

Associations Between Deficit Accumulation Frailty and Baseline Markers of Lifestyle in the US POINTER Trial

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ABSTRACT

BACKGROUND: Multidomain lifestyle interventions may have the potential to slow biological aging as captured by deficit accumulation frailty indices. We describe the distribution and composition of the 49-component frailty index (FI) developed by the U.S. POINTER clinical trial team of investigators and assess its cross-sectional associations with sociodemographic factors and markers chosen to be representative of behaviors targeted by the trial's multidomain interventions.

METHODS: We draw baseline data from the 2111 volunteers enrolled in U.S. POINTER who were ages 60-79 years and at increased risk for cognitive decline. Frailty components were grouped into nine domains. Associations that FI scores and their domains had with behavioral markers were described with correlations and canonical correlation.

RESULTS: The 25th, 50th, and 75th percentiles of the frailty index score distribution were 0.153, 0.189, and 0.235. Higher frailty scores tended to occur among individuals who were older, male, and living in areas of greater deprivation (all $p < 0.001$). They were also associated with poorer self-reported diet, less physical activity, and higher Framingham risk scores (all $p < 0.001$). Associations were diffusely distributed among the frailty component domains, indicating that no individual domain was dominating associations.

CONCLUSIONS: The U.S. POINTER deficit accumulation frailty index had expected relationships with sociodemographic factors and sensitivity to the behaviors targeted by the trial's interventions. Our analysis supports its use as a secondary outcome to assess whether the multidomain interventions differentially impact an established marker of biological aging.

KEY WORDS: Aging; Health status; Lifestyle; Cognitive function

Introduction

Behavioral interventions designed to promote healthy lifestyles have the potential to slow biological aging and increase health span. Evidence for this comes from clinical trials of interventions variously focused on improving diet, increasing physical activity, restricting caloric intake, and promoting social engagement and cognitive activity. These approaches have proven to successfully benefit aging-related indices and biomarkers such as multimorbidity, the Kleméra–Doubal index, the frailty phenotype, disability-free life expectancy, and telomere length (1-7). Multidomain interventions that simultaneously target multiple behaviors may particularly be promising by increasing the number of interrelated processes that might be benefited (8-10).

Deficit accumulation frailty indices (FIs) are increasingly used as measures of aging and health status in clinical trials and cohort studies (11,12). FI scores are robust predictors of worsening physical disability and disability-free life years (13). Relatively accelerated increases in FI scores over time have been associated with subsequent poorer trajectories of cognitive and physical function and increased rates of mortality (14), supporting their use as markers of the aging process. A multidomain lifestyle intervention that targeted caloric restriction, increased physical activity, improved diet, and monitoring to control cardiometabolic risk factors has been shown to produce long-term benefits in reducing the progression of a FI by approximately one year (15,16).

The pivotal U.S. Study to Protect Brain Health through Lifestyle Intervention to Reduce Risk (U.S. POINTER) is a 2-year trial of multidomain intensive lifestyle intervention in older adults in the U.S. who are at increased risk for cognitive decline and dementia (17). It targets improvements in four health-related behaviors: physical activity, diet, social and intellectual engagement, and cardiometabolic risk factor monitoring. As such, the U.S. POINTER interventions hold promise to slow biological aging as captured by a FI. This led U.S.

POINTER investigators to develop a FI for use in the trial using data collected from the study cohort at baseline. This manuscript is organized to describe this FI and to characterize its cross-sectional relationships with demographic characteristics and markers of each of the four behaviors targeted by the U.S. POINTER interventions. This accordingly sets the backdrop for a future investigation of whether the U.S. POINTER interventions differentially affect FI progression.

METHODS

The U.S. POINTER cohort is comprised of cognitively normal adults (60-79 years of age) chosen to be at increased risk for cognitive decline due to 1) sedentary lifestyles, 2) suboptimal diet, 3) systolic blood pressure ≥ 125 mmHg, low density lipoprotein cholesterol ≥ 115 mg/dL, and/or glycated hemoglobin (HbA1c) $\geq 6.0\%$, 4) first degree family history (mother, father, sister, brother) of memory impairment, 5) African American/Black, Native American, or Hispanic/Latinx race or ethnicity, and/or 6) age 70-79 years. Enrollment began February 2019 and was completed in March 2023 (17). Recruitment occurred at five regional sites: Chicagoland, Houston, New England/Rhode Island, North Carolina, and Northern California (see Supplemental eTable3). Protocols were approved by a central Institutional Review Board and all participants provided written informed consent.

Deficit accumulation frailty index

Deficit accumulation frailty indices are formed from at least 30 components that collectively represent multiple health-related domains, e.g., geriatric syndromes, risk factors, function and abilities, mood and affect, and lifestyle (12,18). Each deficit is scored as 0 or 1 if absent or present, or an intermediate value depending on severity. The FI is the sum of these scores divided by the number that are evaluated, potentially ranging from 0 to 1. The 49

components of the U.S. POINTER FI are listed in Supplemental eTable1. These components are drawn from self-reported medical history, standardized laboratory assays and clinical measures, and questionnaires. We have grouped these components into nine subclasses: 1) Physical function and abilities, 2) Cognitive function, 3) Mood and affect, 4) Activities and daily function, 5) General health and lifestyle, 6) Clinical biomarkers, 7) Sleep, 8) Age-related chronic diseases, and 9) Sensorineural abilities. We calculated scores for each of these subclasses as the number of deficits divided by the number of components in the subclass to account for the varying numbers of components contributing to the subclasses.

Sociodemographic data

Sociodemographic data on U.S. POINTER participants during their trial enrollment were based on self-report questionnaires. Participants were given the option of self-reporting female or male sex. The Area Deprivation Index was used to order the census blocks of participant's residences according to national socioeconomic status, with scores potentially ranging from 0 to 100 (19,20).

Markers of behavioral domains targeted by U.S. POINTER interventions

U.S. POINTER participants were randomly assigned with equal probability to one of two multidomain lifestyle interventions that featured either a self-guided or a structured approach to behavioral change (17). Both interventions were designed to promote the adoption of a healthy diet, increasing physical and cognitive activity, greater social engagement, and regular monitoring cardiovascular risk factors. The interventions differ in format, intensity, and accountability (17). To assess whether our FI may be sensitive to behaviors targeted by the U.S. POINTER interventions, we examined cross-sectional associations with the following four markers. Diet quality was assessed with a screener for the MIND Diet Score

(21). The MIND Diet Score sums scores across 9 brain-healthy food groups (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, poultry, and extra virgin olive oil) and 5 unhealthy food groups (red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast food). Standardized questionnaires were used for participants to report the number of minutes per week engaged in moderate intensity physical activity and the frequency per week engaged in cognitive stimulating activities (17). The Framingham Risk Score (FRS), a measure of 10-year risk of cardiovascular disease, was used to summarize current control of cardiometabolic risk factors (22); higher scores reflect greater risk. Higher FRS has been demonstrated in other studies to be associated with higher risk of cognitive decline (23,24). The physical and laboratory data to calculate FRS were collected based on standardized protocols.

Statistical analysis

The distribution of the U.S. POINTER FI scores and their relationship with calendar age were described using scatterplots and linear regression. Pairwise associations with other sociodemographic factors were assessed with correlation coefficients, and associations with behavioral markers were assessed with Pearson correlations, without and with covariate adjustment for sociodemographic factors. The U.S. POINTER interventions jointly target each of the four behaviors represented by the markers in our analyses. To describe the multivariable relationships the four markers have with our FI, we used canonical correlation. This yields a single correlation linking the FI with an optimal linear combination of the four behavioral markers to express the percent of overall variability among the markers that may be explained by the FI. We also assessed relationships with the individual nine subclasses of components contributing to the FI (Supplemental eTable1). Rates of missing frailty

components were low, ranging from 0% (for many variables) to 8% for central laboratory assessments (Supplemental eTable2), and replaced via single imputation.

RESULTS

Figure 1 portrays the distribution of FI scores, which as expected is right skewed with relatively fewer high scores. The 25th, 50th, and 75th percentiles were 0.153, 0.189, and 0.235 respectively.

Table 1 describes how mean FI scores varied across sociodemographic groups. FI scores tended to be greater among men, older participants, and those residing in areas with the greatest levels of deprivation. As also seen in Table 1, there was variability in FI scores among the cohorts recruited in the five geographical areas, with relatively higher scores among those recruited by the North Carolina and Houston sites. Supplemental eFigure 1 provides more granularity in the association that FI scores had with chronological age. The overall correlation between FI scores and age was $r=0.26$ ($p<0.001$).

Table 2 describes the associations that FI scores had with markers for targets of the U.S. POINTER interventions: diet quality, physical activity, cognitive stimulation, and metabolic risk factors. FI scores were negatively correlated with MIND diet scores and self-reported minutes of moderate physical activity (both $p<0.001$). Higher FI scores were associated with higher Framingham risk ($p<0.001$). Covariate-adjustment for age, sex, site, and Area Deprivation Index attenuated some of these relationships, but all three remained statistically significant. FI scores were unrelated to self-reported level of cognitive stimulation.

The canonical correlation analysis yielded a correlation of $r=0.42$ linking FI scores to a linear combination of the four behavioral markers with higher scores associated with better diet quality, higher physical activity, more cognitive stimulation, and lower Framingham risk.

Table 3 examines pairwise associations that the nine subclasses of FI components had with the markers of behavior. Included are mean (SD) scores for each subclass of components, calculated as the number of deficits divided by the number of components in the class to account for the varying numbers of components contributing to the subclass score. Correlations meeting nominal ($p < 0.01$) levels of significance, i.e., those correlations with absolute values meeting or exceeding 0.06, are marked with an asterisk. While some pairwise associations would be expected to be observed given overlapping components (e.g., the FRS includes some components of the FI such as total cholesterol and systolic blood pressure), the table demonstrates a rich set of associations between individual behavioral markers and FI component classes that contribute to the overall composite associations seen in Table 2. Overall, the correlations are not large, indicating that relationships with FI are not dominated by individual domains. Covariate adjustment for age, sex, site, and Area Deprivation Index attenuated some relationships, but most remained evident.

DISCUSSION

The distribution of frailty index scores in the U.S. POINTER cohort is representative of a cohort of older individuals at somewhat increased risk for cognitive decline due to risk factors such as health status, lifestyle, and family history (17). Other trials have had similar distributions. For example, the cohort of the Action for Health in Diabetes (Look AHEAD) trial, adults (ages 45-76) at increased risk for cognitive decline due to established type 2 diabetes and either overweight or obesity, had 25th, 50th, and 75th percentiles of 0.17, 0.21, and 0.25 (15), which are similar to and overlap those seen in U.S. POINTER. The compositions of FIs for U.S. POINTER and Look AHEAD differed, but included some common elements and the distribution of both were similarly right skewed.

The Systolic Blood Pressure Intervention Trial (SPRINT) enrolled adults (≥ 50 years) with i) elevated blood pressure and ii) cardiovascular disease, elevated risk for cardiovascular disease, and/or chronic kidney disease (25), factors that placed its participants at increased risk for cognitive decline (26). The 25th, 50th, and 75th percentiles of the SPRINT FI at baseline were 0.11, 0.16, and 0.22, thus slightly lower but overlapping those for U.S. POINTER. The Aspirin in Reducing Events in the Elderly (ASPREE) cohort of adults (ages 65-98) that excluded individuals with deficits in cognition and physical function and those with history of cardiovascular disease, had 25th, 50th, and 75th percentiles for FI scores of 0.07, 0.10, and 0.14, i.e., an overall lower distribution of FI scores than U.S. POINTER (13). While some differences among cohorts likely reflect the differing compositions of the FI, together these comparisons suggest that U.S. POINTER, in enrolling participants meeting eligibility requirements related to the presence of age-related health deficits, accrued a distribution of FI scores commensurate with an elevated risk for cognitive decline.

The U.S. POINTER baseline FI scores demonstrate expected associations with sociodemographic characteristics. FI scores were modestly, not strongly, correlated with age, consistent with the distinction between biological and chronological aging. There are inconsistent reports of sex-related differences in FI scores (27). Some, like U.S. POINTER have found FI scores to be higher among men than women (15,28). Others, unlike U.S. POINTER, have reported higher FI scores among women compared with men (13,26,29) and some have reported no differences (30). We know of no other reports linking FI scores to the Area Deprivation Index, however our finding that higher scores are associated with residence in areas with greater deprivation is consistent with reports that higher scores are more common in lower socio-economic neighborhoods (30).

Lower U.S. POINTER FI scores were associated with better diet, more frequent physical activity, and better control of cardiometabolic risk factors, both without and with covariate

adjustment for sociodemographic factors. U.S. POINTER multidomain lifestyle intervention secondary outcomes are based on similar measures, suggesting that FI may be a sensitive measure to the trial's targeted outcomes. FI scores were uncorrelated with self-reported frequency of cognitive stimulating activities. It is possible that this may reflect compensatory behaviors among individuals with poorer health. Also, it has been noted that many cognitively stimulating activities, e.g., reading, computer usage, are performed while sedentary (31), and thus may have indirect associations with physical frailty.

Collectively, the markers related to U.S. POINTER intervention targets and the baseline cognitive function scores account for 18% (square of $r=0.42$) of the total variability of FI scores. This reflects a rich inter-relationship that U.S. POINTER is poised to explore as longitudinal data accrue.

As Table 3 demonstrates, these associations are not driven by individual components of the FI. When components of the FI are grouped according to health-related classes, the association that domain-specific scores have with behaviors are diffuse, with multiple domains contributing correlations with each behavior in unadjusted analyses. Associations remained diffuse after covariate adjustment for age, site, sex, and Area Deprivation Index. The associations were not attributable to chronological age or sociodemographic differences. We note that the domain labeled "Activities and Daily Function" had scores clustered at 0 (mean=0.01). While it may not contribute materially to the current FI, we felt it important to include for future use in evaluating potential changes over time during the trial follow-up.

A recent meta-analysis has found evidence that deficit accumulation frailty indices may serve as effect modifiers in trials of both pharmacological and nonpharmacological interventions (32). It may be the the U.S. POINTER FI may serve to identify subgroups of individuals for whom multidomain lifestyle intervention may yield the greatest benefits.

Limitations

As volunteers for a clinical trial of multidomain lifestyle interventions, and as circumscribed by its inclusion/exclusion criteria, the U.S. POINTER cohort may not reflect general populations. This is also a cross-sectional analysis of the baseline characteristics, which limits our ability to ascertain the directionality of the long-term impact of these factors on frailty. With this limitation, longitudinal analysis is planned for future to gain a deeper understanding of how lifestyle interventions may influence FI and related components, and potentially modify the trajectories within this study population. The development of the U.S. POINTER FI was not an original aim during the design of the trial, and thus its components are limited to data collected at baseline as set by the study protocol. The components of the FI include both subjective measures and those relying on self-report so that the validity of individual components may vary. In particular, the self-reported minutes of exercise included in our analysis are not consistent with the recruitment of a cohort that was established to be sedentary, and likely represents an over-reporting bias that is not uncommon among research studies (33,34).

Summary

The U.S. POINTER FI was developed as a secondary outcome for the trial to assess whether the multidomain lifestyle interventions may differentially impact trajectories of an age-related marker over two years of implementation. To serve this purpose, the FI should be sensitive to the behavioral domains targeted by the FI, but also to meet standard approaches for the development of a FI. The U.S. POINTER FI has expected cross-sectional associations with markers of socio-demography and behaviors which are diffusely contributed to by sub-domains of FI components. This analysis provides support for the validity of the U.S. POINTER FI as a secondary outcome for the trial.

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Figure Legend:

Figure 1: Distribution of deficit accumulation frailty scores (49 components) at baseline for the 2,111 U.S.POINTER participants.

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Table 1: Characteristics of the U.S. POINTER cohort at baseline and mean deficit accumulation frailty index scores among subgroups.

Characteristic	Mean (SD) Frailty Score	p-value ^a
Sex		
Female (N=1453)	0.154 (0.062)	<0.001
Male (N=658)	0.173 (0.059)	
Age, years		
60-64 (N=622)	0.177 (0.057)	<0.001
65-69 (N=586)	0.189 (0.059)	
70-74 (N=629)	0.203 (0.060)	
75-79 (N=274)	0.224 (0.061)	
Site		
ChicagoLand (N=463)	0.149 (0.059)	<0.001
Houston (N=455)	0.166 (0.063)	
North Carolina (N=404)	0.173 (0.064)	
Northern California (N=413)	0.158 (0.060)	
Rhode Island / NE (N=376)	0.154 (0.062)	
Area Deprivation Index (Missing=21)		
Least deprived 0-19 (N=602)	0.151 (0.061)	<0.001
20-39 (N=688)	0.155 (0.061)	
40-59 (N=422)	0.166 (0.061)	
60-79 (N=266)	0.174 (0.062)	
Most deprived 80-100 (N=112)	0.183 (0.068)	

^aAnalysis of variance

Table 2: Mean (SD) and correlation of deficit accumulation frailty index scores with markers for targets for U.S. POINTER interventions, without and with adjustment for age, sex, site, and Area Deprivation Index. The raw canonical correlation is $r=0.42$ ($p<0.001$). After covariate adjustment, the canonical correlation is $r=0.25$ ($p<0.001$)

Marker	N	Mean (SD)	Without Adjustment Correlation (p-value)	With Adjustment ^a Correlation (p-value)
MIND Diet Score	2111	7.04 (1.42)	-0.09 (<0.001)	-0.10 (<0.001)
Minutes Moderate Intensity Activity per Week	2097	745 (513)	-0.11 (<0.001)	-0.12 (<0.001)
Frequency of Cognitive Activities Per Week	2095	17.7 (11.4)	-0.02 (0.48)	-0.02 (0.40)
Framingham Risk Score	1830	24.3 (16.1)	0.40 (<0.001)	0.21 (<0.001)

^aCovariate adjustment for age, sex, site, and Area Deprivation Index

Table 3: Pairwise correlations between frailty index domain scores and markers of domains targeted by the U.S. POINTER interventions. Domain score = (# Deficits)/(# Possible within domain). Correlations with nominal $p < 0.01$ have superscripts*.

Unadjusted scores

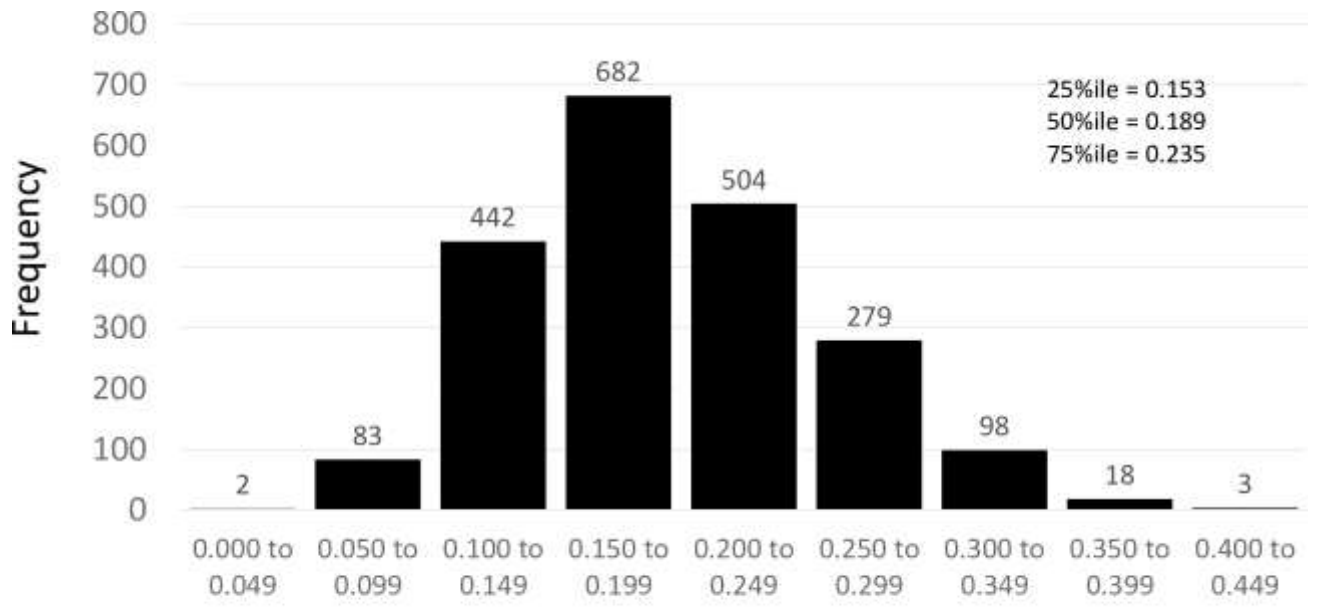
	Physical Function and Abilities	Cognitive Function	Mood and Affect	Activities and Daily Function	General Health and Lifestyle	Clinical Biomarkers	Sleep	Age-Related Chronic Diseases	Sensorineural Abilities
Domain Score*	0.10	0.12	0.08	0.01	0.31	0.31	0.17	0.08	0.06
Mean (SD)	(0.01)	(0.21)	(0.19)	(0.17)	(0.20)	(0.09)	(0.31)	(0.08)	(0.17)
MIND Diet Score	-0.03	-0.01	-0.10*	-0.00	-0.04	-0.08*	-0.06*	-0.01	-0.01
Moderate Intensity Activity	-0.14*	-0.01	-0.13*	-0.02	-0.06*	-0.06*	-0.06*	-0.01	0.06*
Cognitive Activities	-0.05	-0.12*	-0.04	-0.00	0.03	0.01	-0.02	0.06*	0.04
Framingham	0.15*	0.25*	0.02	-0.02	0.22*	0.44*	-0.08*	0.03	0.12*

Risk									
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Adjusted for age, site, sex, and Area Deprivation Index

	Physical Function and Abilities	Cognitive Function	Mood and Affect	Activities and Daily Function	General Health and Lifestyle	Clinical Biomarkers	Sleep	Age- Related Chronic Diseases	Sensorineural Abilities
MIND Diet Score	-0.04	-0.00	-0.10*	-0.01	-0.04	-0.07*	-0.06*	-0.04	-0.01
Moderate Intensity Activity	-0.14*	-0.01	-0.12*	-0.02	-0.06*	-0.08*	-0.05	-0.02	0.05
Cognitive Activities	-0.02	-0.11*	-0.03	0.00	0.03	-0.00	-0.01	0.04	0.01
Framingham Risk	0.10*	0.06*	0.05	-0.00	0.14*	0.25*	-0.02	-0.01	0.01

Figure 1



Baseline FI

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