

Research Article

Drivers of Frailty from Adulthood into Old Age: Results from a 27-Year Longitudinal Population-Based Study in Sweden

Emma Raymond, MSc,¹ Chandra A. Reynolds, PhD,² Anna K. Dahl Aslan, PhD,^{1,3} Deborah Finkel, PhD,^{3,4} Malin Ericsson, PhD,^{1,6} Sara Hägg, PhD,^{1,6} Nancy L. Pedersen, PhD,¹ and Juulia Jylhävä, PhD^{1,*}

¹Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. ²Department of Psychology, the University of California at Riverside. ³Institute of Gerontology and Aging Research Network – Jönköping (ARN-J), School of Health and Welfare, Jönköping University, Sweden. ⁴Department of Psychology, Indiana University Southeast, New Albany.

*Address correspondence to: Juulia Jylhävä, PhD, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels väg 12A, 17165 Stockholm, Sweden. E-mail: juulia.jylhava@ki.se

Received: November 12, 2019; Editorial Decision Date: April 20, 2020

Decision Editor: Anne Newman, MD, MPH

Abstract

Background: Frailty is a strong predictor of adverse outcomes. However, longitudinal drivers of frailty are not well understood. This study aimed at investigating the longitudinal trajectories of a frailty index (FI) from adulthood to late life and identifying the factors associated with the level and rate of change in FI.

Methods: An age-based latent growth curve analysis was performed in the Swedish Adoption/Twin Study of Aging ($N = 1,842$; aged 29–102 years) using data from up to 15 measurement waves across 27 years. A 42-item FI was used to measure frailty at each wave.

Results: A bilinear, two-slope model with a turning point at age 65 best described the age-related change in FI, showing that the increase in frailty was more than twice as fast after age 65. Underweight, obesity, female sex, overweight, being separated from one's co-twin during childhood, smoking, poor social support, and low physical activity were associated with a higher FI at age 65, with underweight having the largest effect size. When tested as time-varying covariates, underweight and higher social support were associated with a steeper increase in FI before age 65, whereas overweight and obesity were associated with less steep increase in FI after age 65.

Conclusions: Factors associated with the level and rate of change in frailty are largely actionable and could provide targets for intervention. As deviations from normal weight showed the strongest associations with frailty, future public health programs could benefit from monitoring of individuals with abnormal BMI, especially those who are underweight.

Keywords: Deficit accumulation, Latent growth curve, Trajectories, Longitudinal

Frailty is an age-related condition of sizeable public health importance. It is characterized by increased vulnerability to multiple adverse outcomes, such as disability, hospitalization, and mortality (1). The importance of increased screening and timely identification of the risk factors among community-dwelling adults has been stressed by recent research (2) and several midlife risk factors, such as low physical activity (3), sedentary life style (4), and obesity (5) have been identified as risk factors of frailty in old age. A wealth of research has also been devoted to understanding the population tra-

jectories of frailty, and studies are in good agreement with elevated trajectories with age (6,7). Some studies have also identified distinct frailty trajectories over age, that is, clusters of individuals that follow a similar growth pattern (8–10). Low education has been associated with likelihood of being in the high frailty trajectory (8,10) and associate with a steeper rate of change in frailty (11). However, studies assessing the factors that influence changes in frailty over a long period of time (decades) and use multiple, repeated measurements in both frailty and the risk factors are lacking. Such studies are never-

theless instrumental in identifying the determinants of frailty trajectories as early as possible to be able to target the driving forces. Moreover, as recent research by others (12) and us (13–15) suggests that an increase in frailty exhibits a relatively greater mortality risk in younger and middle-aged adults than in old individuals, it is pertinent to include also younger adults in these studies.

There are several approaches to assess frailty, the Fried frailty phenotype (FP) (16), and the frailty index (FI) developed by Rockwood and colleagues (17) being the most frequently used ones. The FP views frailty as a physical syndrome and categorizes individuals as robust, prefrail, and frail based on exhaustion, weight loss, weak grip strength, slow walking speed, and low energy expenditure. The FI is a continuous scale measure that can be constructed from various health-related items, including a minimum of 30 variables that meet the standard criteria (17). Provided that a range of different health domains are included, the FI captures the multidimensional nature of frailty. While both measures predict adverse aging outcomes (18,19), the FI is more sensitive in identifying risks at the lower (healthier) end of the frailty continuum (20,21), and thus is better suited for younger adults.

In the present study, we aimed to add to the understanding of the longitudinal development of frailty and the factors associated with the level and rate of change in FI with a up to 27 years follow-up and 15 waves of repeated measurements in the Swedish Adoption/Twin Study of Aging (SATSA; age range 29–103 years at enrolment). As the development of frailty is a highly multifactorial process and often occurs over a longer period of time and, covariates across various domains were considered and simultaneous changes in the key factors associated with frailty were accounted for. Availability of repeated measurements of frailty and the covariates allowed us to obtain more accurate estimates on the associations between the level and changes in frailty and its risk factors across adulthood and old age.

Methods

Sample

SATSA is a longitudinal program in gerontological genetics (22). The participants are same-sexed twins, where some twin pairs have been reared together and some separated before age 11 and reared apart. SATSA was initiated in 1984, ended in 2014 and is comprised of 9 questionnaires (Q) and 10 in-person testing (IPT) waves. Data collection periods are presented in the [Supplementary Figure 1](#). New participants in IPT waves were enrolled up until IPT5 and only individuals who were aged 50 and older were invited to the IPTs. SATSA data collection, sampling procedures, and the data sets until the seventh Q and seventh IPT have been previously described and are publicly available (23). The present study includes data from 1987 to 2014, from all Q and IPT waves except Q1, IPT1, IPT4, and Q6 (from which an FI could not be constructed), yielding 15 measurement waves. In total, 1,842 individuals (1,074 women, 768 men; 654 complete twin pairs) participated. The number of waves the individuals participated in ranged between one and 15 (mean 5.2, standard deviation [SD] 4.0), where 1,324 individuals (71.9%) participated in three or more waves and 523 (28.4%) participated in seven or more waves. As with all longitudinal samples, attrition occurred in SATSA; assessment of attrition in the present sample is described in the [Supplementary Methods and Results](#).

Study Variables

A Rockwood-based FI has previously been created and validated for SATSA (14), and contains 42 self-reported health deficits such

as diseases, symptoms, mood, and activities in daily living identically constructed across the 15 waves. The FI variables and their scoring are presented in the [Supplementary Table S1](#). The deficits across the items were scored and the FI was defined as the sum of deficits divided by the number of deficits considered. For example, an individual having eight deficits had an FI of $8/42 = 0.19$. Although the theoretical maximum of the FI is 1, over 99% of individuals in almost every study cohort have an FI < 0.7, indicating that accumulation of deficits beyond this point is lethal (24).

Sex was coded as 0 = female and 1 = male. The birth cohort was coded as 0 = born prior 1926 and 1 = born 1926 or later, reflecting the division of the old and the middle cohort in the Swedish Twin Registry (STR) (25). Rearing status was coded as 0 = reared apart before age 11 (reference) and 1 = reared together. Educational attainment and childhood social class were derived from the first questionnaire in 1984 and the STR. Educational attainment was coded as 0 = basic education (<7 years; reference) and 1 = higher education (≥ 7 years). Childhood social class, based on self-reported parental occupation for the rearing parents, was coded as 0 = unskilled manual employees, 1 = skilled manual workers, lower nonmanual employees, and farmers, 2 = self-employed (excluding professionals), 3 = intermediate nonmanual workers, and 4 = higher nonmanual workers, including professionals (26). Information about smoking and partner status were derived from the first measurement occasion at which an FI was obtained. Smoking status was coded as 0 = nonsmoker, 1 = former smoker, and 2 = current smoker, and treated as ordinal in the analysis. Partner status, which included both marital and nonmarital spouse, was coded as 0 = no partner (reference) and 1 = has partner. Information about body mass index (BMI) was collected at each measurement occasion, calculated as self-reported weight divided by height squared (kg/m^2), and categorized as follows: 0 = normal weight ($18.5 \leq \text{BMI} < 25.0$; reference category), 1 = underweight ($\text{BMI} < 18.5$), 2 = overweight ($25.0 \leq \text{BMI} < 30.0$), and 3 = obese ($\text{BMI} \geq 30.0$). Social support, which was available in Q2, IPT2, Q3, Q4, Q5, Q7, Q8, and Q9, was a standardized continuous score (min -26.8 , max 20.6) containing information about the participant's relationships to friends and relatives (27). A negative score indicated low social support, while a positive score indicated high social support. Leisure time physical activity, available in IPT3, Q4, Q5, Q7, Q8, and Q9, was a standardized, continuous score (min 31.4 , max 72.4) in which a higher value corresponded to higher physical activity (28). Alcohol consumption was available in Q2, Q3, and IPTQ2 and assessed as the sum of the quantity in grams of beer, wine, and liquor per month and per relative weight and then transformed to log scores. As this variable was available in 1,235/1,842 (67%) participants, we considered alcohol consumption as a sensitivity analysis where the baseline value, that is, each individual's first available measure was used.

Statistical Analysis

An age-based latent growth curve model (LGM) was used to assess the longitudinal trajectories in the FI and to identify the determinants for the level and the rate of change in the FI. In LGM, each observation (FI measurement) is a function of a latent intercept, one or several latent slope(s) and random error. The model estimates both a mean trajectory for the entire sample (fixed effects) as well as intra- and interindividual variation around this trajectory (random effects). In this study, variation around the mean trajectory was estimated on three levels. Level 1 constituted the observations. Level 2 and 3 constituted the participants and the twin pairs, respectively. Due to convergence issues, however, we omitted the random slopes for

level 3 (twin pairs) and only included a random intercept for level 3. Detailed description of the LGM is provided in the [Supplementary Methods and Figure 2](#)). Correlations between the FI values across waves were analyzed using Spearman's rho.

The raw FI trajectory plots were produced in RStudio (R v.3.4.1; RStudio Inc., Boston, MA) using *ggplot2* (29) (v.3.1.0). To identify the best-fitting functional form (linear, quadratic, or bilinear two-slope) to model the change in the FI, age-based unconditional growth curve models were performed in Stata v.15.1 (StataCorp LP, College Station, TX) using the *xtmixed* command. Best fit was assessed by Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values, where smaller fit statistics indicate better fit.

Sex, birth cohort, rearing status, educational attainment, smoking, alcohol consumption, childhood social class, partner status, BMI categories, social support, and physical activity were tested for their associations with the intercept and the rate of change, which was assessed using a bilinear trajectory with two slopes (see Results). A sensitivity analysis on rearing status was performed to assess whether the degree of relatedness, based on the relationship of the rearing individuals to the twin, is associated with the FI. Information on the degree of relatedness to rearing individuals was available for 1,546/1,842 individuals (83.9%) of whom 935 were in pairs who were reared together, 173 were reared by biological parents (while the co-twin was adopted away), 148 were adopted to relatives, and 290 were adopted to nonrelatives. Twins reared together were considered as the reference category.

Social support, physical activity, and BMI categories were available across several waves (see previously) and hence were additionally tested as time-varying covariates ([Supplementary Methods and Supplementary Table S2](#)). In this model, the associations with both the intercept and slopes were tested using the time-varying covariates (social support, physical activity, and BMI categories). Smoking status, childhood social class, social support, and physical activity were centered at their mean so that the modeled intercepts represent the expected value of FI for an average person in the sample. The BMI categories underweight, overweight, and obesity were contrasted to normal weight, as frailty and BMI exhibit a U-shaped association with both high and low BMI increasing the risk of frailty (30,31). In addition, we followed up the described TVC analyses with models that dissociate between-person and within-time effects of the TVCs to evaluate whether the associations of the TVCs are simply a consequence of between individual effects of the covariate or time-based effects of the covariate (see eMethods) (32).

Due to the skewed distribution of the FI (left-skewed, data not shown), natural logarithm (ln) of the FI was used in the LGM. Prior to normalization, a constant of 0.01 was added to all FI values to facilitate the transformation of values $FI = 0$. For graphical visualization of the FI trajectories, lnFI values were back-transformed to the original FI scale. Significance level was set to $\alpha = 0.05$.

Ethics

All participants have given their informed consent. The SATSA study was approved by the Regional Ethics Review Board in Stockholm (Dnr 80:80, 84:61, 86:148, 98:319, 2007/151-31, 2010/657-31/3), 2015/1729-31/5).

Results

[Table 1](#) provides descriptive information about the study sample at the effective baseline (Q2) where the majority ($N = 1,477$; 80.2%) of the analysis sample had data available. Characteristics of the study

sample at each wave are presented in the [Supplementary Table S3](#). Characteristics of the study sample based on the number of waves the individuals participated in are presented in the [Supplementary Table S4](#). In comparison to individuals with less than seven complete waves, participants in seven or more waves tended to be younger and more educated, have higher levels of social support, and were more likely to have a partner compared to those participating only once or twice. These individuals also had a lower FI; hence, our analyses likely underestimated the extent of change with age. A correlation matrix for the FI across the waves is presented in the [Supplementary Table S5](#). Most of the correlations were >0.5 , and ranged from 0.57 to 0.86 between adjacent waves.

Comparison of the fits of the models based of lnFI ([Supplementary Table S6](#)) indicated that a bilinear two-slope model with an inflection point (intercept) at age 65 years provided the best fit to the data. In this model, the first slope (hereafter denoted as slope 1) represents the change in the FI until the age of 65 and the second slope (hereafter denoted as slope 2) represents the change from this age onwards ([Figure 1b](#)). For estimation of the bilinear trajectory, the model used individuals with three or more observations. Individuals with fewer than three data points only contributed to the estimation of the intercept. Thousand three hundred and twenty-four participants (71.9%) participated in at least three waves; thus, they contributed to the estimations of all three latent factors (intercept, slope 1, and slope 2).

A sensitivity analysis for the unconditional growth model using only participants with ≥ 3 FI measurements was performed to test whether the intercept is upward-shifted due to frailer participants (who likely contributed only 1 or 2 observations), which could in turn make the slope estimates lower.

The estimated growth curve models using the bilinear fit are presented in [Table 2](#) (only fixed effects are shown). The same models including the random effects are presented in the [Supplementary Table S7](#). The unconditional (unadjusted) growth model demonstrated that the mean level of lnFI at age 65 years (ie, the intercept) is -2.57 (corresponding to $FI = 0.07$ on the untransformed scale) and the yearly increase is 0.014 until the age of 65 years and 0.038 after the age of 65 years ([Table 2](#), Model A). Individual raw trajectories for the untransformed FI by age and the estimated bilinear two-slope model for the FI trajectory are presented in [Figure 1](#). The same trajectories but based on the lnFI are presented in the [Supplementary Figure 3](#). The sensitivity analysis for the unconditional growth model showed that the intercept is slightly higher in the full sample, whereas the slope estimates remain essentially unchanged ([Supplementary Table S7](#), Model A_{SENS}).

In Model B ([Table 2](#)), the following time-invariant covariates (baseline/first available measurement used) were associated with lower levels of frailty at the age 65: male sex, having a partner, higher social support, and higher leisure time physical activity. Being reared apart, underweight, overweight, obese, and smoking were associated with higher levels of FI at age 65. Baseline social support and overweight were also associated with the rate of change; higher social support was associated with a steeper increase in FI before age 65 and overweight was associated with slower increase in FI after age 65. Birth cohort and alcohol consumption were not associated with the FI, and childhood social class and educational attainment were not significant after addition of other covariates; so, they were excluded from the model. In the sensitivity analysis for the degree of relatedness (based on Model B) where rearing status was replaced with the degree of separation, only those who were adopted to nonrelatives had significantly higher FI levels ($\beta = 0.13$, standard error [SE] = 0.049, $p = .009$) compared to those reared

Table 1. Characteristics of the SATSA Participants at Baseline (ie, when the FI was first assessed for each individual)

SATSA N = 1,842	Mean (SD)
Age (years)	62.1 (13.8)
Sex, N (%)	
Females	1074 (58.3)
FI, median (range)	0.08 (0.00–0.63)
Birth cohort, N (%)	
Born 1926 or later	863 (46.9)
BMI	24.7 (3.6)
BMI categories, N (%)	
Normal weight	1,022 (55.5)
Underweight	34 (1.8)
Overweight	24 (33.9)
Obese	139 (7.5)
Childhood social class, N (%)	
Unskilled manual employees	398 (21.6)
Skilled manual workers, lower nonmanual employees and farmers	896 (48.6)
Self-employed (excluding professionals)	100 (5.4)
Intermediate nonmanual workers	133 (7.2)
Higher nonmanual workers (including professionals)	57 (3.1)
Education, N (%)	
Higher (≥ 7 y)	269 (14.6)
Partner status, N (%)	
Has partner	1,205 (65.4)
Physical activity	49.8 (10.1)
Social support	-0.07 (7.5)
Smoking status, N (%)	
Nonsmoker	1,293 (70.2)
Former smoker	105 (5.7)
Current smoker	419 (22.7)
Rearing status, N (%)	
Reared apart	907 (49.2)
Alcohol consumption	3.63 (1.99)

Notes: Values are mean (standard deviation, SD) unless otherwise indicated. FI is defined as the sum of deficits divided by total number of deficits, that is, 42. BMI = body mass index; FI = frailty index,

together. Twins who stayed with their biological parents while their co-twin was adopted away ($\beta = 0.04$, $SE = 0.058$, $p = .5$) and twins who were adopted to relatives ($\beta = 0.08$, $SE = 0.06$, $p = .2$) did not have significantly higher FI levels compared to twins reared together. In Model C that was based on Model B (Table 2), social support, physical activity, and BMI categories were tested simultaneously as time-varying covariates. Variables that were associated with the level of FI in this model were akin to Model B, with the exception that partner status was no longer significant and thus excluded from the model. For the associations with the rate of change in FI, higher social support and underweight were associated with a steeper increase in FI before age 65, whereas overweight and obesity were associated with a less steep increase in slope 2 (Table 2, Model C). Physical activity was not associated with the slopes, so its interaction terms with age were excluded from the model. FI trajectories (with lnFI values back-transformed to the original FI scale) based on this model by time-varying measures on social support and BMI categories are presented in Figure 2. Same trajectories but using the lnFI are presented in the Supplementary Figure 4.

Across all the Models A–C, there was significant interindividual variation in the FI trajectories (Supplement; Random effects in

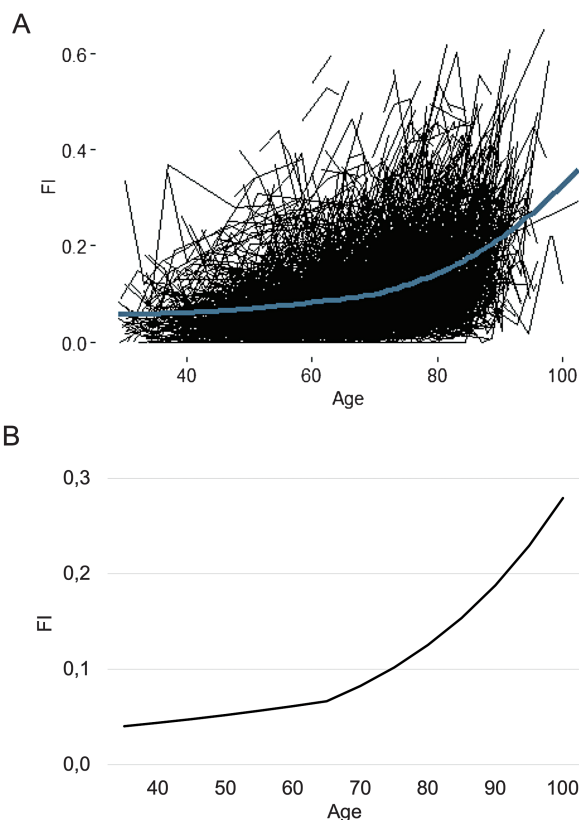


Figure 1. Individual raw trajectories for the frailty index (FI) by age (A) and the estimated population mean FI trajectory from the unconditional bilinear two-slope growth curve model with an inflection point at the age 65 years (B). The blue line in panel A represents a loess-fitted smoothing curve over the data, not assuming within-individual dependency in the observations. Estimates from the unconditional model are based on ln-transformed FI and back-transformed to the original scale to facilitate interpretation (B).

Supplementary Table S7). The positive covariance between intercept and slope 1 and negative one between intercept and slope 2 indicated that individuals having a steeper rate of increase up to the age of 65 years have higher FI levels at the inflection point but after that their rate of increase is relatively decreased. The negative covariance between the two slopes, although not statistically significant in Model C, likewise indicated that those having a less steep increase up to the age of 65 years catch up after that. However, random effects for the slopes between twin pairs (level 3) could not be assessed due to convergence issues, so the models only included a random intercept for between-pair effects (Supplementary Table S7).

Discussion

This study investigated the developmental trajectories and determinants of frailty as measured by the FI over an extended period: from adulthood into very old age. The population trajectory indicated a moderate increase in frailty up to the age of 65 years—an inflection point after which the increase in frailty more than doubled. In a model using baseline measurements for all the covariates, female sex, being reared apart (separated from one's co-twin in childhood), not having a partner, smoking, low physical activity, underweight, overweight, obesity, and poor social support were associated with a higher level of frailty at age 65 (ie, intercept). Higher baseline social

support was also associated with a faster increase in frailty before age 65, reflecting only a catch-up of growth (convergence) though, as higher social support was associated with lower frailty at age 65. Baseline overweight was associated with a slower increase in frailty after age 65. To address simultaneous changes in the covariates and frailty, we extended the model by including time-varying, repeated measurements of social support, physical activity, and BMI categories. In this model, higher social support and underweight were associated with a faster rate of increase in frailty before the age of 65 years, and overweight and obesity were associated with a slower rate of increase in frailty after age 65. The decelerated rates of change in frailty for those who were obese or overweight were large enough to make the frailty cross over the frailty trajectories for normal weight persons after age 85. Physical activity showed no associations with the rate of change, and having a partner was no longer associated with the level of frailty in this model.

Table 2. Latent Growth Curve Models for FI Trajectories Across 27 Years in the SATSA Sample

Association with	Model A	Model B	Model C
Intercept			
Intercept	-2.57 (0.02)*	-2.61 (0.04)*	-2.75 (0.04)*
Sex			
Male		-0.12 (0.04)*	-0.18 (0.04)*
Rearing status			
Reared apart		0.08 (0.04)*	0.10 (0.04)*
Partner status			
Has a partner		0.08 (0.04)*	
Smoking status		0.04 (0.02)*	0.05 (0.02)*
Social support		-0.008 (0.002)*	-0.009 (0.002)*
Physical activity		-0.006 (0.001)*	-0.004 (0.001)*
BMI categories			
Underweight		0.43 (0.16)*	0.56 (0.20)*
Overweight		0.12 (0.04)*	0.21 (0.04)*
Obese		0.21 (0.08)*	0.34 (0.07)*
Association with slope 1 (<65 years)			
Age	0.014 (0.002)*	0.012 (0.002)*	0.010 (0.003)*
Social support		0.0007 (0.0002)*	0.0007 (0.0003)*
BMI categories			
Underweight			0.066 (0.031)*
Overweight			0.005 (0.005)
Obese			0.015 (0.008)
Association with slope 2 (> 65 years)			
Age	0.038 (0.001)*	0.040 (0.002)*	0.042 (0.002)*
BMI categories			
Underweight		-0.0005 (0.014)	-0.005 (0.011)
Overweight		-0.006 (0.003)*	-0.009 (0.004)*
Obese		-0.002 (0.006)	-0.015 (0.006)*

Notes: Model A represents the unconditional growth model. Model B tested the associations of all covariates as time-invariant covariates. Model C tested social support, physical activity and BMI categories as time-varying covariates. Estimates (standard error) are based on an ln-transformed FI. Slope 1 represents age <65 years and slope 2 represents age >65 years. Model A has *n* = 1,842 individuals and *n* = 9,534 observations; Model B has *n* = 1,331 individuals and *n* = 8,401 observations; Model C has 1,361 individuals and 3,025 observations.

^aMean lnFI at the age of 65 years.

**p* < .05.

Frailty has been traditionally regarded as a syndrome of the old, and longitudinal studies into frailty trajectories including younger individuals or covering the entire adult lifespan are scarce. With repeated measurements of frailty up to across 27 years, our study provides new insights into the developmental trajectories of frailty. The fact that we observed a turning point for the frailty trajectory at age 65, after which the rate of change more than doubles, suggests that an effective window for prevention might be well before old age. Our estimates for the level and rate of change after age 65 are comparable to those reported in the Longitudinal Aging Study Amsterdam for individuals aged 65+, where they used lnFI in the modeling akin to us (33). However, comparing our (back-transformed) estimates to those for the Swedish population in the Survey of Health, Ageing and Retirement in Europe (SHARE), suggests somewhat lower estimates in our study (11). The SHARE study modeled the rate of change as a single slope for individuals aged 50 and older, which may partly explain the differences. More studies into frailty trajectories covering the entire adult lifespan are nevertheless needed to resolve whether our findings on the bilinear growth and a tipping point at age 65 are generalizable to other populations.

As factors associated with the level and the rate of change in frailty have rarely been analyzed in longitudinal settings using repeated measurements both on frailty and the covariates, the results of our study add to the understanding of the independent factors associated longitudinally with frailty. Many of the factors that we found to associate with higher levels of frailty, such as female sex, underweight, overweight, obesity, smoking, poor social support, low physical activity, and not having a partner have also been identified in previous studies (30,31,33,34). Some studies have also identified low socioeconomic position and lower education associated with higher FI (11,33). In our study, socioeconomic position and education were however not associated with the level of frailty after inclusion of other covariates, suggesting that other risk factors may override socioeconomic adversity. As a new risk factor for frailty, we identified being separated from one's co-twin in childhood to be associated with higher level of frailty. Sensitivity analysis for the degree of relatedness to rearing individuals indicated that in comparison to twins reared together, only those who were adopted to non-relatives had significantly higher levels of frailty, although there was a suggestive trend towards increasing frailty with increasing degree of relatedness. Socioeconomic adversity alone is unlikely to underlie the association as those nonrelative families that could adopt a child at the time were likely wealthier than the families that gave away their child for adoption. The higher frailty among the adoptees may thus reflect early life stress, caused by being separated from one's biological family. A similar finding on childhood stress and frailty was recently reported in the Helsinki Birth Cohort Study; those men who were evacuated abroad unaccompanied by their parents in childhood during World War II had a higher risk of frailty (measured using the FP) in late life compared to nonseparated men (35). However, the Finnish study found no associations in women. These findings nevertheless call for more research into how different types of childhood stressors may increase the risk of frailty.

Our results are in general in agreement with previous findings on a U-shaped relationship between BMI and the level of frailty (30). Although frailty is partly viewed as a "wasting syndrome" and malnutrition in old age is an established risk factor for it (36), there is a paucity of longitudinal studies looking specifically into underweight and frailty. Our approach using repeated measurements for both frailty and BMI allowed us to disentangle this relationship. We not only identified underweight as a major risk factor for higher

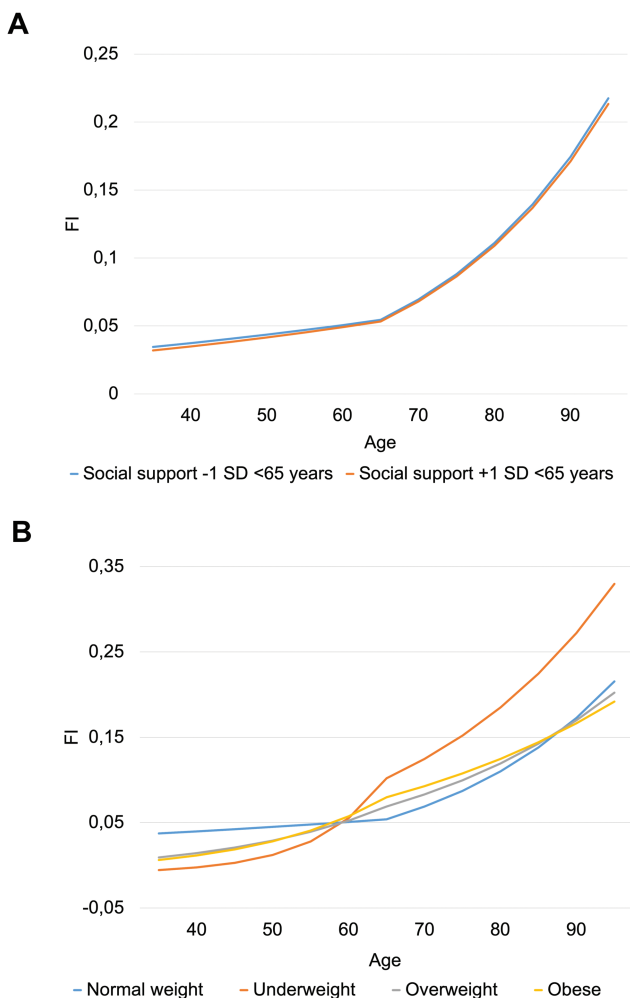


Figure 2. Frailty index (FI) trajectories by repeated time-varying measures on social support (A) and body mass index categories (B) based on a two-slope growth model with an inflection point at age 65 years. For social support, the estimated trajectories are shown for -1 and $+1$ SD difference before age 65. The model estimates are based on ln-transformed FI and back-transformed to the original FI scale to facilitate interpretation.

level of frailty at age 65, but also found an association between time-varying underweight and a faster increase in frailty before age 65. The number of underweight individuals in our study was, however, low at baseline and decreased further in the subsequent waves, decreasing our chances to detect potential associations with the rate of change after age 65. The very large effect sizes between underweight and the level and rate of increase in frailty (before age 65) nevertheless indicate that underweight is a key driver of frailty.

Time-varying overweight or obesity were not associated with the rate of change in frailty before age 65 but both were associated with a slower increase after age 65. At the age of 85, deceleration rates were large enough to cross over the frailty trajectory for normal weight individuals, indicating that older persons being overweight or obese had the fewest frailty deficits. However, as our observations started to get sparse from age 90 onwards, our projections cannot be used to infer whether the decelerated rates would result in significantly lower levels of frailty for overweight and obese individuals at the oldest ages. Existence of potential biases, for example, due to mortality selection and involuntary weight loss, calls for cautious interpretation. Pertaining to the latter, the category of normal weight (at

any given measurement occasion) contains those who are constantly lean as well as those that have lost weight due to disease, making this group potentially heterogeneous in terms of health status. Weight loss, especially in old age, commonly occurs as a result of underlying pathology, which per se may be accompanied with increase in frailty. Although less common in old age, high muscle or lean body mass may in turn sometimes manifest as overweight, and being “fat and fit” as opposed to “lean and unfit” has been considered beneficial for some age-related diseases and mortality (37–39). Whether such obesity paradox exists for frailty in very old age is unknown. Results from the Helsinki Businessmen Study lend partial support against it (40). They analyzed the association between incident frailty at mean age ~ 79 (measured using the FP) and past weight trajectories from age 25 years, and found no protective effect of being constantly overweight or gaining weight (BMI < 25 in the beginning and ≥ 25 in the end) (40). Instead, they found that those who lost weight (BMI ≥ 25 in the beginning and < 25 in the end) had a higher risk of incident frailty compared to constantly normal weight (40). The role of underweight was nevertheless not specifically assessed in this study as none of the men had a BMI < 18.5 in midlife.

Although dietary patterns were not assessed in our study, the strong association between underweight and frailty suggests that undernutrition, defined as inadequate energy and protein intake and micronutrient deficiencies, may underlie the development of frailty. Numerous observational studies have linked poor nutritional status to increasing frailty and a few randomized controlled trials have also found a beneficial effect of protein supplementation, either with or without energy and micronutrient supplements on frailty (41,42). While the evidence on protein supplementation seems relatively firm, randomized controlled trials on other types of supplements, such as vitamin D and fatty acids are more scarce. It also warrants further investigation on whether protein supplementation is equally effective regardless of the BMI status.

Overall, interventions based on physical activity, commonly combined with nutritional supplementation though, have thus far shown most promise in preventing or reversing frailty (41,43). Although we found that both baseline and time-varying physical activity were associated with lower level of frailty at age 65, the effect size was rather modest and there was no association with the rate of change. One potential explanation is that since this was an observational study, cross-time changes in physical activity are likely to be more subtle than in interventional studies, and a bigger effect size would probably be required to detect significant associations with the rate of change. In addition, physical activity was available only in 6 out of 15 of the measurement occasions, decreasing the number of available repeated measurements. It is also possible that other factors, such as BMI, are stronger in their independent effects, and that there are interactions, such as moderation, between BMI and physical activity. Partially supporting this assertion, a study using latent growth curve analysis on (physical) frailty has shown that obesity has a stronger effect on the progression of frailty in those older individuals who have low physical activity (34).

This study has some limitations. Measures on frailty and covariates are based on self-reported data. However, regarding BMI, a previous study in SATSA has demonstrated high correlations (≥ 0.93) between self-reported and measured BMI and that the misclassification of BMI based on self-reported data is stable over time (44). As pertinent to all studies with long follow-ups into old age, individuals who were younger, less frail, and had more favorable values in the covariates provided more measurement occasions, and thus contributed more to the estimates. Moreover, our results

cannot be used to infer the direction of the changes between frailty and the covariates. The fact that the interindividual variation in the frailty trajectories did not essentially decrease with the addition of the covariates nevertheless suggests that a large part of the variation arises due to factors that were not measured in our study as well as stochastic events. However, in supplemental models, which further dissociated within-person time-varying effects from between-person effects of the time-varying covariates, we showed that social support has a cumulative benefit to lower frailty after age 65 on top of between-person effects that likewise show a benefit. Moreover, we showed that the BMI effects, both as continuous and categorical, were evident at the between-person level with worse frailty for those that deviate from normal weight, while being underweight added cumulatively to increased risk vis-à-vis time-related trends after age 65 with associations of increasingly worse frailty. Hence the time-varying effects in the original analysis (Table 2), contain a mixture of between and within effects (plus any growth effects in the TVC itself), whereas the supplemental analysis that separates out between- from within-person effects provides added clarity of the benefit of social support to lower frailty as well as the contributions of BMI to increased frailty.

The apparent strengths of this study include the very long follow-up, covering the entire period from adulthood into very old age, ample measurement occasions and availability of a wide array of covariates that enabled us to identify factors that are independently associated with frailty. Based on the findings, future public health programs and prevention efforts could benefit from closer monitoring of individuals with abnormal BMI in adulthood, especially those who are underweight. As a psychosocial component seemed to be involved in the risk of frailty, timely identification of those with low levels of social support and/or having experienced early life stress might prove useful. General health advice on lifestyle choices, such as abstaining from smoking and increasing physical activity seems likewise advisable. Most importantly, however, recognizing the multi-dimensional nature of frailty itself and its antecedents by healthcare providers could lead to better health outcomes in the future.

In conclusion, our study finds that the factors associated with the level of frailty are largely modifiable and could thus be considered as targets for intervention. The association between adoption status and frailty however warrants more research to resolve whether it mostly taps into early life stress or also captures socioeconomic circumstances. As underweight appeared as a driver for increased rate of change before age 65, targeting undernutrition in adulthood might prove useful in preventing future frailty. Any interventional strategy might nevertheless have their effective window before the sharp increase in the rate of change at age 65. Lastly, further studies are needed to resolve whether having extra weight confers some protection against progression of frailty in the advanced ages.

Supplementary Material

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

Funding

The SATSA study was supported by National Institutes of Health (grant numbers R01 AG04563, AG10175, AG028555); the MacArthur Foundation Research Network on Successful Aging; the Swedish Council for Working Life and Social Research (FAS/FORTE) (grant numbers 97:0147:1B, 2009-0795); and the Swedish Research Council (825-2007-7460, 825-2009-6141). This

study is supported by the Swedish Research Council (grant numbers 521-2013-8689, 2015-03255, 2018-02077; 2016-03081; 2019-01272); JPNDSwedish Research Council (2015-06796); FORTE (2013-2292); the Loo & Hans Osterman Foundation to S.H. and J.J.; the Foundation for Geriatric Diseases to S.H.; the Magnus Bergwall Foundation to S.H.; the Strategic Research Program in Epidemiology at Karolinska Institutet to S.H. and J.J. and the King Gustaf V's and Queen Victoria's Freemason Foundation to S.H.

Acknowledgments

E.R. and J.J. performed statistical analyses and wrote the manuscript. J.J. conceived the study design. C.A.R. contributed to the study design, statistical analysis plan, and statistical analyses. M.E. contributed to the statistical analysis plan. N.L.P. is the founder and principal investigator of the SATSA study. N.L.P., A.K.D.A., D.F., M.E., and S.H. contributed to the acquisition of the study variables. All authors contributed to the writing of the manuscript and interpretation of the results.

Conflict of Interest

None reported.

References

1. Vermeiren S, Vella-Azzopardi R, Beckwée D, et al.; Gerontopole Brussels Study group. Frailty and the prediction of negative health outcomes: a meta-analysis. *J Am Med Dir Assoc*. 2016;17:1163.e1-1163.e17. doi:10.1016/j.jamda.2016.09.010
2. Ofori-Asenso R, Chin KL, Mazidi M, et al. Global incidence of frailty and prefrailty among community-dwelling older adults: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2:e198398. doi:10.1001/jamanetworkopen.2019.8398
3. Savelle SL, Koistinen P, Stenholm S, et al. Leisure-time physical activity in midlife is related to old age frailty. *J Gerontol A Biol Sci Med Sci*. 2013;68:1433-1438. doi:10.1093/gerona/glt029
4. Susanto M, Hubbard RE, Gardiner PA. Association of 12-year trajectories of sitting time with frailty in middle-aged women. *Am J Epidemiol*. 2018;kwy111-kwy111. doi:10.1093/aje/kwy111
5. Stenholm S, Strandberg TE, Pitkälä K, Sainio P, Heliövaara M, Koskinen S. Midlife obesity and risk of frailty in old age during a 22-year follow-up in men and women: the Mini-Finland Follow-up Survey. *J Gerontol A Biol Sci Med Sci*. 2014;69:73-78. doi:10.1093/gerona/glt052
6. Rockwood K, Song X, Mitnitski A. Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey. *CMAJ*. 2011;183:E487-E494. doi:10.1503/cmaj.101271
7. Mitnitski A, Song X, Rockwood K. Trajectories of changes over twelve years in the health status of Canadians from late middle age. *Exp Gerontol*. 2012;47:893-899. doi:10.1016/j.exger.2012.06.015
8. Chamberlain AM, St Sauver JL, Jacobson DJ, et al. Social and behavioural factors associated with frailty trajectories in a population-based cohort of older adults. *BMJ Open*. 2016;6:e011410. doi:10.1136/bmjopen-2016-011410
9. Chamberlain AM, Finney Rutten LJ, Manemann SM, et al. Frailty trajectories in an elderly population-based cohort. *J Am Geriatr Soc*. 2016;64:285-292. doi: 10.1111/jgs.13944
10. Howrey BT, Al Snih S, Middleton JA, Ottenbacher KJ. Trajectories of frailty and cognitive decline among older Mexican Americans. *J Gerontol A Biol Sci Med Sci*. 2020. doi:10.1093/gerona/glz295
11. Stolz E, Mayerl H, Waxenegger A, Rasky E, Freidl W. Impact of socioeconomic position on frailty trajectories in 10 European countries: evidence from the Survey of Health, Ageing and Retirement in Europe (2004-2013). *J Epidemiol Community Health*. 2017;71:73-80. doi:10.1136/jech-2016-207712
12. Tran DTT, Tu JV, Dupuis JY, Bader Eddeen A, Sun LY. Association of frailty and long-term survival in patients undergoing coronary artery bypass grafting. *J Am Heart Assoc*. 2018;7:7:e009882. doi:10.1161/jaha.118.009882

13. Williams DM, Jylhävä J, Pedersen NL, Hägg S. A frailty index for UK Biobank Participants. *J Gerontol A Biol Sci Med Sci*. 2018;gly094–gly094. doi:10.1093/gerona/gly094
14. Jiang M, Foebel AD, Kuja-Halkola R, et al. Frailty index as a predictor of all-cause and cause-specific mortality in a Swedish population-based cohort. *Aging (Albany NY)*. 2017;9:2629–2646. doi:10.18632/aging.101352
15. Li X, Ploner A, Karlsson IK, et al. The frailty index is a predictor of cause-specific mortality independent of familial effects from midlife onwards: a large cohort study. *BMC Med*. 2019;17:94. doi:10.1186/s12916-019-1331-8
16. Fried LP, Tangen CM, Walston J, et al.; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146–M156. doi:10.1093/gerona/56.3.m146
17. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr*. 2008;8:24. doi:10.1186/1471-2318-8-24
18. Makary MA, Segev DL, Pronovost PJ, et al. Frailty as a predictor of surgical outcomes in older patients. *J Am Coll Surg*. 2010;210:901–908. doi:10.1016/j.jamcollsurg.2010.01.028
19. Armstrong JJ, Mitnitski A, Launer LJ, White LR, Rockwood K. Frailty in the Honolulu-Asia Aging Study: deficit accumulation in a male cohort followed to 90% mortality. *J Gerontol A Biol Sci Med Sci*. 2015;70:125–131. doi:10.1093/gerona/glu089
20. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. *J Gerontol A Biol Sci Med Sci*. 2007;62:738–743. doi:10.1093/gerona/62.7.738
21. Blodgett J, Theou O, Kirkland S, Andreou P, Rockwood K. Frailty in NHANES: Comparing the frailty index and phenotype. *Arch Gerontol Geriatr*. 2015;60:464–470. doi:10.1016/j.archger.2015.01.016
22. Finkel D, Pedersen NL. Processing speed and longitudinal trajectories of change for cognitive abilities: the Swedish Adoption/Twin Study of Aging. *Aging, Neuropsychology, and Cognition*. 2004;11:325–345. doi:10.1080/13825580490511152
23. Pedersen NL. Swedish Adoption/Twin Study on Aging (SATSA), 1984, 1987, 1990, 1993, 2004, 2007, and 2010. *Inter-University Consortium for Political and Social Research, The National Archive of Computerized Data on Aging (NACDA)* 2015. <https://www.icpsr.umich.edu/web/NACDA/studies/3843>
24. Rockwood K, Mitnitski A. Limits to deficit accumulation in elderly people. *Mech Ageing Dev*. 2006;127:494–496. doi:10.1016/j.mad.2006.01.002
25. Lichtenstein P, De Faire U, Floderus B, Svartengren M, Svedberg P, Pedersen NL. The Swedish Twin Registry: a unique resource for clinical, epidemiological and genetic studies. *J Intern Med*. 2002;252:184–205. doi:10.1046/j.1365-2796.2002.01032.x
26. Ericsson M, Lundholm C, Fors S, et al. Childhood social class and cognitive aging in the Swedish Adoption/Twin Study of Aging. *Proc Natl Acad Sci USA*. 2017;114:7001–7006. doi:10.1073/pnas.1620603114
27. Bergeman CS, Plomin R, Pedersen NL, McClearn GE, Nesselroade JR. Genetic and environmental influences on social support: the Swedish Adoption/Twin Study of Aging. *J Gerontol*. 1990;45:P101–P106. doi:10.1093/geronj/45.3.p101
28. Finkel D, Andel R, Pedersen NL. Gender differences in longitudinal trajectories of change in physical, social, and cognitive/sedentary leisure activities. *J Gerontol B Psychol Sci Soc Sci*. 2018;73:1491–1500. doi:10.1093/geronb/gbw116
29. Wickham H. *ggplot2: Elegant Graphics for Data Analysis*. New York, NY: Springer-Verlag; 2016.
30. Hubbard RE, Lang IA, Llewellyn DJ, Rockwood K. Frailty, body mass index, and abdominal obesity in older people. *J Gerontol A Biol Sci Med Sci*. 2010;65:377–381. doi:10.1093/gerona/glp186
31. Woods NF, LaCroix AZ, Gray SL, et al.; Women's Health Initiative. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. *J Am Geriatr Soc*. 2005;53:1321–1330. doi:10.1111/j.1532-5415.2005.53405.x
32. McNeish D, Matta TH. Flexible treatment of time-varying covariates with time unstructured data. *Struct Equ Modeling*. 2020;27:298–317. doi:10.1080/10705511.2019.1627213
33. Hoogendijk EO, Rockwood K, Theou O, et al. Tracking changes in frailty throughout later life: results from a 17-year longitudinal study in the Netherlands. *Age Ageing*. 2018;47:727–733. doi:10.1093/ageing/afy081
34. Ding YY, Kuha J, Murphy M. Multidimensional predictors of physical frailty in older people: identifying how and for whom they exert their effects. *Biogerontology*. 2017;18:237–252. doi:10.1007/s10522-017-9677-9
35. Haapanen MJ, Perälä MM, Salonen MK, et al. Early life stress and frailty in old age: the Helsinki birth cohort study. *BMC Geriatr*. 2018;18:179. doi:10.1186/s12877-018-0873-5
36. Feng Z, Lugtenberg M, Franse C, et al. Risk factors and protective factors associated with incident or increase of frailty among community-dwelling older adults: a systematic review of longitudinal studies. *PLoS One*. 2017;12:e0178383. doi:10.1371/journal.pone.0178383
37. Kalantar-Zadeh K, Horwich TB, Oreopoulos A, et al. Risk factor paradox in wasting diseases. *Curr Opin Clin Nutr Metab Care*. 2007;10:433–442. doi:10.1097/MCO.0b013e3281a30594
38. Carnethon MR, De Chavez PJ, Biggs ML, et al. Association of weight status with mortality in adults with incident diabetes. *JAMA*. 2012;308:581–590. doi:10.1001/jama.2012.9282
39. Nilsson G, Hedberg P, Öhrvik J. Survival of the fattest: unexpected findings about hyperglycaemia and obesity in a population based study of 75-year-olds. *BMJ Open*. 2011;1:e000012. doi:10.1136/bmjopen-2010-000012
40. Strandberg TE, Stenholm S, Strandberg AY, Salomaa VV, Pitkälä KH, Tilvis RS. The “obesity paradox,” frailty, disability, and mortality in older men: a prospective, longitudinal cohort study. *Am J Epidemiol*. 2013;178:1452–1460. doi:10.1093/aje/kwt157
41. Hernandez Morante JJ, Gomez Martinez C, Morillas-Ruiz JM. Dietary factors associated with frailty in old adults: a review of nutritional interventions to prevent frailty development. *Nutrients*. 2019;11:pii: E102. doi:10.3390/nu11010102
42. Apostolo J, Cooke R, Bobrowicz-Campos E, et al. Effectiveness of interventions to prevent pre-frailty and frailty progression in older adults: a systematic review. *JBI Database System Rev Implement Rep*. 2018;16:140–232. doi:10.11124/JBISRIR-2017-003382
43. Puts MTE, Toubasi S, Andrew MK, et al. Interventions to prevent or reduce the level of frailty in community-dwelling older adults: a scoping review of the literature and international policies. *Age Ageing*. 2017;46:383–392. doi:10.1093/ageing/afw247
44. Dahl AK, Hassing LB, Fransson EI, Pedersen NL. Agreement between self-reported and measured height, weight and body mass index in old age—a longitudinal study with 20 years of follow-up. *Age Ageing*. 2010;39:445–451. doi:10.1093/ageing/afq038