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Association of healthy aging with parental longevity

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Abstract Various measures incorporated in geriatric assessment have found their way into frailty indices (FIs), which have been used as indicators of survival/mortality and longevity. Our goal is to understand the genetic basis of healthy aging to enhance its evidence base and utility. We constructed a FI as a quantitative measure of healthy aging and examined its characteristics and potential for genetic analyses. Two groups were selected from two separate studies. One group (OLLP for offspring of long-lived parents) consisted of unrelated participants at least one of whose parents was age 90 or older, and the other group of unrelated participants (OSLP for offspring of short-lived parents), both of whose parents died before age 76. FI_{34} scores were computed from 34 common health variables and compared between the two groups. The FI_{34} was better correlated than chronological age with mortality. The mean FI_{34} value of the OSLP was 31 % higher than that of the OLLP (P=0.0034). The FI_{34} increased exponentially, at an instantaneous rate that accelerated 2.0 % annually in the OLLP (P=0.024) and 2.7 % in the OSLP ($P << 0.0001$) consequently yielding a 63 % larger accumulation in the latter group (P= 0.0002). The results suggest that accumulation of health deficiencies over the life course is not the same in the two groups, likely due to inheritance related to parental longevity. Consistent with this, sib pairs were significantly correlated regarding FI_{34} scores, and heritability of the FI_{34} was estimated to be 0.39. Finally, hierarchical clustering suggests that the OLLP and OSLP differ in their aging patterns. Variation in the FI_{34} is, in part, due to genetic variation; thus, the FI_{34} can be a phenotypic measure suitable for genetic analyses of healthy aging.

Keywords Frailty · Deficits · Longevity · Aging · Heritability · Age

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Introduction

Aging can be defined as the progressive decline in the ability to withstand damage and stress, which is associated with an increase in the incidence of disease and degenerative disorders (Finch 1990). This definition separates biological aging from a strict relationship with chronological age. Aging processes involve many factors, both genetic and nongenetic. The complexity of human aging is further increased by various interactions

that occur among these factors in the development and progression of aging-related changes.

In an attempt to systematically approach human aging, Rowe and Kahn (1997) defined the concept of successful aging as: (1) relatively low risk of disease and disease-related disability, (2) relatively high mental and physical function, and (3) active and productive engagement with life. A quantitative approach to successful aging was developed by estimating the amount of physical and functional loss that occurs during the life course and incorporating these losses into a condition termed "frailty" (Rockwood et al. 1994, 1999). Fried et al. (2001) defined frailty as a clinical syndrome involving five features: weight loss, exhaustion, muscle weakness, slow gait speed, and low physical activity. They found that the prevalence of frailty increases with age. Mitnitski et al. (2001) developed an expanded approach to frailty by introducing a frailty index (FI), as the proportion of accumulated deficits in a set of 92 health variables surveyed for an individual at a given age. Their health variables included symptoms, signs, laboratory measurements, diseases, and disabilities. The purpose of the FI was to enumerate a broad spectrum of changes that occur in multiple domains of the human body. Since then, different FIs with different numbers of health variables have been studied (Rockwood and Mitnitski 2007; Rockwood et al. 2007), and others taking the FI approach have used the term deficit index (DI) (Kulminski et al. 2007b, 2008).

The FI appears to be a promising tool for studying human aging as an indicator of biological age and predictor of survival (Mitnitski et al. 2001, 2002a, b; Kulminski et al. 2007a, b). The FI seems to be relatively robust and consistent between studies, as long as the number of health variables is reasonably large (≥20) and sufficiently diverse to represent multiple domains of body function (Mitnitski et al. 2006; Rockwood et al. 2007; Searle et al. 2008).

Despite the potentially useful features of the FI in human aging research, studies addressing its utility in genetic analyses are extremely limited. In a twin study, Kulminski et al. (2009) found geriatric diseases can be used as cumulative indices to predict lifespan among family members. Matteini et al. (2010), in a family study, estimated the heritability of 28 health-related variables to range from 0.01 to 0.45, individually or in statistical combinations.

Here, we have constructed a FI based on 34 health variables (FI_{34}) and studied its properties as a composite phenotype. Our 34 variables include diseases and symptoms throughout the body, deficiencies in physical and cognitive functioning, and self-rated health status. We validate the FI_{34} as a predictor of survival and mortality. We also describe its behavior across age groups in a family-based sample and determine its heritability. Finally, we replicate these features of the FI_{34} in subjects drawn from a sample of unrelated individuals, which, together with its heritability, suggests the utility of the FI_{34} in genetic studies of aging.

Materials and methods

Participants

Louisiana residents from the New Orleans Greater Metropolitan Area who were at least 90 years old and their offspring (N=320) were recruited to the Healthy Aging Family Study (HAFS) (Online Resource Table 1). Ethnicity was self-declared. Eighty-nine offspring were randomly sampled each from a different family, and this group was named "offspring of long-lived parents" (OLLP).

The Louisiana Healthy Aging Study (LHAS) and demographic characteristics of its participants were described elsewhere (Jazwinski et al. 2010). Unrelated individuals (N=869), ranging in age from 20 to over 100 years old, were recruited from eight parishes within a 40-mi radius of Baton Rouge, Louisiana, by random sampling from Voters' Registration and CMS enrollment database files. Ethnic affiliation was determined using structure analysis (0.8 assignment probability) (Pritchard et al. 2000; Jazwinski et al. 2010), and LHAS subjects were selected to match the HAFS sample (Online Resource Table 1). Forty-eight LHAS participants were identified whose parents died at ages ≤75 and named "offspring of short-lived parents" (OSLP). The age range of these OSLP individuals approximates that of the OLLP individuals, as summarized in Table 1.

Ages of participants were verified using both documentary evidence (birth certificates, passports, and driver's licenses) and demographic questionnaires. All participants provided informed consent according to protocols approved by the Institutional Review Boards.

Data management

The variables used to count health deficits in both HAFS and LHAS are listed in Online Resource Table 2.

Table 1 Age of participants sampled from the Healthy Aging Family Study (HAFS) and the Louisiana Healthy Aging Study (LHAS). Numbers are the mean age ± standard deviation (sample number)

Study	Group	Female	Male	Both
HAFS	Total	64±6 (132)	64±6 (69)	64±6 (201)
	OLLP	64±7 (57)	63±5 (32)	64±6 (89)
LHAS	Total	66±24 (415)	69±22 (258)	67±23 (673)
	OSLP	60±13 (28)	60±12 (20)	60±12 (48)

OLLP offspring of long-lived parents, *OSLP* offspring of short-lived parents

Collected data are quantitative measures, either continuous or discrete, or categorical responses from medical history questionnaires. Binary categorical responses were numerically coded: 0 for the absence of deficit and 1 for the presence of deficit. Quantitative data and multicategorical responses were recoded essentially in the same way as reported previously (Searle et al. 2008) or with modifications as shown in Online Resource Table 2. Mortality data were collected using Social Security Death Index search. For the analyses of FI_{34} in mortality and survival, we calculated the follow-up period (in months) for each individual as follows: for those who died, the follow-up period is the time elapsed from the date of deficit data collection to the recorded date of death (82.5±20.6). For the survivors, the follow-up period is the time passed between the date of deficit data collection and the date of mortality data collection (38.3±24.1).

Data analyses

All statistical analyses were performed in R (R 2008). Only Caucasian participants were included in the analyses to avoid confounding by population admixture and because of sample size considerations. The FI_{34}, with positive skewness, was considered not normally distributed in both study samples (Online Resource Fig. 1). Therefore, in statistical tests that assume a normal distribution, we applied both parametric and nonparametric tests and compared the outcomes. In all instances, both outcomes were very similar, and we present only those from the parametric tests. Fitting of the exponential function $a \cdot e^{(b \cdot \text{age})}$, where a and b are parameters, and weighted least squares estimation of the parameters were performed using the *nls* function in the R *stats* package. The *integrate* utility was used to calculate the definite integral of this function with the lower and upper limits of age set at 40 and 90 years, and permutation analysis (10,000 random samples) was used to test significance of differences between OSLP and OLLP. For hierarchical clustering of 34 variables and age, which are binary or quantitative, we used the general dissimilarity coefficient of Gower (Gower 1971), which is available in the function *daisy* in the *cluster* library with standardization (Kaufman and Rousseeuw 2005). This metric is known to be capable of handling different types of variables at the same time. Hierarchical clustering analyses based on the dissimilarity matrices were performed using the *hclust* function in the base package *stats* and plotted using the *plot* function in R. In addition to the "complete" method that we used to generate Fig. 2, we used different agglomeration methods, such as "ward" and "average," all of which gave essentially the same clustering patterns. All reported *P* values are two-tailed.

Heritability estimation

Heritability in the narrow sense (h^2), the ratio of the additive genotypic variance to the total phenotypic variance (σ_a^2/σ^2), was estimated for 86 full sib pairs with an equal sibship size (k=2), as described by Hartl (1980) and its standard error as described by Roff (1997) (Online Resource Table 3).

Results

FI_{34} as a predictor of mortality

First, we determined the extent to which the FI_{34} is associated with age (the chronological age at the time

Table 2 Correlation between FI_{34}, age, and time to death in the Louisiana Healthy Aging Study (LHAS)

FI_{34} frailty index based on 34 items

Variable 1	Variable 2	*n*	Coefficient	95 % CI	*P* value
FI_{34}	Age	673	0.698	0.657–0.735	<<0.0001
FI_{34}	Time to death	191	−0.207	−0.339 to −0.067	0.0041
Age	Time to death	191	−0.145	−0.282 to −0.004	0.045

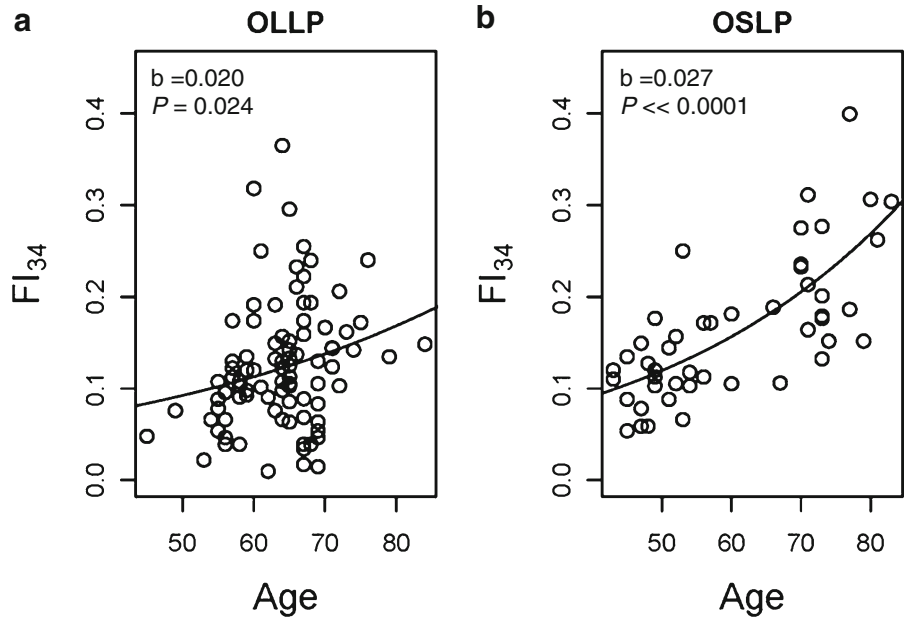

Fig. 1 Scatter plots of FI_{34} scores by age in the **a** "offspring of long-lived parents" (OLLP) and **b** the "offspring of short-lived parents" (OSLP), fitted with exponential curves. Using the FI_{34} as a dependent variable and age as an independent variable, the exponential function $a \cdot e^{(b \cdot \text{age})}$ was fitted to estimate parameters a and b. In both cases, a= 0.03 and shown are the estimated b values with corresponding P values under the null hypothesis that slope = 0

of test) and time to death (the time elapsed from the date of test to the date of death). We used the LHAS sample for simple correlation tests because HAFS consists of nuclear families resulting in lack of independence of certain observations. As expected, there was a strong correlation between the FI_{34} and age (coefficient = 0.70, $P << 0.0001$), but the FI_{34} was better associated with time to death than age was (coefficient = −0.207, P= 0.0041 for FI_{34} and coefficient = −0.145, P=0.045 for age) (Table 2).

Next, we tested the performance of the FI_{34} as a predictor of survival/mortality using Cox proportional hazards regression. Again, we used the LHAS sample for the survival analysis because the HAFS sample contains related individuals and the number of deaths was low. Both age and the FI_{34} were significantly associated with survival times, which included both censored and uncensored data ($P << 0.0001$ for both). However, when the Cox regression was limited to time to death (uncensored survival times), only the FI_{34} had a significant

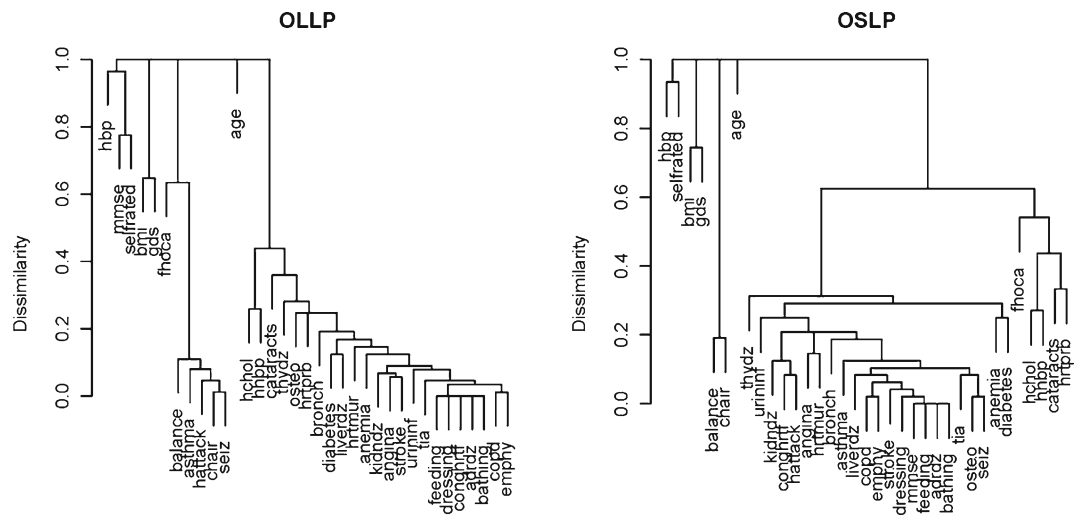

Fig. 2 Hierarchical clustering of 34 variables and age in **a** the "offspring of long-lived parents" (OLLP) and **b** "offspring of short-lived parents" (OSLP). The variable names and descriptions are as in Online Resource Table 2. The dissimilarity matrix was constructed using the Gower metric with standardization (Gower 1971)

effect on the hazard of death, whereas chronological age did not (P=0.0041 for FI_{34} vs. P=0.12 for age) (Table 3). These results indicate that the FI_{34} performs as well as previously reported FIs.

Differences in FI_{34} accumulation between OLLP and OSLP

Our goal was to test whether part of the variation in the FI_{34} is attributable to genetic differences and, if so, to estimate the extent of the genetic effect. To achieve this goal, we formed two study groups, OLLP from the HAFS and OSLP from the LHAS. These two groups differed in parental longevity. Differences in the FI_{34} between the two groups can be ascribed to differences in parental longevity, upon matching for other demographic parameters.

As shown in Table 4, the mean FI_{34} of the OSLP (0.163) was about 31 % higher than that of the OLLP (0.124), and this difference was statistically significant (P=0.0034). The difference in FI_{34} between the OSLP and OLLP groups was more accurately assessed using a multiple linear regression to adjust for the differences in sex and age (Table 5). The group variable was significantly associated with the FI_{34} ($P << 0.0001$), which confirms a significant difference in FI_{34} between the OSLP and the OLLP. Sex had no effect on the FI_{34} ($P >> 0.05$), and age was significantly associated with it as before.

The association of the FI_{34} with parental longevity was uncovered in a cross-study comparison. To replicate this association within a single study, we used 90 additional LHAS participants with known parental longevity status. A multiple linear regression including OSLP and subjects with at least one parent aged ≥90 as a group variable showed that the FI_{34} was significantly associated with parental longevity (P=0.0047) (Table 6).

Difference in FI34 between OLLP and OSLP at later ages

The two study groups were each dichotomized using age 60 as a cutoff for comparison (Online Resource Fig. 2). The mean FI_{34} was 34 % greater in 'young' (age < 60) OSLP compared to 'young' (age < 60) OLLP and 57 % greater in 'old' (age ≥ 60) OSLP compared to 'old' (age ≥ 60) OLLP (Online Resource Table 4). These differences between two age groups imply that the rate of deficit accumulation may be larger at later age in the OSLP than in the OLLP.

Previous studies indicated that deficits accumulate exponentially with age, and the greater difference in FI_{34} between OSLP and OLLP at later ages suggests this to be the case here. We estimated the rate of accumulation in each group by fitting an exponential model, $a \cdot e^{(b \cdot \text{age})}$:

$$FI_{34}{}^{OLLP} = 0.03 \cdot e^{(0.020 \cdot age)} \quad P = 0.024 \tag{1}$$

$$FI_{34}{}^{OSLP} = 0.03 \cdot e^{(0.027 \cdot age)} \quad P << 0.0001. \tag{2}$$

According to this model, the instantaneous rate of accumulation of deficits accelerates at an annual rate of 2 % in the OLLP and 2.7 % in the OSLP (Fig. 1). Integration of these equations in the

Table 3 Cox regression for time to death as a function of FI_{34} or age in the Louisiana Healthy Aging Study (LHAS)

Variable	β	Exp (β)	P value	R^2	Wald test P
FI_{34}	2.358[a]	10.570[a]	0.0042	0.040	0.00416
Age	0.01695	1.017	0.124	0.014	0.124

FI_{34} frailty index based on 34 items

[a] The coefficient (β) and its exponentiated value (Exp (β)) are for a unit increase in FI_{34}. FI_{34} scores range from 0 to 1, but a FI_{34} score of 1 is practically impossible. Therefore, to better estimate the effect of the covariate, we should compute the values for a fractional increase, i.e., 0.1 rather than the whole unit (1). In this case, $e^{(0.1 \cdot \beta)} = 1.27$, which means an increase in the hazard by 27 % for a tenth of the unit increase in FI_{34}

Table 4 FI_{34} scores of subjects in different study groups

Study group	Sex	n	Mean ± SD	P value[b]
OLLP	Both	89	0.124±0.069[a]	0.0034
	Female	57	0.128±0.068	
	Male	32	0.116±0.071	
OSLP	Both	48	0.163±0.077[a]	
	Female	28	0.159±0.085	
	Male	20	0.168±0.065	

FI_{34} frailty index based on 34 items, *OLLP* offspring of long-lived parents, *OSLP* offspring of short-lived parents

[a] $P >> 0.05$ between sexes in each group

[b] Wilcoxon rank-sum test comparing the OLLP and OSLP totals

Table 5 Comparison of FI_{34} between OLLP and OSLP by multiple linear regression ($FI_{34} = \beta_0 + \beta_1 \cdot \text{sex} + \beta_2 \cdot \text{age} + \beta_3 \cdot \text{group}$, where group is coded 0 for OLLP and 1 for OSLP and sex is coded 0 for female and 1 for male)

Variable	β[a]	SE (β)[a]	P value	R^2 (P value)
Sex	−0.00169	0.0111	0.879	0.285 (<<0.0001)
Age	0.00389	0.000607	<<0.0001	df=133
Group	0.0534	0.0115	<<0.0001	

FI_{34} frailty index based on 34 items, *OLLP* offspring of long-lived parents, *OSLP* offspring of short-lived parents

[a] Regression coefficient and its standard error

interval of 40 to 90 years of age results in FI_{34} of 5.736 and 9.349 for OLLP and OSLP, respectively, which differs by 63 % (P=0.0002). This confirms that the rate at which FI_{34} increases differs between these two groups.

Sib correlation and heritability of FI_{34}

We next determined the extent of familial aggregation and heritability of the FI_{34}. For this purpose, each OLLP individual was paired with his/her sib (or a sib was randomly selected in case of multisib (≥3) families), and using the 86 full sib pairs only, sib correlation and narrow-sense heritability were estimated. The correlation coefficient was 0.459 (df=84, 95 % CI= 0.273–0.611, $P << 0.0001$) and the estimated heritability was 0.391 (standard error = 0.209).

Group-specific profiles of healthy aging

Lastly, we checked interrelationships of the deficits by grouping them into clusters of statistically related variables, using hierarchical clustering methods. Figure 2 shows the resulting dendrograms for both OLLP and OSLP. In both cases, the 34 variables were grouped into four clusters with the variable age forming an additional cluster by itself. Most of the 34 variables were assigned to one large cluster. However, the way that these variables were grouped in this cluster was not the same between the study groups. For example, the variables 'angina' and 'stroke' were clustered together in the OLLP, but in the OSLP, they were separate and paired with different variables. The differences in clustering suggest that the pattern of deficit accumulation during aging may be associated with parental longevity.

Discussion

The main conclusion of our work is that parental longevity has a significant impact on healthy aging because FI_{34} scores of offspring significantly differed depending on their parents' longevity. This finding was made by comparing two different study groups and was confirmed by an analysis of a within-study sample. Using the sib pair data, we found siblings within sibships significantly correlated with each other with regard to their FI_{34} scores and estimated the heritability to be 0.39.

Our variables cover cardiovascular-related diseases and symptoms (10), deficiencies in physical functioning (6), respiratory functioning (4), cognitive functioning (3), and other diseases and symptoms throughout the body. Our FI_{34} performed as well or better than other FIs. For example, the FI_{34} was better correlated with time to death than age was, which replicates the previous finding by Mitnitski et al. (2001) in which their FI was based on 92 variables. The effect of our FI_{34} on the hazard of death, as shown by a Cox regression, is also consonant with the finding by Mitnitski et al. (2002a) based on 20 variables, though the effect we observe is stronger. They used

Table 6 Test for association of FI_{34} with parental longevity in LHAS using multiple linear regression ($FI_{34} = \beta_0 + \beta_1 \cdot \text{sex} + \beta_2 \cdot \text{age} + \beta_3 \cdot \text{parental longevity}$). Parental longevity was coded 0 for those (n=90) with either or both parents long-lived (age ≥ 90) and 1 for OSLP (n=48) and. Sex was coded 0 for female and 1 for male

Variable	β[a]	SE (β)[a]	P value	R^2 (P for model)
Parental longevity	0.0524	0.0182	0.0047	0.284(<<0.0001)
Age	0.00369	0.000549	<<0.0001	df=134
Sex	−0.00635	0.00121	0.60	

FI_{34} frailty index based on 34 items

[a] Regression coefficient and its standard error

biological age derived from their FI, but these are not independent variables. Matteini et al. (2010) performed principal component analyses on 28 variables and found no single component responsible for more than 14 % of the variance. Thus, the robustness of this type of index is likely to reflect interrelationships between biological systems at many different levels (Mitnitski et al. 2001). In this context, it is very interesting to note the differences in the clustering patterns of variables between the two groups characterized by different parental longevity. Perhaps, the difference reflects differing interactions of biological systems depending on the genetic backgrounds transmitted from previous generations.

In examining the rate of increase in FI_{34} with age, we rely on cross-sectional data. The trend of deficit accumulation with age may differ among different birth cohorts (Yang and Lee 2010). A few reports based on a longitudinal study and other cross-sectional data available to date suggest that accumulation of deficits increases in a nonlinear fashion (Mitnitski et al. 2001; Kulminski et al. 2007a, b; Yang and Lee 2010; Kulminski et al. 2011). Our data also fit an exponential model of deficit accumulation. The instantaneous rate of increase in deficits at a given age can be obtained by differentiating Eqs. 1 and 2. Thus, for example, the instantaneous rate of FI_{34} increase is 12 % for OLLP and 20 % for OSLP, respectively, at age 70.

Herskind et al. (1996) reported the heritability of human longevity ranging 0.23–0.26 with no evidence for an impact of shared (family) environment. All subsequent estimates of heritability of longevity fall between 0.15 and 0.35 (Gudmundsson et al. 2000; Kerber et al. 2001). In addition, a number of studies reported heritability during aging of physical and cognitive functions (McClearn et al. 1997; Carmelli et al. 2000; Frederiksen et al. 2002), and even a measure of health-related quality of life (Romeis et al. 2005). Our estimate of heritability of FI_{34}, 0.39, falls within the range that Matteini et al. (2010) estimated for 28 different variables, alone and in combinations. It is also within the 95 % CI of heritability, 0.31–0.53, recently reported by Dato et al. (2012) for their "frailty phenotype," which is based on survival, age, MMSE, Katz's index of ADL, BMI, and self-reported health rating. The inclusion of survival and age lessens the utility of this frailty phenotype as a predictive tool, however.

In genetic analyses of a complex trait such as aging, the selection of an appropriate phenotype is paramount. Ho et al. (2011) investigated association of women's frailty with single-nucleotide polymorphisms (SNPs) in candidate genes. In that study, the FI was based on a five-point scale from measurements of muscle weakness, slow gait speed, weight loss, fatigue, and low physical activity. The candidate genes were selected based on their roles in skeletal muscle function and inflammation. However, no SNPs passed statistical significance. Edwards et al. (2011) collected data from 214 Amish subjects over age 80 for 13 variables. These variables belonged to the three domains of successful aging, as described earlier (Rowe and Kahn 1997). Linkage analysis of the binary trait of successful aging (yes/no) led to identification of three genomic regions. Although the numbers and selections of health variables were limited in these studies and the results await replication and validation, these studies suggest that a multidimensional phenotype like FI_{34} will be useful for genetic analyses.

In sum, we showed that (1) our FI changes with age at different rates, depending on the longevity of parents; (2) this index is heritable; and (3) it discriminates between different patterns of aging. Unraveling of these additional properties of the FI was possible due to the collected information on familial longevity.

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