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Association with Mortality and Heritability of the Scale of Aging Vigor in Epidemiology (SAVE)

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Abstract

Background—Vigor may be an important phenotype of healthy aging. Factors that prevent frailty or conversely promote vigor are of interest. Using the Long Life Family Study (LLFS), we investigated the association with mortality and heritability of a rescaled Fried frailty index, the Scale of Aging Vigor in Epidemiology (SAVE), to determine its value for genetic analyses.

Design/Setting—Longitudinal, community-based cohort study of long lived individuals and their families (N=4075 genetically-related individuals) in the United States and Denmark.

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Please see Supplemental Material for a full list of LLFS investigators.

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Methods—The SAVE was measured in 3599 participants and included weight change, weakness (grip strength), fatigue (questionnaire), physical activity (days walked in prior 2 weeks), and slowness (gait speed), each component scored 0, 1 or 2 using approximate tertiles, and summed from 0 (vigorous) to 10 (frail). Heritability was determined with a variance-component based family analysis using a polygenic model. Association with mortality in the proband generation (N=1421) was calculated with Cox proportional hazards mixed effect models.

Results—Heritability of the SAVE was 0.23 ($p = 1.72 \times 10^{-13}$) overall (n=3599), 0.31 ($p = 2.00 \times 10^{-7}$) in probands (n=1479), and 0.26 ($p = 2.00 \times 10^{-6}$) in offspring (n=2120). In adjusted models, compared with lower SAVE scores (0–2), higher scores were associated with higher mortality (score 5–6 HR, 95%CI = 2.83, 1.46–5.51; score 7–10 HR, 95% CI = 3.40, 1.72–6.71).

Conclusion—The SAVE was associated with mortality and was moderately heritable in the LLFS, suggesting a genetic component to age-related vigor and frailty and supporting its use for further genetic analyses.

Keywords

Epidemiology; Longevity; Genetics; Phenotype; Frailty

INTRODUCTION

Aging is often accompanied by disease, disability, and frailty. Much has been learned about the causes and consequences of aging by focusing on frailty, and yet a notable observation remains: in the Cardiovascular Health Study, where the most widely used index of frailty was derived by Fried et al, stratifying the population on this frailty scale results in roughly half the population classified as “not frail,” despite their average age of 72 years old.¹ Undoubtedly, in this population of community dwelling older adults, there is heterogeneity of health outcomes among the “not frail.” By further stratifying the wide range of individuals in the “not frail” group, investigators can gain the opportunity to characterize the exceptionally healthy in old age.

Those who remain healthy, functional, and even vigorous in late life are exceptional, and factors that promote healthy aging and longevity are of great interest to gerontology in addition to factors which promote frailty. Conceptually, a complementary classification to frailty may be termed vigor in old age, which may be defined as an absence of frailty or alternatively by the presence of positive attributes such as strength, speed, and energy. Creating a scale which simultaneously captures vigor and frailty illustrates the true distribution of health in an older population and allows investigators to study longevity, not just frailty.²

We developed the Scale of Aging Vigor in Epidemiology (SAVE) that rescales frailty to capture the most vigorous as well as the frail.² Frailty has been conceptualized as a clinical syndrome consequent to the accumulation of deficits in physiologic reserve.³ Frailty predicts functional decline, hospitalization, and death.^{1,4} Genetic variants may modify susceptibility to frailty or promote resistance to frailty through maintaining vigor. For example, genetic

analysis of frailty has suggested a role for genes involved with apoptosis and transcriptional control.⁵

The heritability of frailty and vigor has not been fully examined. In two Danish cohorts frailty was defined as a constellation of disability in activities of daily living, low hand grip strength, low body mass index (BMI), poor self-rated health, and poor cognition. In that study, heritability of this phenotype was moderate, similar to other complex age-related traits.⁶ In this study, we evaluated the heritability of the SAVE in the context of a family study of longevity.

MATERIALS AND METHODS

Long Life Family Study population

The LLFS is a family-based cohort study designed to characterize exceptional health well beyond what is expected in the general population. Previous analyses have confirmed the exceptionality of LLFS participants.⁷ Families were recruited by four collection sites across the United States and Denmark. Family eligibility and ascertainment has been previously described (overall N=551 families and 4875 individuals, including 4075 genetically-related individuals).^{8,9} At the time of analysis, 3599 of 4075 genetically-related participants (1479 probands and siblings and 2120 offspring) from all sites were included with complete data to construct the SAVE. Of the individuals excluded, 63% were spousal controls that are not included in heritability estimates and 21% did not have in-person examinations to allow calculation of the SAVE, with the remaining 16% of participants having incomplete data to calculate the SAVE. Annual follow ups are conducted over the phone to update health and vital status. For this analysis, mortality was calculated through the last vital status contact with the proband generation, August 19, 2013. The LLFS is approved by the Institutional Review Boards of all participating institutions and all participants provided informed consent.

Construction of the Scale of Aging Vigor in Epidemiology in the Long Life Family Study

To remove the ceiling effect of the original Fried frailty score and achieve greater differentiation of vigor/frailty status we considered tertiles of each frailty component.² The best tertile received a score of 0, the middle tertile a score of 1, and the worst tertile a score of 2 (see Table 1 for component cut points), and adding the five component scores created the new SAVE from 0 (most vigorous) to 10 (fraillest). LLFS-specific values were used. Gait speed (m/sec) was calculated for 4 or 3 meter walk, depending on site-specific protocols. Gait speed was stratified by median height and gender. For grip strength, the maximum grip strength of the dominant hand was used and stratified by gender and BMI quartile. Physical activity was determined by questionnaire as the number of days walked in the previous 2 weeks. Unintentional weight change was scored as: 0 (no weight change), 1 (weight gain), 2 (weight loss). Weight change was scored in this manner given that prior studies show low body weight and weight loss are consistently associated with greater mortality; obesity is consistently associated with disability at all ages and, in some studies, with increased mortality at older ages; and weight cycling is associated with greater mortality in older adults.¹⁰ Fatigue was determined by questionnaire using the sum of answers to two

questions on effort (“How often did you feel everything done was an effort?”) and exhaustion (“How often could you not get going?”).

Potential Confounders

Potential confounders were chosen for their known association with frailty or vigor. Age, sex, and years of education were ascertained by self-report. Smoking was assessed by a standardized interview.¹¹ Blood pressure, height, and weight were assessed by standardized protocols. BMI was calculated as kilograms per meter squared using height and weight. For consistency, we tabulated clinically diagnosed chronic conditions using the same methods as in the original report of the SAVE in the CHS and LLFS.^{2,12} Pulmonary disease, diabetes, kidney disease, and arthritis were assessed by self-report of physician diagnosis to depict what would be diagnosed disease. Depression was defined on the basis of a score > 10 on a modified 10-item CES-D score.^{13,14} Reports of cardiovascular disease and stroke were confirmed by review of medications and medical records.

Statistical Analysis

Overall characteristics of the population by cohort were depicted using mean (SD) or n (%). To illustrate differences in covariates by level of the SAVE, the SAVE score was categorized, and means or frequency were depicted for each SAVE category. To test for differences in covariates by level of the SAVE accounting for familial clustering, we modeled the SAVE as a continuous scale and determined the p-value from non-parametric correlations or analysis of variance, where appropriate. For heritability analysis we included age, age² and study site as covariates in the regression model. All analyses were carried out using SOLAR (v4.1.0) software, which implements a variance-component based family analysis.¹⁵ A polygenic model was fit to the data, and significance was estimated using a multivariate *t*-distribution (for better conformity with non-normal data). All heritability estimates are specific to the generation listed. Associations of the SAVE with mortality were tested using Cox proportional hazards mixed effect models with the R package *coxme*,¹⁶ which accounts for the family correlation structure by incorporating a kinship matrix using its *varlist* option. Mortality was calculated for the proband generation only given the much younger mean age and lower mortality of the offspring generation during the follow-up period.

RESULTS

The mean (SD) SAVE score was 4.2 (2.2) in the overall population, 5.5 (1.9) in probands, and 3.3 (1.9) in offspring (Table 1). Despite an average age of 89 years, probands had a relatively low burden of most comorbidities except osteoarthritis (43.7%). Higher SAVE scores were associated with older age, female gender, higher BMI, less education, and higher prevalence of several chronic health conditions ($p < 0.004$ to 0.0001) (Table 2 and Supplemental Table 1). SAVE score was not associated with ever smoking.

The residual heritability of the SAVE was 0.23 ± 0.04 (SE) ($p = 1.72 \times 10^{-13}$) in the overall cohort, 0.31 ± 0.07 ($p = 2.00 \times 10^{-7}$) in probands, and 0.26 ± 0.06 ($p = 2.00 \times 10^{-6}$) in offspring, adjusting for age, age² and study site. When the cohort was gender stratified, the

residual heritability was 0.28 ± 0.06 ($p = 4.31 \times 10^{-8}$) in women and was 0.21 ± 0.07 ($p = 0.001$) in men.

Of the 1421 probands, 633 (45%) were deceased after mean (SD) follow-up of 3.9 (1.5) years. The SAVE was significantly associated with mortality (Table 3). In fully adjusted models, a 1 point greater SAVE score was associated with an 18% increase in mortality (95% CI 1.13–1.24). Compared to the lowest (most vigorous) scores of 0–2, mortality was higher for probands with scores 5–6 (HR, 95% CI = 2.83, 1.46–5.51) and scores 7–10 (HR, 95% CI = 3.40, 1.72–6.71), but was not statistically significantly different for probands with scores 3–4 (HR, 95% CI = 1.49, 0.77–2.90).

DISCUSSION

This is the first report of the heritability of a phenotype measuring vigor and frailty which is validated by its strong association with mortality. The SAVE expands the widely validated Fried phenotype, and allows it to be easily generalized to other studies. In this study of long lived individuals and their families, we found the SAVE to be moderately and significantly heritable. Heritability was greater among probands, suggesting that the genetic component of vigor or frailty may strengthen with increasing age, similar to findings by Dato *et al.* in two Danish cohorts.⁶ Heritability did not differ between men and women (the standard errors around the estimates overlap) though gender-modification may have been minimized by incorporating gender-specific cut points for components of the SAVE, an *a priori* decision to create a longevity phenotype which can apply to men and women to understand common longevity pathways. Furthermore, the SAVE was significantly independently associated with mortality, a pre-requisite for a phenotype of longevity. These findings support the use of the SAVE as a phenotype for genetic analysis of vigor and frailty in humans.

Heritability estimates for composite frailty phenotypes are lacking. In two Danish cohorts, one a general population survival cohort, the other a sample of Danish twins, frailty was estimated to be moderately heritable with $h^2 = 0.43$ (95% CI 0.31–0.53).⁶ This heritability is slightly greater than that found in the overall LLFS population. When stratified by study site, the heritability of the SAVE in the LLFS population was 0.307 in Denmark and 0.218 in the United States, which may suggest more of a genetic component to the SAVE in Denmark, though these differences are small. Notably, Dato *et al.* used a different population sampling strategy, frailty components (Mini Mental status exam for cognitive function, Activities of Daily Living for functional activity, grip strength for physical performance, and self-reported health status), frailty component scoring system, and statistical method for determining heritability. It is difficult to determine whether the greater heritability estimate in their study represents a truly greater heritability in the Danish sample, or whether it is due to different study designs.

Although heritability estimates for composite frailty phenotypes are sparse heritability estimates for components of frailty have been published. Studies of grip strength, gait speed, and physical activity are most prevalent. In the LLFS, Matteini *et al.* created longevity endophenotypes using principal components analysis.¹⁷ As part of that analysis, Matteini *et al.* found heritability of average grip strength and maximum grip strength to be 0.41 to 0.43,

but heritability of gait speed was only 0.1 and of physical activity was near zero.¹⁷ In another study of 1757 Danish twin pairs aged 45–96 years, heritability of grip strength was 0.52.¹⁸ Heritability of physical activity has varied widely due to markedly different population substructures, sample sizes, and mostly subjective measurements of physical activity, ranging from 0% to 57% in family studies and 0% to 78% in twin studies.¹⁹ With objective measurement of physical activity in a large Danish twin study, den Hoed *et al.* estimated heritability of physical activity as 0.47 (95% CI 0.23–0.53).¹⁹ Higher heritability estimates are often seen with simple traits that are “pure” or less heterogeneous, while complex traits often display more modest heritability if significant, though this is not always the case. Thus, heritability of a complex vigor or frailty phenotype is likely to be lower than that of individual components. We encourage future studies of the SAVE and other validated phenotypes in order to arrive at more accurate estimates of the genetic contribution to vigor or frailty.

The main strengths of this study are the use of a longevity phenotype (SAVE) which expands on the most widely validated Fried frailty score to more accurately classify the range of vigor in the large number of individuals previously lumped together as “not frail;” the supporting survival analysis, and the unique LLFS population within which to examine the genetics of longevity and healthy aging. The major limitation is that because the LLFS collected families selected for longevity, a greater proportion of the variance in the SAVE in this population might be due to genetics, so there may be a potential over-estimate of its heritability. Without twins or half-sibs, it is difficult to disentangle genetics from shared environmental effects. Additionally, because the SAVE could not be calculated for participants that had only phone interviews, we had missing data on some participants. In the original frailty phenotype, physical activity was represented by kilocalories of energy expenditure calculated from questionnaires, though these questionnaires were not used in the LLFS. We substituted days walked in the prior two weeks as a marker of physical activity. Because these measures are not identical, it may results in different effects of heritability, though we believe the effect should be minimal given that kilocalories of energy expenditure is highly correlated to days walked in the prior two weeks.

In conclusion, we demonstrate that the SAVE is moderately heritable in the LLFS. The SAVE appears to be a viable candidate phenotype for use in genetic studies attempting to identify genetic variants associated with vigor or frailty. Future work should focus on validating these results and determining heritability of other complex phenotypes and their components, particularly those with a wide distribution that can identify the most vigorous and most frail.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Cut points for components of the Scale of Aging Vigor in Epidemiology in the Long Life Family Study

SAVE Component	Best tertile Score = 0	Middle tertile Score = 1	Worst tertile Score = 2
<i>Gait speed</i>			
Men			
Height 173.5 cm	> 1.07 m/sec	0.80 m/sec to 1.07 m/sec	0.80 m/sec
Height > 173.5 cm	> 1.26 m/sec	1.04 m/sec to 1.26 m/sec	1.04 m/sec
Women			
Height 159.9 cm	> 1.03 m/sec	0.72 m/sec to 1.03 m/sec	0.72 m/sec
Height > 159.9 cm	> 1.26 m/sec	1.08 m/sec to 1.26 m/sec	1.08 m/sec
<i>Grip strength</i>			
Men			
BMI 24.7 kg/m ²	> 40 kg	27 kg to 40 kg	27 kg
BMI 24.7 to 27.1 kg/m ²	> 42 kg	32 kg to 42 kg	32 kg
BMI 27.1 to 29.9 kg/m ²	> 44 kg	32 kg to 44 kg	32 kg
BMI > 29.9 kg/m ²	> 45 kg	35 kg to 45 kg	35 kg
Women			
BMI 23.0 kg/m ²	> 26 kg	18 kg to 26 kg	18 kg
BMI 23.0 to 25.8 kg/m ²	> 26 kg	20 kg to 26 kg	20 kg
BMI 25.8 to 29.6 kg/m ²	> 26 kg	18 kg to 26 kg	18 kg
BMI > 29.6 kg/m ²	> 26 kg	20 kg to 26 kg	20 kg
<i>Physical activity</i>			
Days walked in prior 2 weeks	14 days	6 to 13 days	0 to 5 days
<i>Unintentional weight change</i>			
Self report	No weight change	Weight gain	Weight loss
<i>Fatigue</i>			
Sum of scores for questions on effort and exhaustion	Rarely or none	Some or little	Moderate or more

Abbreviations: BMI, body mass index. cm, centimeters. kg, kilograms. m, meters. SAVE, Scale of Aging Vigor in Epidemiology. sec, second.

Table 2

Demographic and disease characteristics of Long Life Family Study participants

	Overall (<i>n</i> = 3599)	Probands (<i>n</i> = 1479)	Offspring (<i>n</i> = 2120)
SAVE scale, mean, (sd)	4.2 (2.2)	5.5 (1.9)	3.3 (1.9)
Age, years, minimum-maximum	32–105	49–105	32–88
Age, years, mean (sd)	72.3 (16.1)	89.3 (6.7)	60.5 (8.3)
Male, <i>n</i> (%)	1570 (43.6)	673 (45.5)	897 (42.3)
Ever smoke, <i>n</i> (%)	1520 (42.3)	560 (37.9)	960 (45.3)
BMI, kg/m ² , mean (sd)	27.0 (4.8)	26.1 (4.2)	27.6 (5.1)
Education less than college, <i>n</i> (%)	2011 (55.9)	1077 (72.9)	934 (44.1)
Coronary heart disease, <i>n</i> (%)	351 (9.8)	269 (18.2)	82 (3.9)
Cerebrovascular disease, <i>n</i> (%)	112 (3.1)	81 (5.5)	31 (1.5)
Diabetes, <i>n</i> (%)	252 (7.7)	134 (9.5)	118 (6.4)
Pulmonary disease, <i>n</i> (%)	455 (12.6)	173 (11.7)	282 (13.3)
Kidney disease, <i>n</i> (%)	77 (2.1)	46 (3.1)	31 (1.5)
Osteoarthritis, <i>n</i> (%)	1174 (32.7)	643 (43.7)	531 (25.1)
Depression, <i>n</i> (%)	578 (16.1)	177 (12.0)	401 (18.9)

Abbreviations: BMI, body mass index. SAVE, Scale of Aging Vigor in Epidemiology.

Table 3

Association of the Scale of Aging Vigor in Epidemiology with mortality in the Long Life Family Study

SAVE score category	Events per 1000 pyrs	HR (95% CI) Unadjusted	HR (95% CI) Age, Sex	HR (95% CI) Multivariate*
HR per unit of index	–	1.24 (1.19, 1.29)	1.17 (1.12, 1.23)	1.18 (1.13, 1.24)
HR per category of index				
0–2	36.8	1.00	1.00	1.00
3–4	76.9	2.20 (1.24, 3.89)	1.61 (0.90, 2.87)	1.49 (0.77, 2.90)
5–6	126.6	3.80 (2.17, 6.64)	2.67 (1.47, 4.84)	2.83 (1.46, 5.51)
7–10	172.3	5.28 (3.00, 9.28)	3.28 (1.82, 5.91)	3.40 (1.72, 6.71)

Abbreviations: CI = confidence interval; HR = Hazard ratio; pyrs = person years; SAVE, Scale of Aging Vigor in Epidemiology

* Adjusted for age, sex, smoking, BMI, education, coronary heart disease, cerebrovascular disease, diabetes, pulmonary disease, kidney disease, osteoarthritis, depression