The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences, 2025, **80**(2), glae279
https://doi.org/10.1093/gerona/glae279
Advance access publication: 16 November 2024
Research Article

Associations Between Deficit Accumulation Frailty and Baseline Markers of Lifestyle in the U.S. POINTER Trial

Mark A. Espeland, PhD,[1,2,*] Yitbarek N. Demesie, MS,[2] KayLoni Olson, PhD,[3] Samuel N. Lockhart, PhD,[1] Sarah E. Tomaszewski Farias, PhD,[4] Maryjo L. Cleveland, MD,[1] Christy C. Tangney, PhD,[5] Lucia Crivelli, PhD,[6] Heather M. Snyder, PhD,[7] Michele K. York, PhD,[8] Laura D. Baker, PhD,[1,9] Rachel A. Whitmer, PhD,[10] Rena R. Wing, PhD,[3] Katelyn R. Garcia, MS,[2] Kathryn E. Callahan, MD, MS,[1] and the U.S. POINTER Research Group

[1]Section of Gerontology and Geriatric Medicine, Department of Internal Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA.
[2]Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA.
[3]Department of Psychiatry and Human Behavior, The Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA.
[4]Department of Neurology, University of California, Davis, California, USA.
[5]Department of Clinical Nutrition, Rush University Medical Center, Chicago, Illinois, USA.
[6]Department of Cognitive Neurology, Fleni, Buenos Aires, Argentina.
[7]Department of Medical and Scientific Relations, Alzheimer's Association, Chicago, Illinois, USA.
[8]Division of Neuropsychology, Department of Neurology, Baylor College of Medicine, Houston, Texas, USA.
[9]Department of Neurology, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA.
[10]Department of Public Health Sciences, University of California, Davis, California, USA.

*Address correspondence to: Mark A. Espeland, PhD. E-mail: mespelan@wakehealth.edu

Decision Editor: Roger A. Fielding, PhD (Medical Sciences Section)

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 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 2 111 volunteers enrolled in U.S. POINTER who were ages 60–79 years and at increased risk for cognitive decline. Frailty components were grouped into 9 domains. Associations that frailty index 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 $p < .001$). They were also associated with poorer self-reported diet, less physical activity, and higher Framingham risk scores (all $p < .001$). 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. ClinicalTrials.gov Identifier: NCT03688126.

Keywords: Aging, Cognitive function, Health status, Lifestyle

Behavioral interventions designed to promote healthy lifestyles have the potential to slow biological aging and increase healthspan. 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 Klemera–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

Received: June 25 2024; Editorial Decision Date: September 16 2024.

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 1 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 United States who are at increased risk for cognitive decline and dementia (17). It targets improvements in 4 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 4 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.

Method

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 (i) sedentary lifestyles, (ii) suboptimal diet, (iii) systolic blood pressure ≥125 mmHg, low density lipoprotein cholesterol ≥115 mg/dL, and/or glycated hemoglobin (HbA1c) ≥6.0%, (iv) first degree family history (mother, father, sister, brother) of memory impairment, (v) African American/Black, Native American, or Hispanic/Latinx race or ethnicity, and/or (vi) age 70–79 years. Enrollment began in February 2019 and was completed in March 2023 (17). Recruitment occurred at 5 regional sites: Chicagoland, Houston, New England/Rhode Island, North Carolina, and Northern California (see Supplementary Table 3). Protocols were approved by a central Institutional Review Board, and all participants provided written informed consent.

Deficit Accumulation FI

Deficit accumulation FI are formed from at least 30 components that collectively represent multiple health-related domains, for example, 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 Supplementary Table 1. These components are drawn from self-reported medical history, standardized laboratory assays and clinical measures, and questionnaires. We have grouped these components into 9 subclasses: (i) physical function and abilities, (ii) cognitive function, (iii) mood and affect, (iv) activities and daily function, (v) general health and lifestyle, (vi) clinical biomarkers, (vii) sleep, (viii) age-related chronic diseases, and (ix) 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 1 of 2 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 of 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 4 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 a 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 4 behaviors represented by the markers in our analyses. To describe the multivariable relationships the 4 markers have with our FI, we used canonical correlation. This yields a single correlation linking the FI with an optimal linear combination of the 4 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 9 subclasses of components contributing to the FI (Supplementary Table 1). Rates of missing frailty components were low, ranging from 0% (for many variables) to 8% for central laboratory

assessments (Supplementary Table 2), 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 0.232, 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 5 geographical areas, with relatively higher scores among those recruited by the North Carolina and Houston sites. Supplementary Figure 1 provides more granularity in the association that FI scores had with chronological age. The overall correlation between FI scores and age was $r = 0.26$ ($p < .001$).

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 $p < .001$). Higher FI scores were associated with higher Framingham risk ($p < .001$). Covariate-adjustment for age, sex, site, and area deprivation index attenuated some of these relationships, but all 3 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 4 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 9 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 ($p < .01$) levels of significance, that is, 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 (eg, 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 FI 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, that is, 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.

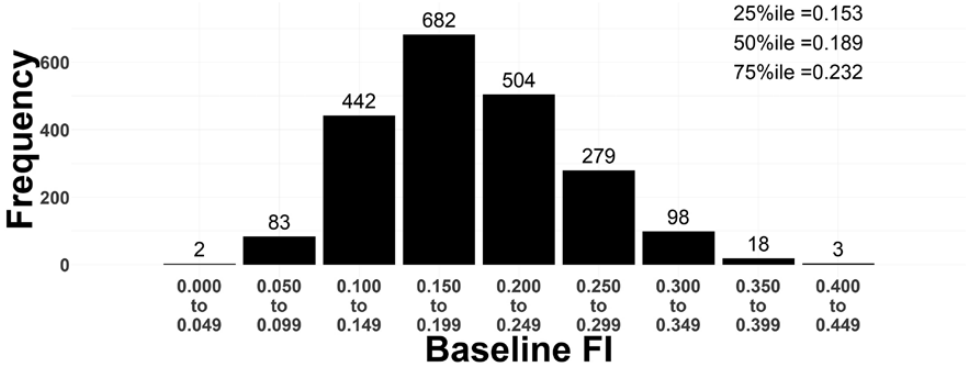

Figure 1. Distribution of deficit accumulation frailty scores (49 components) at baseline for the 2111 U.S.POINTER participants.

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 socioeconomic 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 simulating activities, for example, 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 interrelationship 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 was 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 FI may serve as effect modifiers in trials of both pharmacological and nonpharmacological interventions (32). It may be that 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 effect of these factors on frailty. With this limitation, longitudinal analysis is planned for the future to gain a deeper understanding of how lifestyle

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* = 1 453)	0.154 (0.062)	<.001
Male (*N* = 658)	0.173 (0.059)	
Age, years		
60–64 (*N* = 622)	0.177 (0.057)	
65–69 (*N* = 586)	0.189 (0.059)	<.001
70–74 (*N* = 629)	0.203 (0.060)	
75–79 (*N* = 274)	0.224 (0.061)	
Site		
ChicagoLand (*N* = 463)	0.149 (0.059)	
Houston (*N* = 455)	0.166 (0.063)	
North Carolina (*N* = 404)	0.173 (0.064)	<.001
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)	
20–39 (*N* = 688)	0.155 (0.061)	<.001
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)	

[a]Analysis of variance. *Note*: *SD* = standard deviation.

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 $r = 0.42$ ($p < .001$). After Covariate Adjustment, the Canonical Correlation is $r = 0.25$ ($p < .001$)

Marker	*N*	Mean (*SD*)	Without Adjustment Correlation (*p*-Value)	With Adjustment[a] Correlation (*p*-Value)
MIND diet score	2 111	7.04 (1.42)	−0.09 (<.001)	−0.10 (<.001)
Minutes moderate intensity activity per week	2 097	745 (513)	−0.11 (<.001)	−0.12 (<.001)
Frequency of cognitive activities per week	2 095	17.7 (11.4)	−0.02 (.48)	−0.02 (.40)
Framingham Risk Score	1 830	24.3 (16.1)	0.40 (<.001)	0.21 (<.001)

[a]Covariate adjustment for age, sex, site, and area deprivation index. *Note*: *SD* = standard deviation.

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 $p < .01$ 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* mean (*SD*)	0.10 (0.01)	0.12 (0.21)	0.08 (0.19)	0.01 (0.17)	0.31 (0.20)	0.31 (0.09)	0.17 (0.31)	0.08 (0.08)	0.06 (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 risk	0.15*	0.25*	0.02	−0.02	0.22*	0.44*	−0.08*	0.03	0.12*

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

Note: *SD* = standard deviation.

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 represent an overreporting bias that is not uncommon among research studies (33,34).

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 Alzheimer's Association (Grant 19-611541). Additional support for the U.S. POINTER program was provided by the National Institute on Aging of the National Institutes of Health (Grants AG066910, AG062689, AG064440, AG063744).

Conflict of Interest

MAE is a member of the editorial board of the Journal of Gerontology Medical Sciences. The authors report no other conflicts of interest.

Acknowledgments

M.A.E. conceived the project, obtained funding, collaborated on the analysis, and wrote the original draft. Y.N.D. collaborated on the analysis and reviewed multiple drafts. K.O., S.M.N., S.E.T.F., M.L.C., C.C.T., L.C., H.M.S., M.K.Y., L.D.B., R.A.W., R.R.W., K.R.G., and K.E.C. all reviewed and contributed to multiple drafts of the manuscript. H.M.S. and L.D.B. also collaborated on obtaining funding. The U.S. POINTER study group at baseline is listed in Supplementary Table 3.

References

1. Cesari M, Vellas B, Hsu FC, et al. A physical activity intervention to treat the frailty syndrome in older persons-results from the LIFE-P study. *J Gerontol A Biol Sci Med Sci*. 2015;70(2):216–222. https://doi.org/10.1093/gerona/glu099
2. Belsky DW, Huffman KM, Pieper CF, Shalev I, Kraus WE. Change in the rate of biological aging in response to caloric restriction: CALERIE Biobank analysis. *J Gerontol A Biol Sci Med Sci*. 2017;73:4–10. https://doi.org/10.1093/gerona/glx096
3. Marengoni A, Rizzuto D, Fratiglioni L, et al. The effect of a 2-year intervention consisting of diet, physical exercise, cognitive training, and monitoring of vascular risk on chronic morbidity–the FINGER randomized controlled trial. *J Am Med Dir Assoc*. 2018;19(4):355–360.e1. https://doi.org/10.1016/j.jamda.2017.09.020
4. Gregg EW, Lin J, Bardenheier B, et al. Impact of intensive lifestyle intervention on disability-free life expectancy: the Look AHEAD Study. *Diabetes Care*. 2018;41:1040–1048. https://doi.org/10.2337/dc17-2110
5. Espeland MA, Gaussoin SA, Bahnson J, et al. Impact of an 8-year intensive lifestyle intervention on an index of multimorbidity. *J Am Geriatr Soc*. 2020;68(10):2249–2256. https://doi.org/10.1111/jgs.16672
6. Sindi S, Solomon A, Kåreholt I, et al. Telomere length change in a multidomain lifestyle intervention to prevent cognitive decline: a randomized clinical trial. *J Gerontol A Biol Sci Med Sci*. 2021;76(3):491–498. https://doi.org/10.1093/gerona/glaa279
7. Buttet M, Bagheri R, Ugbolue UC, et al. Effect of a lifestyle intervention on telomere length: a systematic review and meta-analysis. *Mech Ageing Dev*. 2022;206:111694. https://doi.org/10.1016/j.mad.2022.111694
8. Blancafort Alias S, Cuevas-Lara C, Martínez-Velilla N, et al. A multi-domain group-based intervention to promote physical activity, healthy nutrition, and psychological wellbeing in older people with losses in intrinsic capacity: AMICOPE Development Study. *Int J Environ Res Pub Health*. 2021;18(11):5979. https://doi.org/10.3390/ijerph18115979
9. Bevilacqua R, Soraci L, Stara V, et al. A systematic review of multidomain and lifestyle interventions to support the intrinsic capacity of the older population. *Front Med (Lausanne)*. 2022;9:929261. https://doi.org/10.3389/fmed.2022.929261
10. Oh G, Lee H, Park CM, et al. Long-term effect of a 24-week multicomponent intervention on physical performance and frailty in community-dwelling older adults. *Age Ageing*. 2021;50(6):2157–2166. https://doi.org/10.1093/ageing/afab149
11. Aguayo GA, Hulman A, Vaillant MT, et al. Prospective association among diabetes diagnosis, HbA1c, glycemia, and frailty trajectories in an elderly population. *Diabetes Care*. 2019;42:1903–1911. https://doi.org/10.2337/dc19-0497
12. Hanlon P, Butterly E, Lewsey J, Siebert S, Mair FS, McAllister DA. Identifying frailty in trials: an analysis of individual participant data from trials of novel pharmacological interventions. *BMC Med*. 2020;18:309. https://doi.org/10.1186/s12916-020-01752-1
13. Ryan J, Espinoza S, Ernst ME, et al. Validation of a deficit-accumulation frailty index in the Aspirin in Reducing Events in the Elderly Study and its predictive capacity for disability-free survival. *J Gerontol A Biol Sci Med Sci*. 2022;77:19–26. https://doi.org/10.1093/gerona/glab225
14. Espeland MA, Justice JN, Bahnson J, et al. Eight-year changes in multimorbidity and frailty in adults with type 2 diabetes mellitus: associations with cognitive and physical function and mortality. *J Gerontol A Biol Sci Med Sci*. 2022;77:1691–1698. https://doi.org/10.1093/gerona/glab342
15. Simpson FR, Pajewski NM, Nicklas B, et al. Impact of multidomain lifestyle intervention on frailty through the lens of deficit accumulation in adults with type 2 diabetes mellitus. *J Gerontol A Biol Sci Med Sci*. 2020;75:1921–1927. https://doi.org/10.1093/gerona/glz197
16. Evans JK, Usoh CO, Simpson FR, et al. Long-term Impact of a 10-year intensive lifestyle intervention on a deficit accumulation frailty index: Action for Health In Diabetes (Look AHEAD) Trial. *J Gerontol A Biol Sci Med Sci*. 2023;78(11):2119–2126. https://doi.org/10.1093/gerona/glad088
17. Baker LD, Snyder HM, Espeland MA, et al. Study design and methods: U.S. study to protect brain health through lifestyle intervention to reduce risk (U.S. POINTER). *Alzheimer's Dementia*. 2024;20(2):769–782. https://doi.org/10.1002/alz.13365
18. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr*. 2008;8:24. https://doi.org/10.1186/1471-2318-8-24
19. Singh GK. Area deprivation and widening inequalities in US mortality, 1969–1998. *Am J Public Health*. 2003;93:1137–1143. https://doi.org/10.2105/ajph.93.7.1137
20. Kind AJH, Jencks S, Brock J, et al. Neighborhood socioeconomic disadvantage and 30-day rehospitalization: a retrospective cohort

study. *Ann Intern Med*. 2014;16:765–774. https://doi.org/10.7326/M13-2946
21. Morris MC, Tangney CC, Wang Y, et al. MIND diet slows cognitive decline with aging. *Alzheimer's Dementia*. 2015;11:1015–1022. https://doi.org/10.1016/j.jalz.2015.04.011
22. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837–1847. https://doi.org/10.1161/01.cir.97.18.1837
23. Kaffashian S, Dugravot A, Nabi H, et al. Predictive utility of the Framingham general cardiovascular disease risk profile for cognitive function: evidence from the Whitehall II study. *Eur Heart J*. 2011;32:2326–2332. https://doi.org/10.1093/eurheartj/ehr133
24. von Cederwald BF, Josefsson M, Wåhlin A, Nyberg L, Karalija N. Association of cardiovascular risk trajectory with cognitive decline and incident dementia. *Neurol*. 2022;98:e2013–e2022. https://doi.org/10.1212/WNL.0000000000200255
25. Pajewski NM, Williamson JD, Applegate WB, et al. Characterizing frailty status in the Systolic Blood Pressure Intervention Trial. *J Gerontol A Biol Sci Med Sci*. 2016;71:649–655. https://doi.org/10.1093/gerona/glv228
26. Rapp SR, Gaussoin SA, Sachs BC, et al. Effects of intensive versus standard blood pressure control on domain-specific cognitive function: a substudy of the SPRINT Randomised Controlled Trial. *Lancet Neurol*. 2020;19(11):899–907. https://doi.org/10.1016/S1474-4422(20)30319-7
27. Kane AE, Howlett SE. Sex differences in frailty: comparisons between humans and preclinical models. *Mech Ageing Dev*. 2021;198:111546. https://doi.org/10.1016/j.mad.2021.111546
28. Bartley MM, Geda YE, Christianson TJH, Shane Pankratz V, Roberts RO, Petersen RC. Frailty and mortality outcomes in cognitively normal older people: sex differences in a population-based study. *J Am Geriatr Soc*. 2016;64:132–137. https://doi.org/10.1111/jgs.13821
29. Wu AH, Setiawan VW, Stram DO, et al. Racial, ethnic, and socioeconomic differences in a deficit accumulation frailty index in the Multiethnic Cohort Study. *J Gerontol A Biol Sci Med Sci*. 2023;78:1246–1257. https://doi.org/10.1093/gerona/glac216
30. Blodgett JM, Pérez-Zepeda MU, Godin J, et al. Frailty indices based on self-report, blood-based biomarkers and examination-based data in the Canadian Longitudinal Study on Aging. *Age Ageing*. 2022;51:1–9. https://doi.org/10.1093/ageing/afac075
31. Collins AM, Molina-Hidalgo C, Aghjayan SL, et al. Differentiating the influence of sedentary behavior and physical activity on brain health in late adulthood. *Exp Gerontol*. 2023;180:112246. https://doi.org/10.1016/j.exger.2023.112246
32. Yao A, Gao L, Zhang J, Cheng JM, Kim DH. Frailty as an effect modifier in randomized controlled trials: a systematic review. *J Gen Intern Med*. 2024;39:1452–1473. https://doi.org/10.1007/s11606-024-08732-8
33. Olds TS, Gomersall SR, Olds ST, Ridley K. A source of systematic bias in self-reported physical activity: the cutpoint bias hypothesis. *J Sci Med Sport*. 2019;22:924–928. https://doi.org/10.1016/j.jsams.2019.03.006
34. Steene-Johannessen J, Anderssen SA, van der Ploeg HP, et al. Are self-report measures able to define individuals as physically active or inactive? *Med Sci Sports Exerc*. 2016;48(2):235–244. https://doi.org/10.1249/MSS.0000000000000760