± *SD*	12 ± 7	9 ± 8	<.001

Note: APOE = Apolipoprotein E; EC = exceptional cognition; NS = not significant statistical test at 5% significance level ($p > .05$).

The differences between EC and non-EC families in the average values of waist circumference did not reach significance (data not shown). Consistent with previous LLFS findings (12), EC families also showed significantly better scores for the physical/pulmonary profile compared with non-EC families (average scores of 0.52 ± 4.8 vs 0.01 ± 4.8 respectively, $p = .042$). We did not find significant differences in the cardiovascular profiles (blood pressure or lipid) between EC and non-EC families.

To test whether the presence of an *APOE*-e4 allele, reported in literature as a predictor of both dementia risk and mortality, might influence our results, analyses were repeated among strata defined by the presence or absence of the e4 allele. The *APOE*-e4 stratified results (Supplementary Table 1) showed that the association of EC and the more favorable metabolic/cardiovascular profile is exclusively found in the noncarriers of the *APOE*-e4 allele (average scores of −0.48 ± 4.4 vs 0.11 ± 4.8 respectively, $p = 0.021$).

Discussion

Exceptional longevity (EL) can be defined in a number of ways, including survival to a specific extreme age (longevity), disability-free (active life expectancy), disease-free (healthy aging), or cognitively intact survival. Results from the LLFS, have consistently suggested that preservation of cognitive function is a key feature of exceptional longevity. We have demonstrated that the offspring of long-lived probands showed better cognitive performance on multiple cognitive tasks compared with individuals without a family history of longevity (9). We also demonstrated there is a familial correlation of exceptional episodic memory (EM) performance in LLFS families, suggesting that genetic variants might influence memory performance in long-lived families (10). Furthermore, genome-wide linkage analysis of long-lived families selected on the basis of their exceptional episodic memory provided strong evidence for a potential candidate gene related to EM on chromosome 6q24 region (11). When investigating whether LLFS participants were protected against cognitive impairment characteristic of Alzheimer's disease (AD), we found that the sons and daughters of probands had significantly lower rates of dementia than spouse controls, suggesting a delayed onset of cognitive impairment in families with exceptional longevity (13).

Centenarian studies in United States have also demonstrated familial aggregation of EL and have found that siblings of centenarians live longer than their peers (19). Offspring of centenarians have favorable lipid profiles (20) and lower relative prevalence of heart disease, hypertension, and diabetes (21). In the LLFS study, both probands and their offspring were less likely to have diabetes, chronic pulmonary disease, and peripheral artery disease and had better measures of physical function and a lower prevalence of cardiovascular risk factors compared with similarly aged peers in the Cardiovascular Health Study and the Framingham Heart Study (14). Similar findings have been reported in non-U.S.-based centenarian studies (22–25).

Table 2. Generalized Estimated Equations Results of Age-Related Biomarkers Between EC and Non-EC LLFS Families

	EC		Non-EC		Parameter estimates						
Age-Related Biomarkers	*N*	Nfam	*N*	Nfam	β	*SE*	*p*	Avg_{EC}	SE_{EC}	Avg_{Non-EC}	SE_{Non-EC}
Physical/pulmonary	400	28	2,508	425	0.51	0.25	.042	0.52	4.80	0.01	4.80
Metabolic/cardiovascular	400	28	2,508	425	-0.63	0.23	**.006**	-0.53	3.42	0.10	3.81
Cardiovascular BP	400	28	2,508	425	-0.29	0.22	.188	0.07	3.54	0.35	3.55
Cardiovascular lipid related	400	28	2,508	425	0.24	0.20	.230	0.26	3.28	0.03	3.22

Note: avgEC (SEC) = avgNon-EC: average value (and *SE*) of the dependent variable (endophenotype) for the individuals in EC and Non-EC families, respectively. BP = blood pressure; EC = exceptional cognition; LLFS = Long Life Family Study; NEC = Non-EC: Number of the individuals with nonmissing data for dependent variable and covariates in EC and Non-EC families, respectively. Bold values correspond to the age-related biomarkes that are statistically significant at 5% nominal level.

Table 3. Generalized Estimated Equations Analysis Results of BMI Categories Within EC and Non-EC Families Stratified by Age Group

		EC		Non-EC		Parameter Estimates			
Age Strata	BMI Categories	*N*	%	*N*	%	β	exp(β)	*SE*	*p*
All	Obese (BMI ≥ 30)	95	38	796	49	0.56	1.8	0.30	.062
	Normal (BMI 18.5–24.9)	154	62	816	51				
	Overweight (BMI 25–29.9)	147	49	841	51	0.16	1.2	0.15	.319
	Normal (BMI 18.5–24.9)	154	51	816	49				
≤80 y	Obese (BMI ≥ 30)	83	38	697	51	0.76	2.1	0.31	.015
	Normal (BMI 18.5–24.9)	136	62	658	49				
	Overweight	126	48	673	51	0.25	1.3	0.17	.140
	Normal (BMI 18.5–24.9)	136	52	658	49				
>80 y	Obese (BMI ≥ 30)	12	40	97	38	−1.76	0.2	0.69	.011
	Normal (BMI 18.5–24.9)	18	60	156	62				
	Overweight	21	54	166	52	−0.41	0.7	0.51	.424
	Normal (BMI 18.5–24.9)	18	46	156	48				

Note: BMI = body mass index; EC = exceptional cognition.

In line with these previous observations, our results demonstrated that the healthier metabolic/cardiovascular profile exhibited by EC families is significantly related, in an age-dependent fashion, to the prevalence of obesity. For LLFS participants less than 80 years of age, the prevalence of obesity in EC families was significantly lower than in non-EC families, suggesting a detrimental effect of obesity on cognition. However, the higher prevalence of obesity among older EC family members (>80 years) suggest a benign or even beneficial effect on cognitive performance.

The nature of the BMI-mortality association in elderly subjects continues to be a subject of debate, becaues studies have reported both negative and positive associations. Some studies in elderly populations have suggested that their relationship varies according to age: higher BMI seems to be predictive of mortality for subjects younger than 75–80 years of age (26), while among subjects aged 80 years and older, higher BMI has been associated with lower mortality (27). A meta-analysis of longitudinal data of adults aged 65 years and older (28) reported no association between higher BMI and increased risk of mortality. However, these findings contradict results from prospective studies showing that higher BMI is significantly associated with higher rates of mortality at ages 80–89 years (29). Among the possible explanations for the reported inverse associations between BMI and mortality are weight loss because of preexisting disease and lack of adjustment for tobacco use. Moreover, obesity has also been associated with a range of detrimental metabolic alterations that increase the risk of developing type 2 diabetes (30), coronary artery disease (31), hypertension (32), nonalcoholic liver disease (33), and cancer (34).

Although our analysis excluded LLFS participants classified as demented, we cannot completely rule out a potential link between obesity and dementia risk. Several meta-analysis studies concluded that being underweight, overweight, or obese in midlife (ages 40–45) predicted higher risk of dementia (35–37). However, results from studies in elderly cohorts showed mixed results regarding the relationship between BMI, cognitive function, and the risk of dementia (35,38,39). The Honolulu-Asia Aging Study (HAAS) examined the natural history of weight change in Japanese American men aged 77–98 years with and without incident dementia. HAAS results showed differences in BMI between participants with and without dementia over the 6 years prior to the diagnosis (additional weight loss in those with dementia) (40). However, others studies have shown a broadly consistent protective association of obesity with cognitive function in late-life, that is, overweight and obese elderly subjects are at lower risk of cognitive impairment, compared with having a normal weight after adjusting for confounding factors, such as health behavior and health status (41–46). Among these studies, are the results from a study of Japanese participants aged 80 years and older (Keys to Optimal Cognitive Aging Project, KOCOA) assessing the association between baseline components of metabolic syndrome (such as BMI) and longitudinal cognitive functions supported evidence that the positive association between metabolic syndrome and cognitive function might not hold for the oldest old (47).

Several potential underlying mechanisms have been proposed to explain this reversal association between BMI and dementia in late life, sometimes referred to as the "obesity paradox." Reductions in lean body mass and muscle mass, lower bone mineral density,

compromised nutrition, and impaired physical function may be attenuated in elderly subjects with higher BMI (48). Neuroimaging studies suggested that higher BMI may have beneficial cognitive effects in the older adult population through a mediated relationship with brain function (49).

We also found that subjects who do not carry any copy of the *APOE*-e4 allele exhibited a more favorable metabolic/cardiovascular profile (p = .021). However, the association may have been overestimated due to the small sample size of the APOE-e4 noncarriers group.

EC families also showed significantly better scores for the physical/pulmonary endophenotype when compared with non-EC families (β = 0.51, SE = 0.25, p = .042). Our result is consistent with previous findings (12) reporting the significant association between physical/pulmonary endophenotype and decreased mortality in the LLFS and Health, Aging and Body Composition Study (Health ABC) cohorts.

In this study, we found that among LLFS families with exceptional longevity (EL), those exhibiting the most exceptional cognitive performance (EC families) showed also a healthier metabolic and a physical/pulmonary profiles, compared with non-EC families. These findings suggest that the effect of cognitive, metabolic, and physical function might contribute to their exceptional longevity. Thus, the phenotype of EL, like other complex traits, is a multidimensional phenotype (50), that is, a phenotype that likely includes multiple domains such as cognition, physical/pulmonary, metabolic, etc., each of them measuring multiple indicators of healthy aging.

There are some limitations of our study. First, since the selected threshold to declare EC is somewhat arbitrary, it is possible that some LLFS families have been misclassified. Second, none of the statistical models adjusted for prescription medication used by LLFS participants that may have influenced the disease status of the participants. Third, the FLoSS score was derived for enrollment purposes and may fail to reflect final survival probabilities of deceased LLFS participants. Finally, the BMI measurements used in this study does not take into account fat mass/fat-free mass ratio, nutritional status, cardiorespiratory fitness, body fat distribution, or other factors affecting health risks and mortality (51).

Further research is needed to investigate the biological mechanisms underlying the association between healthy metabolic profiles, cognition and successful aging and the role of additional factors such as genetic variation and environmental exposures on these associations.

Supplementary Material

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

Funding

This work was supported by the National Institute on Aging (U01-AG023712, U01-AG23744, U01-AG023746, U01-AG023749, U01-AG023755, and P01-AG08761) and The VELUX Foundation (31205).

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