

Research Article

Genetic and Environmental Influences on Longitudinal Frailty Trajectories From Adulthood into Old Age

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Received: May 7, 2022; Editorial Decision Date: September 14, 2022

Decision Editor: Lewis A. Lipsitz, MD, FGSA

Abstract

Background: Frailty is a complex, dynamic geriatric condition, but limited evidence has shown how genes and environment may contribute to its longitudinal changes. We sought to investigate sources of individual differences in the longitudinal trajectories of frailty, considering potential selection bias when including a sample of oldest-old twins.

Methods: Data were from 2 Swedish twin cohort studies: a younger cohort comprising 1 842 adults aged 29-96 years followed up to 15 waves, and an older cohort comprising 654 adults aged ≥79 years followed up to 5 waves. Frailty was measured using the frailty index (FI). Age-based latent growth curve models were used to examine longitudinal trajectories, and extended to a biometric analysis to decompose variability into genetic and environmental etiologies.

Results: A bilinear model with an inflection point at age 75 best described the data, indicating a fourfold to fivefold faster FI increase after 75 years. Twins from the older cohort had significantly higher mean FI at baseline but slower rate of increase afterward. FI level at age 75 was moderately heritable in both men (42%) and women (55%). Genetic influences were relatively stable across age for men and increasing for women, although the most salient amplification in FI variability after age 75 was due to individual-specific environmental influences for both men and women; conclusions were largely consistent when excluding the older cohort.

Conclusion: Increased heterogeneity of frailty in late life is mainly attributable to environmental influences, highlighting the importance of targeting environmental risk factors to mitigate frailty in older adults.

Keywords: Deficit accumulation, Latent growth curve, Older adults, Trajectories, Twins

Frailty is a dynamic state of heightened vulnerability to stressors, reflecting age-related multisystem decline (1). Despite the absence of a gold standard (2), one of the most widely adopted operational approaches is the frailty index (FI) (3), which defines frailty as the accumulation of health deficits and captures the heterogeneity of health in people of the same chronological age (4,5). Higher levels of frailty have consistently been shown to predict adverse outcomes such as falls, disabilities, and mortality in both community and hospital settings (6,7). Recent research also supports the predictive ability of

frailty changes, beyond differences in frailty levels at baseline, on mortality (8). While the prevalence of frailty generally increases with age, from ~20% among those ≥ 65 years to over 40% among those \geq 85 years when measured using the FI (9,10), there is sizable heterogeneity in the individual frailty progression (11–13). Understanding determinants of longitudinal changes in frailty, that is, whether individual differences in the level and rate of change are explained by genetic or environmental factors, is essential for designing preventive measures and interventions against frailty.

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Using the fact that monozygotic (MZ) and dizygotic (DZ) twins share on average 100% and ~50% of their segregating alleles, respectively, twin studies by others (14,15) and us (16) have demonstrated that 30%-52% of the variability in FI level is influenced by genetic factors (ie, heritability), and the rest by individual-specific environmental factors. In accordance with the generally higher FI levels in women than in men (17), we also showed previously that women had statistically significantly higher FI heritability than men (52% vs. 45%) (16). Nevertheless, all these results were based on cross-sectional data and were thus unable to account for longitudinal changes. Several studies to date have analyzed the longitudinal trajectories of frailty, although with inconclusive evidence: while some studies revealed an accelerated frailty increase at older compared to younger ages (18-21), others observed similar rate of increase across age (22,23). A growing body of literature has evaluated environmental risk factors for the level and rate of change of frailty. For instance, several sociodemographic (eg, low education), physical (eg, underweight and obesity), psychosocial (eg, low social support), and lifestyle factors (eg, smoking) have been linked to higher frailty scores (24,25). Recent studies also showed that females (18,20), lower socioeconomic position and education (18,20,26,27), deviations from normal weight (21), and lower physical activity (19) may be risk factors for a steeper FI increase. However, how genetic factors may affect frailty longitudinally remains poorly known (13). Moreover, few studies have compared frailty trajectories in a sample of younger versus older adults, where differences may arise not only due to age or cohort effects, but also selection or survival bias in the older participants as they must have survived to a certain age for inclusion in the study (28).

Extending previous research, this study aimed to investigate individual differences in the longitudinal trajectories of frailty across age and sex and to determine how much of the variation is attributable to genetic and environmental influences using the twin study design. As a secondary aim, we examined potential selection bias by evaluating growth processes and their etiologies when including a sample of oldest-old twins.

Method

Study Population

Twin participants were from 2 longitudinal studies, both of which are part of the population-based Swedish Twin Registry (29): the Swedish Adoption/Twin Study of Aging (SATSA) (30), and the Origins of Variance in the Oldest-Old: Octogenarian Twins (OCTO-Twin) (31). SATSA is a longitudinal study of reared together and reared apart same-sex twins, consisting of 9 mailed questionnaires (Q) and 10 in-person testing (IPT) waves between 1984 and 2014. The FI was available in 15 waves between 1987 and 2014, except Q1, IPT1, IPT4, and Q6. All SATSA twins were invited to participate in Q waves, whereas a cohort sequential design was employed for IPT waves where those aged 50 or older were invited to the IPTs, with age-based enrollment occurring through IPT5. Q waves preceded IPT waves by approximately 18 months. Assessment types (Q or IPT) were generally 3 years apart, with a gap after Q4 due to a lapse in funding. Although both members of twin pairs were invited to SATSA, individual participation was welcomed even if a co-twin did not, or could not, participate. Details on sample characteristics and FI correlations across the 15 SATSA waves have been described previously (21). OCTO-Twin is a longitudinal study of the oldest-old twins, consisting of 5 IPT waves at 2-year intervals between 1991

and 2001. A total of 351 same-sex twin pairs (702 individuals) were included; both members in each pair were alive and aged >79 years at baseline. The FI was available in all 5 OCTO-Twin waves (32). Supplementary Figure 1 illustrates the timeline of data collection. This study was approved by the Regional Ethics Review Board in Stockholm (Dnr 2016/1888-31/1). All participants provided informed consent before data collection.

For the current analyses, we excluded observations at particular assessments if missing >20% of the items comprising the FI, yielding a total of 11 597 observations within 2 496 twin individuals (1 842 from SATSA and 654 from OCTO-Twin) who participated in at least one measurement wave. Participants with unknown zygosity (n = 84) were further excluded from the biometric analysis. Twins were categorized into 4 zygosity-by-sex groups: 391 MZ males (164 complete pairs), 505 MZ females (210 complete pairs), 565 samesex DZ males (200 complete pairs), and 951 same-sex DZ females (370 complete pairs).

Frailty Assessment

Using a wide range of self-reported diseases, signs, symptoms, and activities of daily living, we constructed a 42-item FI across the 15 waves for SATSA and a 41-item FI across the 5 waves for OCTO-Twin. The items were similar in both cohorts and were identical across waves (Supplementary Table 1) (32). After excluding observations with >20% missing data across the FI items, we performed imputation to replace missing items in both studies (Supplementary Method 1) (33). Following the deficit accumulation model (3), we computed the FI as a proportion score of the sum of deficits divided by the total number of items (eg, a person having seven deficits out of 42 items would receive an FI of 7/42 = 0.17). The FI ranges from 0 to 1, but we multiplied it by 100 (representing the percentage of deficit accumulated) during model fitting to ease computation.

Statistical Analysis

The analysis consisted of 2 parts: (a) phenotypic models to describe FI trajectories and (b) biometric models to assess genetic and environmental contributions to the individual differences in FI trajectories. Detailed descriptions of the phenotypic and biometric models are provided in Supplementary Methods 2–3.

Raw FI trajectories by study and sex were first plotted for initial inspection of the data. To examine whether the apparent differences between studies may be due to selection bias, we also investigated the raw trajectories of a subsample of SATSA participants aged >75 years and >79 years at baseline. Moreover, all models were performed independently in SATSA and in the full sample (ie, SATSA and OCTO-Twin combined) to explore whether including oldest-old twins from OCTO-Twin, where both twin pair members were required to be alive and eligible for participation at baseline, would change the results.

Phenotypic models

Similar to previous work (21), we modeled FI trajectories using agebased latent growth curve models in the multilevel modeling framework (34), where age was specified in units of the year. This provides estimates of fixed effects (ie, mean trajectory for the sample, represented by an intercept and one or more change parameters), as well as random effects (ie, variation about the mean) on 3 levels: FI measurements (level 1) within individuals (level 2), who were nested within twin pairs (level 3). Unconditional models (ie, without covariates) with different functional forms (linear, quadratic, or bilinear 2-slope) were first fitted to identify the most appropriate shape of FI change over age. A bilinear model with a turning point at age 75 best described the longitudinal FI trajectories (Supplementary Table 2), consisting of an intercept (representing mean FI at 75 years), a slope <75 years ("slope 1," representing mean annual change in FI up to 75 years), and a slope >75 years ("slope 2," representing mean annual change in FI after 75 years). The random effects included variances and covariances of the intercept, slope 1, and slope 2 at individual- and twin pair-levels, and a residual variance (constrained to be equal for each measurement occasion). Subsequently, we tested if adding time-invariant covariates, namely study (OCTO-Twin vs. SATSA, added only when analyzed in full sample) and birth cohort (born ≥1926 vs. <1926), would improve model fit. All fixed and random effects parameters were estimated separately in men and women, except regression coefficients of time-invariant covariates (ie, study and birth cohort effects were constrained to be equal for men and women).

Biometric models

From the best-fitting phenotypic model, we applied twin-based structural equation models to decompose variances and covariances of latent growth parameters into genetic and environmental etiologies: additive genetic (*A*; sum of allelic effects), nonadditive genetic (*D*; dominance), shared environmental (*C*; environment common to twins in a pair), and unique environmental (*E*; individual-specific environment, and measurement error) influences. We compared the goodness of fit of the *ACE*- (ie, model including *A*, *C*, and *E* components), *ADE*-, and *AE*-models, and calculated the expected genetic and environmental variance components across age and sex from the best-fitting model (35). Biometric models were primarily fitted using the Cholesky decomposition method (ie, a constrained principal component analysis ensuring positive definiteness, such that negative variances are not produced). As a sensitivity analysis, we

used an alternative "direct symmetric approach" which allows for negative variances and potentially reduces Type I error (36). Prior to biometric model fitting, we checked the assumptions of equal means and variances across twin order and zygosity via a "constrained saturated model", that is, successively equating means and variances for MZ and DZ twins from an unrestricted growth model. We calculated twin correlations from the fully constrained model of equal means and variances.

R version 4.0.5 was used in all analyses. We fitted phenotypic models using the package *nlme* (version 3.1-152) and biometric models using full-information maximum likelihood estimation in OpenMx (version 2.19.8). Changes in goodness of fit of nested models were assessed by likelihood ratio tests, and the best fit was determined by Akaike information criterion and Bayesian information criterion, where lower values represent better fit (37).

Results

Sample Characteristics

Of the 2 496 twin participants in the full sample, the mean age at baseline was 67.7 years (range 29–98), and 60.4% were women (Table 1). It comprised 1 842 younger and older adults from SATSA (mean age at baseline = 62.1) and 654 oldest-old adults from OCTO-Twin (mean age at baseline = 83.4). In SATSA, 1 008 participants (54.7%) had FI data available at age >75 years, and 330 (17.9%) were >75 years at baseline; all participants in OCTO-Twin aged at least 79 years at baseline. There was a higher proportion of twin participants from complete pairs (ie, whose co-twin also participated) in OCTO-Twin (n = 612; 93.6%) than in SATSA (n = 1 308; 71.0%). The mean FI at baseline was twofold higher in OCTO-Twin than in SATSA (0.209 vs. 0.105; Supplementary Table 3). Participants contributed to a maximum of 15 waves, where 1 324 (71.9%) in SATSA and 393 (60.1%) in OCTO-Twin had at least 3 FI measurements available.

	Studies			
Characteristic	SATSA	OCTO-Twin	Full Sample	
No. of waves	15	5	15	
No. of observations	9 534	2 063	11 597	
No. of individuals	1 842	654	2 496	
No. of FI measurement per individual, median (IQR)	4 (2-7)	3 (2-5)	4 (2-6)	
Women, <i>n</i> (%)	1 074 (58.3)	433 (66.2)	1 507 (60.4)	
Age at baseline*				
Mean (SD)	62.1 (13.8)	83.4 (3.1)	67.7 (15.2)	
Range	29–96	79–98	29-98	
Birth cohort, n (%)				
Born <1926	979 (53.2)	654 (100.0)	1 633 (65.4)	
Born ≥1926	863 (46.9)	0 (0.0)	863 (34.6)	
FI at baseline*				
Mean (SD)	0.105 (0.093)	0.209 (0.104)	0.133 (0.107)	
Median (IQR)	0.080 (0.042-0.143)	0.195 (0.122-0.280)	0.101 (0.049-0.185)	
Range	0-0.631	0.024-0.634	0-0.634	
Zygosity, n (%)				
MZ	617 (33.5)	279 (42.7)	896 (35.9)	
DZ	1 141 (61.9)	375 (57.3)	1 516 (60.7)	
Unknown	84 (4.6)	0 (0.0)	84 (3.4)	
No. of complete MZ/DZ pairs	242/396	132/174	374/570	

Notes: Full sample represents the SATSA and OCTO-Twin combined data. FI = frailty index; SD = standard deviation; IQR = interquartile range; MZ = mono-zygotic twins; DZ = dizygotic twins; SATSA = Swedish Adoption/Twin Study of Aging; OCTO-Twin = Origins of Variance in the Oldest-Old: Octogenarian Twins. *Baseline was defined as when the frailty index was first assessed.

Figure 1. Raw trajectories for the frailty index in the full sample (n = 2 496), stratified by (**A**) study and (**B**) sex. The thick colored lines represent the loess-fitted smoothing curves in each subgroup (not assuming withinindividual dependency in the observations). Of the 1 842 SATSA participants, 1 008 participants (2 866 observations) had Fl data after 75 years, and 330 participants (719 observations) were >75 years at baseline. All the 654 OCTO-Twin participants (2 063 observations) were >79 years at baseline. SATSA = Swedish Adoption/Twin Study of Aqinq; OCTO-Twin = Origins of

Variance in the Oldest-Old: Octogenarian Twins; FI = frailty index.

As shown in the smoothed curves of raw trajectories, the FI in SATSA increased with age and the rate of change appeared to be quicker after age 75; however, the FI had a less prominent increase with age in older adults from OCTO-Twin (Figure 1A). Women appeared to have higher FI than men at most ages (Figure 1B). When limiting to only those aged >75 years at baseline, the smoothed curves in both studies were more comparable and were relatively flat in the rate of increase (Supplementary Figure 2). In the older SATSA participants, single respondents tended to have a steeper FI increase than twins from complete pairs (Supplementary Figure 2B and D). We also observed a similar mean FI of 0.193 among 191 SATSA participants who were aged >79 years, compared to that of 0.209 among OCTO-Twin participants.

Phenotypic Analysis

Table 2 displays the estimated fixed and random effects from the bestfitting phenotypic model (ie, bilinear growth model with intercept at age 75). In SATSA, the mean FI, on the original proportion scale, was higher in women (0.127) than in men (0.105) at age 75. Slope rates in women and men increased fourfold to fivefold, from 0.0021 and 0.0014 before 75 years (corresponds to 0.9 and 0.6 deficits accrued in 10 years), to 0.0085 and 0.0076 after 75 years (corresponds to 3.6 and 3.2 deficits accrued in 10 years), respectively. "Study" was added as a covariate to the model in full sample, indicating that OCTO-Twin participants, compared to SATSA participants, had on average 0.0817 higher FI at age 75 (corresponding to 3.4 more deficits) and 0.0069 lower rate of FI increase after 75 years (corresponding to 2.9 fewer deficits accrued in 10 years). Adding "birth cohort" to the model did not improve fit (Supplementary Table 2). Variances of the intercept were noticeably larger than that of the slopes at both individual- and twin pair-level (Table 2), suggesting that variations in the mean FI trajectory were mostly carried by the intercept. The larger variance in slope 2 than slope 1 also indicated greater individual differences in the rate of increase after age 75.

In SATSA, intraclass (within-twin pair) correlations for the intercept were moderate in both women (0.36) and men (0.29), whereas slope 1 was more correlated in women than in men (0.29 vs. 0.04); these estimates were largely similar in the full sample (Table 2). Nevertheless, intraclass correlations for slope 2 were lower in the full sample (men = 0.09; women = 0.14) than in SATSA (men = 0.20; women = 0.27), indicating that older twins from OCTO-Twin were less alike in their rates of change in FI. Additionally, we calculated intraclass correlations within zygosity-by-sex groups using twinbased structural equation models (Supplementary Table 4) and found larger MZ than DZ correlations for the intercept, implying genetic influence on FI level at age 75. Intraclass correlations for slopes were also mostly higher in MZ than DZ twins; however, most of them were not statistically significant, possibly due to the small variances in rates of change.

Biometric Analysis

Next, a series of biometric models were fitted to analyze genetic and environmental sources of the variability in intercept and slopes of the growth model (Supplementary Table 5). The best fit was an AEmodel, representing additive genetic and unique environmental influences (Figure 2). From this model, the FI heritability in the full sample at age 75 was higher in women (55%) than in men (42%); similar estimates were found in SATSA (Supplementary Table 6). Likewise, slope 1 was more heritable in women (45%) than in men (3%) in both the full sample and SATSA. Heritability of slope 2 was, however, lower in full sample (men = 26%; women = 18%) than in SATSA (men = 28%; women = 36%). We observed strong additive genetic and unique environmental correlations between intercept and slope 1 (0.74 to 0.90 in SATSA; 0.79 to 0.97 in full sample), but small-to-moderate correlations between intercept and slope 2, and between slope 1 and slope 2 (all ranging from -0.56 to 0.35; Supplementary Table 5).

Of note, variance component estimates of growth parameters depend on the centering age (ie, estimates would differ if the intercept was set differently). Hence, we estimated the overall changes in variance components over age, which is more informative of the relative importance of genes and environment on FI trajectories. In the full sample, there was a noticeable increase in total FI variance after age 75 (Figure 3), suggesting that although the intercept variance, as shown in the phenotypic analysis, had the largest impact on the FI trajectory compared to the slope variance, covariance between the intercept and the slope also contributed to a change in the overall variance.



Table 2. Parameter Estimates From the Best-Fitting Phenotypic Mod	el in SATSA and in the Full Sample
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	SATSA (<i>n</i> = 1 842)		Full Sample (<i>n</i> = 2 496)	
	Men	Women	Men	Women
Fixed effects (means)				
Intercept at 75 years	10.46*	12.65*	10.38*	12.88*
OCTO-Twin (ref. SATSA)*	_		8.	17*
Slope 1 (<75 years)	0.14*	0.21*	0.14*	0.22*
Slope 2 (>75 years)	0.76*	0.85*	0.75*	0.78*
OCTO-Twin (ref. SATSA) [†]	_		-0.69*	
Random effects (variances and correlations)				
Level 1: observations				
Residual variance	13.46	16.07	15.11	17.57
Level 2: individual level				
Variance of intercept	34.12	55.29	38.16	63.68
Variance of slope 1	0.03	0.04	0.03	0.04
Variance of slope 2	0.63	0.49	0.60	0.54
Correlation between intercept and slope 1	0.70	0.86	0.67	0.86
Correlation between intercept and slope 2	0.05	0.004	-0.57	-0.38
Correlation between slope 1 and slope 2	0.08	0.17	-0.29	-0.03
Level 3: twin pair level				
Variance of intercept	13.83	30.50	16.17	34.87
Variance of slope 1	0.001	0.01	0.001	0.02
Variance of slope 2	0.16	0.18	0.06	0.09
Correlation between intercept and slope 1	0.32	0.83	0.76	0.90
Correlation between intercept and slope 2	0.03	-0.21	-0.17	-0.38
Correlation between slope 1 and slope 2	0.38	-0.18	-0.08	-0.22
Intraclass (twin) correlations ^{††}				
Intercept at 75 years	0.29	0.36	0.30	0.35
Slope 1 (<75 years)	0.04	0.29	0.03	0.30
Slope 2 (>75 years)	0.20	0.27	0.09	0.14

Notes: The best-fitting model was a bilinear 2-slope latent growth curve model with an inflection point (intercept) at age 75. Slope 1 represents change of the frailty index until age 75, and slope 2 represents change of the frailty index from age 75 onwards. Goodness of fit of models is shown in Supplementary Table 2. The frailty index used in the models was multiplied by 100 (as a percentage of deficit from 0% to 100%) to ease calculation. All parameters were estimated separately for men and women, except for the effect of study on the intercept and slope 2. The full sample represents the SATSA and OCTO-Twin combined data. SATSA = Swedish Adoption/Twin Study of Aging; OCTO-Twin = Origins of Variance in the Oldest-Old: Octogenarian Twins.

*Study (OCTO-Twin vs. SATSA) was added as a time-invariant covariate to the intercept and slope 2. It was not added as a covariate to slope 1 because OCTO-Twin data were only available for individuals aged >79 years. Regression coefficients were assumed to be equal in men and women.

[†]Fixed effects parameters with p < .05.

^{††}Intraclass correlations indicate the extent to which the intercept, slope 1, and slope 2 correlate within twin pairs; they were calculated by the variances at twinpair-level divided by the sum of variances in individual- and twin-pair-levels. Intraclass correlations by zygosity are presented in Supplementary Table 4.

We observed an increasing unique environmental influence relative to the heritable variance of the FI over age, with slightly different patterns in each sex (Figure 3). In men, the genetic variance was similar in size across age, while unique environmental variance had a sharp increase after 75 years. By contrast, both genetic and unique environmental variances increased with age in women, but the magnitude of increase was larger for the latter at old age. Residual variance (ie, unreliable variance not accounted for by the model) was relatively small across age and sex, reflecting that the growth model was adequate in capturing systematic age-related variations of frailty trajectories. As shown in Supplementary Figure 3, despite an apparently greater genetic variance after age 75 in SATSA, the overall trend of increasing relative importance of environmental factors was similar in the full sample and SATSA. In sensitivity analysis, we obtained largely consistent results when applying another model fitting approach that allows for negative variances (Supplementary Figures 4-5).

Discussion

In this longitudinal analysis of 2 496 twins followed up to 27 years, we assessed FI trajectories across age and sex and explored genetic and environmental influences on the individual trajectories. After age 75, there was, on average, a fourfold to fivefold higher rate of FI increase and a greater variability of the FI. In both men and women, the increasing variability in late life was primarily attributable to the magnified individual-specific environmental influences, while genetic influences were rather stable across age for men and increasing for women. When including an older sample of twins who were enrolled after age 79, we noticed possible selection bias in which they tended to have higher FI levels but a less steep increase, although the overall conclusion on how genes and environment affect frailty trajectories was essentially unchanged.

Frailty, as measured by the FI, has been considered as a systemic measure of biological aging which quantifies deficit accumulation, or vulnerability to stressors, during aging (4). Although deficits accumulate with age, there has been inconclusive evidence on its rate of increase with regards to age and sex (13). Prior research studying FI trajectories from middle adulthood (~age 50) onwards usually observed nonlinear or quadratic growth (18–20), while others from age 65 onwards mostly reported linear progression (22,23). Adding to the literature, we included a sample with a wide age range from 29 to 98 years and showed that the rate of FI increase was higher



Figure 2. Best-fitting biometric model and heritability estimates in the full sample. The full sample represents the SATSA, and OCTO-Twin combined data. For simplicity, only 1 twin is shown (path diagram for the co-twin is identical). The growth model consists of 3 latent (circles) factors: intercept at 75 years, slope <75 years ("slope 1"), and slope >75 years ("slope 2"). The upper half of the diagram shows the biometric decomposition of variation about the intercept, slope 1, and slope 2. A indicates additive genetic factors; E indicates unique environmental factors; $h_{\rm M}^{2}$ and $h_{\rm F}^{2}$ are the estimated proportion of variance due to additive genetic factors (heritability) in men and women, respectively; e_{M}^{2} and e_{F}^{2} are the estimated proportions of variance due to unique environmental factors in men and women, respectively. Double-headed arrows indicate additive genetic and unique environmental correlations (estimates shown in Supplementary Table 5). The lower half of the diagram shows the phenotypic model. B_{S11} to B_{S115} and B_{S21} to B_{S215} represent the age-based coefficient of slope 1 and slope 2, respectively. Fl, to Fl_{15} represents the measured (squares) variables of the frailty index. ϵ_0 to $\epsilon_{\rm 15}$ represent residual errors, and $\sigma_{\rm res}^{-2}$ represents residual variance (ie, variation not accounted for by the growth model). M₁, M_{S1}, and M_{S2} represent the mean intercept, mean slope 1, and mean slope 2, respectively. β_{etudul} and $\beta_{study.S1}$ represent the regression coefficients of the study (ie, OCTO-Twin vs. SATSA) on intercept and slope 2, respectively. SATSA = Swedish Adoption/ Twin Study of Aging; OCTO-Twin = Origins of Variance in the Oldest-Old: Octogenarian Twins: FI = frailty index.

after age 75, suggesting that discrepancies in previous studies may be partly due to the different age of participants included. Moreover, we observed both higher levels and rate of change of FI in women than in men. Our annual rates of FI increase were also comparable to that in a recent research of older adults aged ≥ 65 (23). Considering 0.03 as a clinically meaningful change in FI (38), our results may indicate that while it could take up to 14 years in women and 21 years in men to reach a significant FI increase before age 75, such accumulations emerge as soon as 3.5 and 4 years after age 75, hence highlighting the importance of frequent monitoring of frailty levels in older adults. Interestingly, a previous study using the same data from SATSA identified an earlier turning point at age 65 from the best-fitting bilinear model, probably due to the log-transformed FI used in that study (21). Despite a positively skewed distribution, we



Figure 3. Expected changes in the variance of the frailty index (FI) with age in the full sample, stratified by sex. The full sample represents the SATSA and OCTO-Twin combined data. Estimates were obtained from the best-fitting biometric growth model, that is, *AE*-bilinear growth model with an intercept at 75 years. *A* and *E* represent the genetic variance and unique environmental variance, respectively; residual represents the variance that is not accounted for by the growth model and was kept constant with age. The first row shows the estimated changes in genetic, unique environmental, and residual variance components over age in men and women. The second row shows the total variance at each age attributable to the genetic and environmental variance components and residual in men and women. SATSA = Swedish Adoption/Twin Study of Aging; OCTO-Twin = Origins of Variance in the Oldest-Old: Octogenarian Twins.

used the nontransformed FI in our analysis for easier interpretation, and the skewed FI did not seem to affect heritability estimates (16).

In line with previous studies (21,23,27,39), we observed both intra- and interindividual variability in the FI trajectories. Some studies have identified environmental factors that may contribute to the heterogeneity in frailty trajectories (13), yet there is limited evidence on the effects of genetic factors, and how these influences may vary across age. To the best of our knowledge, this is the first study that has investigated genetic and environmental sources of the variability in longitudinal frailty trajectories. We found that FI level at age 75 was moderately heritable, with a higher estimate in women (55%) than in men (42%), which corroborates the age-adjusted FI heritability reported in earlier cross-sectional data (women = 52%, men = 45%) (16). The rate of change in FI, however, was more influenced by individual-specific environmental than genetic factors, leading to an overall amplified environmental influence relative to the importance of heritable effects at old ages. Genetic variance doubled across age for women, as compared to the fourfold increase in environmental variance. One reason for the increasing environmental influence of age could be the increasing prevalence of comorbidities or disabilities in old age as a result of an inability to maintain homeostasis when facing stressors. Moreover, any unaccounted-for geneenvironment interaction (ie, increased or decreased genetic sensitivity to certain environmental conditions) may lead to an inflation of individual-specific environment estimates (40,41). In particular, overweight and obesity may affect the rate of FI increase in late life (21), and genetic influence on FI tends to increase at both low and high body mass index levels (16). Also, epigenetic differences in old age may lead to dissimilarities in FI levels among MZ twins (42). Notably, we observed only small-to-moderate genetic and individual-specific

environmental correlations of slope 2 with the intercept and slope 1, thus giving some indications that the genetic and environmental factors in late life may be somewhat different from those in early adulthood. It is also noteworthy that our heritability estimates were based on systematic variance (ie, corrected for unreliability). Residual variance captured in the models, albeit small in magnitude, may represent random noise and measurement error, as well as fluctuations in individuals' health status due to short-term injuries and infections (39). Previous interventional studies have shown that frailty is potentially reversible with exercise engagement and nutritional supplementation (43), while observational studies generally reported that low socioeconomic status, physical comorbidities, and brain pathology are risk factors for frailty progression (13). To prevent or reduce frailty, it would be crucial for future studies to identify the specific genetic, epigenetic, and the most important environmental risk factors acting on frailty trajectories, and to understand whether these factors may differ for younger versus older adults (44).

Notwithstanding a generally accelerating FI increase with age, oldest-old adults from OCTO-Twin had higher (extrapolated) FI levels at age 75 and lower rate of FI increase compared to SATSA participants of the same age who were followed from early adulthood. Several studies have assessed cohort effects on FI trajectories, consistently observing lower age-specific FI levels in earlier compared to more recent birth cohorts but with mixed results regarding the rate of FI increase (18,20,26,45). On the contrary, we found a higher FI in OCTO-Twin participants who were from an earlier birth cohort born <1926, and that adding the "birth cohort" indicator in addition to "study" did not improve model fit. We, therefore, speculate that while the study may have broadly captured some cohort effects, selection bias may be the main contributor to these differences. In OCTO-Twin, participants who had survived into old age before cohort entry may be a selected group of "healthiest" individuals, in terms of a low rate of deficit accumulation. While the level of frailty, compared to the rate of increase, is generally a stronger indicator of poor health and mortality in younger adults (32), in older survivors who have already accumulated a large number of deficits, any additional deficit could be lethal and thus the rate of frailty increase becomes more reflective of terminal health decline (46-48). In support of our speculations, we observed a mean FI of 0.193 among SATSA participants who were aged >79 years at baseline, which was on par with that of 0.209 among OCTO-Twin participants of the same age. These older SATSA participants similarly had a slow FI increase, particularly in single responders than those twins from complete pairs. Although OCTO-Twin participants were similar in their health status and functioning to nontwins of the same age (49), we could suspect a lower rate of deficit accumulation (ie, representing better health) in these oldest-old participants whose co-twin were also alive at baseline than the general population.

The current analysis included two samples of younger and older Swedish twins with a long follow-up time, enabling us to model frailty changes from early adulthood to the oldest ages. The use of age-based latent growth curve models in combination with biometric analysis also maximized power and allowed the quantification of genetic and environmental influences. Nevertheless, our results should be interpreted with caution. First, the FI in both studies were constructed based on self-reported data, like most FI studies, conceivably causing misclassification. Second, attrition in SATSA may have led to increasingly selected samples of younger and healthier individuals should there be nonrandom dropouts, and it has been shown that those who dropped out from SATSA were more likely to be older, smokers, more frail, less physically active, and obese (21). However, using a full-information maximum likelihood approach is beneficial to address missing data that stems from attrition. Third, small variances about the slopes affected the model stability and thereby leading to nonsignificant twin correlations for the slopes. However, our focus was on the overall variance changes rather than etiologies of growth parameters that are tied to the choice of centering age. Finally, twin analysis relies on the assumptions of random mating and that environments for MZ twins are not more similar than DZ twins (ie, equal environment), although violation of these assumptions appear to have minimal impact on the validity of results (50).

In summary, the rate of frailty progression and individual differences in frailty trajectories increases significantly with age, especially after age 75. There was a relatively stable genetic influence on frailty across age for men and a doubling of genetic variance for women, but the most salient amplification was due to environmental influences in late life for both men and women, with similar conclusions even when including a selected sample of oldest-old adults. These findings provide the basis for future investigations on the specific genetic and environmental factors influencing frailty trajectories and suggest that targeting environmental risk factors may be important for preventing or reducing frailty in older adults.

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 Swedish Research Council (2018-02077, 2019-01272, 2020-06101), the Loo & Hans Osterman Foundation, FORTE (the Swedish Research Council for Health, Working Life, and Welfare), the Strategic Research Program in Epidemiology at Karolinska Institutet, the Karolinska Institutet Foundations, the Svenska Sällskapet för Medicinsk Forskning, and the King Gustaf V and Queen Victoria's Foundation of Freemasons.

Conflict of Interest

None declared.

Acknowledgments

We acknowledge the Swedish Twin Registry for access to data. The Swedish Twin Registry is managed by Karolinska Institutet and receives funding through the Swedish Research Council under the grant number 2017-00641. This study was accomplished within the context of the Swedish National Graduate School on Ageing and Health (SWEAH).

Author Contributions

J.K.L.M, R.K.-H., S.H., J.J., and C.A.R. contributed to the study design and statistical analysis plan. J.K.L.M., G.B., and C.A.R. performed statistical analyses. N.L.P. is the founder and principal investigator of the SATSA study. L.B.H. is the leader of the OCTO-Twin study. J.K.L.M. and C.A.R. wrote the manuscript. All authors contributed to interpretation of the results and read and approved the final manuscript.

Availability of Data and Materials

Analysis codes are provided at the Open Science Framework platform (https://osf.io/xvm5r/?view_only=10dcd2efdb3a48728391d169e67dd112).

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