Online-Only Supplementary Material

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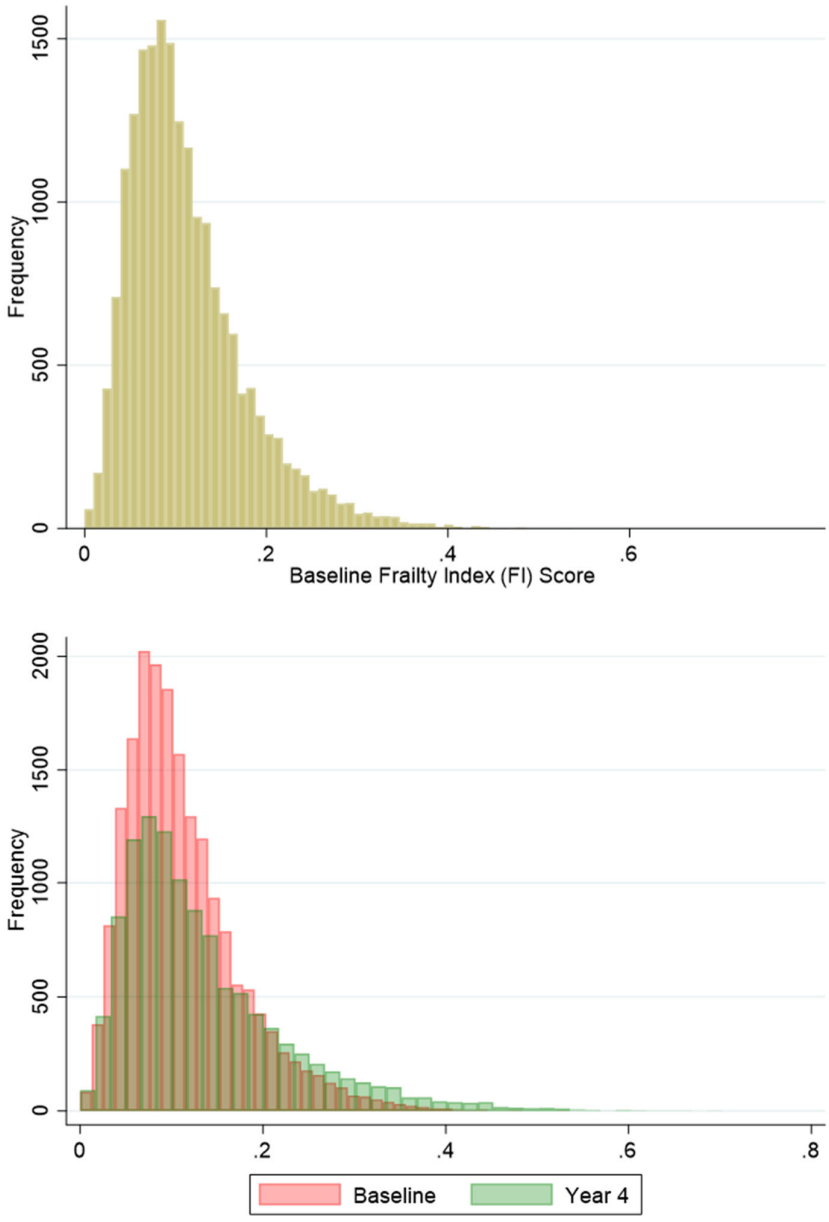

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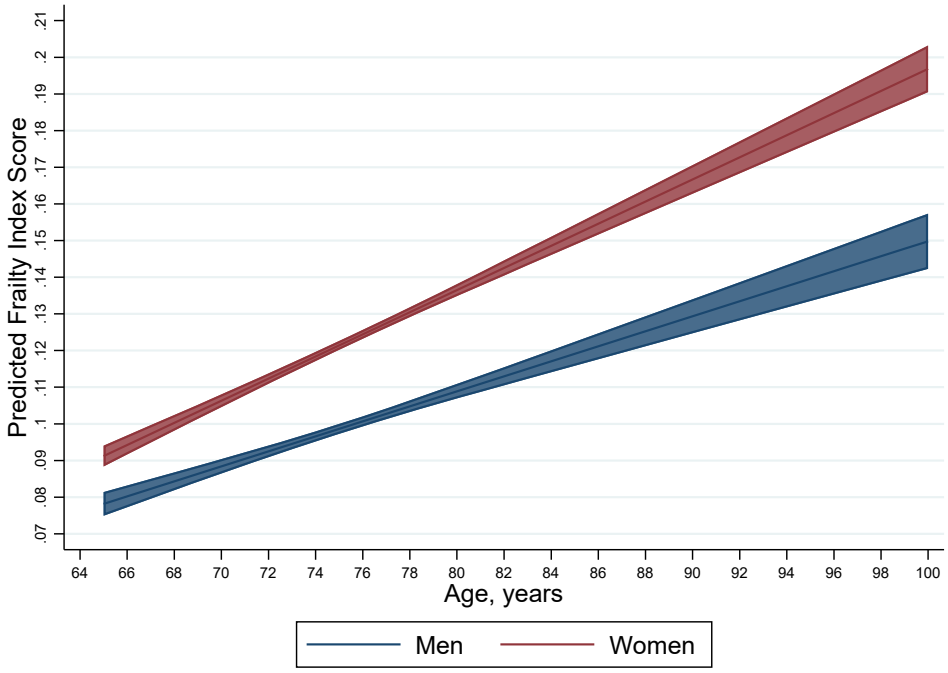

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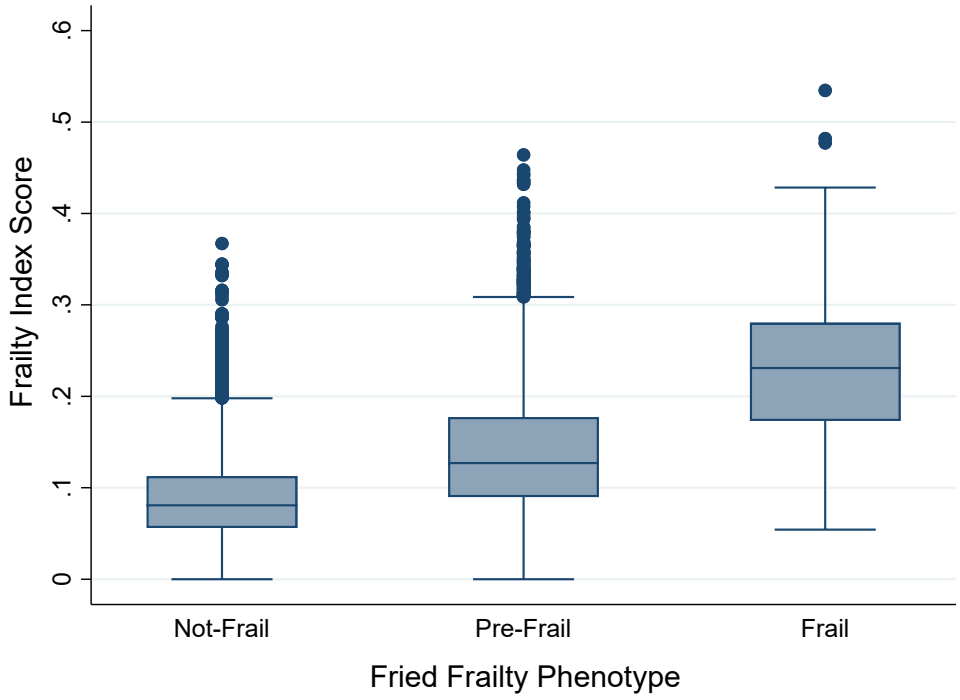
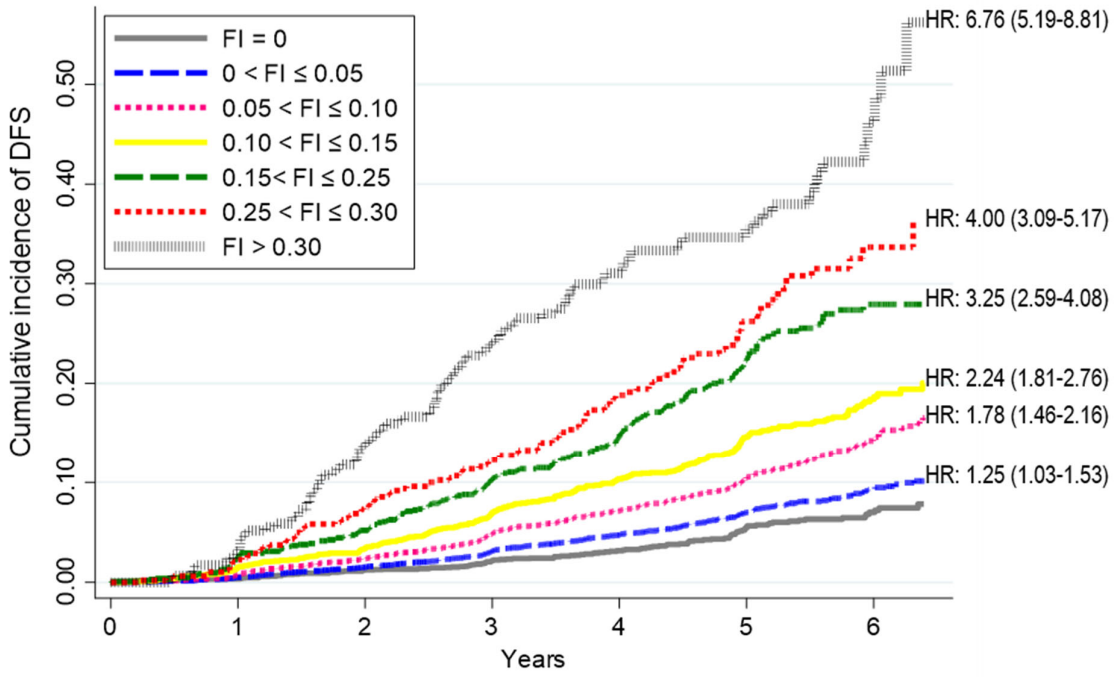


eFigure 3: Frailty Index Score according to Fried frailty phenotype categories.



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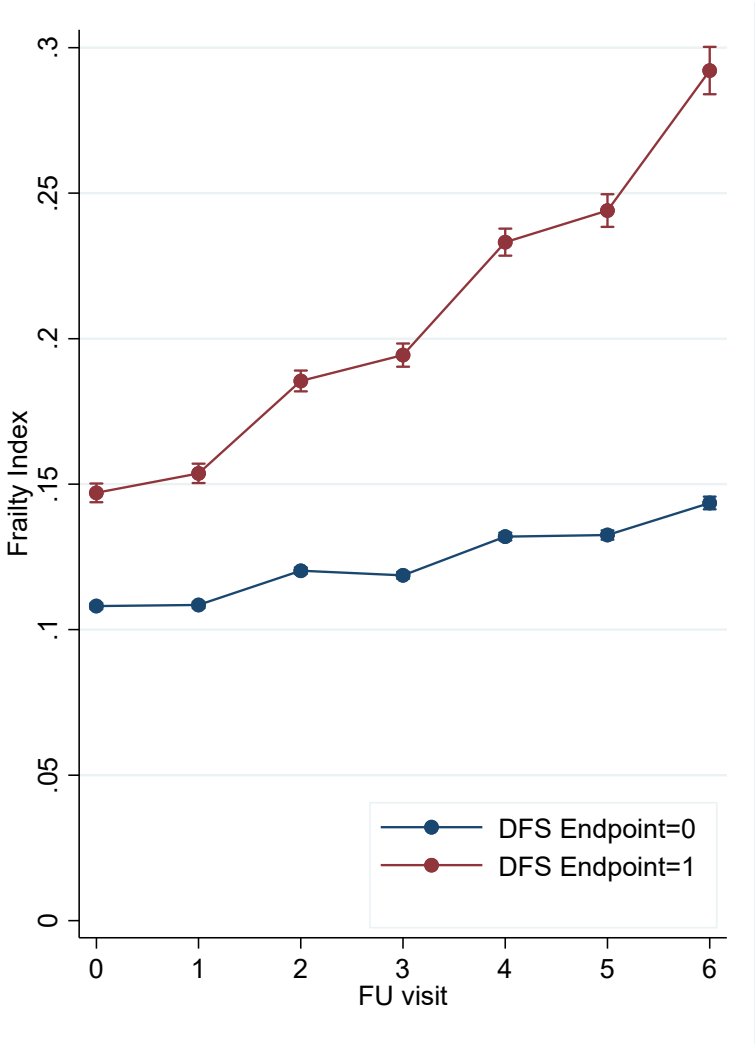

eFigure 5: Mean Frailty Index trajectory in participants who reached the DFS endpoint and those who did not.

eTable 1. The 67-Item ASPREE Frailty Index.

Health deficit	Source	Scoring & cut-offs
Disease diagnosis (11)		
Cancer	ASPREE endpoint (self-report at baseline)	No = 0; Past cancer at baseline = 0.5; Yes = 1
Depression (CES-D-10 score)	ASPREE endpoint	≤ 7 = 0; 8-11 = 0.5; ≥12 or hospitalization for depression = 1
Diabetes	Clinical measure & drugs	No = 0; Yes = 1
Stroke (ischemic or hemorrhagic)	ASPREE endpoint	No = 0; Yes =1
Major Hemorrhage (excluding stroke)	ASPREE endpoint	No = 0; Yes =1
Myocardial infarction	ASPREE endpoint	No = 0; Yes =1
Gastroesophageal reflux disease	Self-report	No = 0; Yes =1
Hospitalization for heart failure	ASPREE endpoint	No = 0; Yes =1
Osteoarthritis	Self-report	No = 0; Yes =1
Osteoporosis	Prescription drugs	No = 0; Yes =1
Urinary incontinence	Prescription drugs	No = 0; Yes =1
Disease indicators (13)		
Albuminuria	Clinical measure	No = 0; micro = 0.5; macro = 1
Anemia	Clinical measure	No = 0; Yes =1 (men <13g/dl & women <12 g/dl)
Central adiposity	Clinical measure	No = 0; Yes = 1 (>105cm men & >88cm women)
Dyslipidemia	Clinical & drugs	No = 0; Yes = 1
Hospitalizations in last year	Medical reports	0 = 0; 1-4 = 0.33; 5-9 = 0.67; ≥10 = 1
Hypertension	Clinical measure	SBP <140mmHg = 0; 140-159 = 0.33; 160-179 = 0.67; ≥ 180 = 1
Hypotension	Clinical measure	No = 0, Yes =1 (SBP <100 mg Hg)
Number of Drugs	Prescription drugs	0 = 0; 1-4 = 0.33; 5-9 = 0.67; ≥10 = 1
Obesity	Clinical measure	BMI <30 = 0; BMI ≥ 30 kg/m^2;
Chronic Kidney Disease	Clinical measure	No = 0; Yes =1 (Estimated Glomerular Filtration Rate, eGFR <60)
Self-rated health status	SF-12 questionnaire	0 = excellent; 0.25 = very good; 0.5 = good; 0.75 = fair; 1 = poor
Smoking	Self-report	Never = 0; Past = 0.5; Current = 1
Underweight	Clinical measure	No = 0; Yes =1 (BMI < 18.5 kg/m^2)
Functional status (26)		
Difficulty with bathing	ADL questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do or requires assistance = 1
Difficulty with dressing	ADL questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do or requires assistance = 1
Difficulty with eating	ADL questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do or requires assistance = 1

Health deficit	Source	Scoring & cut-offs
Difficulty with toileting	ADL questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do or requires assistance = 1
Difficulty with transferring	ADL questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do or requires assistance = 1
Difficulty walking	ADL questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do or requires assistance = 1
Accomplished less	SF-12 questionnaire	None = 0; a little = 0.25; some = 0.50; most = 0.75; always = 1
Climbing stairs limited	SF-12 questionnaire	No = 0; a little = 0.5; a lot = 1
Limited in kind of work/activities	SF-12 questionnaire	None = 0; a little = 0.25; some = 0.50; most = 0.75; always = 1
Moderate activities limited	SF-12 questionnaire	No = 0; a little = 0.5; a lot = 1
Pain interfere with work	SF-12 questionnaire	No = 0; a bit = 0.35; moderate = 0.5; quite a bit = 0.75; extreme = 5
Requires a walking aid	LIFE questions	No = 0; Yes = 1
Any walking outside	LIFE questions	Yes =0, No = 1
Difficulty walking several blocks	FAST questionnaire	No=0, Yes=1
Difficulty walking 8-12 blocks	LIFE questions	No=0, Yes=1
Difficulty climbing 1 flight of stairs	FAST questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do = 1
Difficulty getting into a car	FAST questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do = 1
Difficulty gripping objects	FAST questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do = 1
Difficulty lifting 10 pounds	FAST questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do = 1
Difficulty lifting heavy objects	FAST questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do = 1
Difficulty raising arms above head	FAST questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do = 1
Difficulty running errands	FAST questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do = 1
Difficulty walking 1 block	FAST questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do = 1
Difficulty with light housework	FAST questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do = 1
Difficulty with meal preparation	FAST questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do = 1
Difficulty with shopping	LIFE questions	No=0, Yes=1
Mental & Psychosocial (11)		
Accomplished less due to emotional problems	SF-12 questionnaire	None = 0; a little = 0.25; some = 0.50; most = 0.75; always = 1
A lot of energy	SF-12 questionnaire	Always = 0; most = 0.25; some = 0.50; a little = 0.75; never = 1
Calm or peaceful	SF-12 questionnaire	Always = 0; most = 0.25; some = 0.50; a little = 0.75; never = 1
Difficulty participating in community activities	FAST questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do = 1
Difficulty taking care of family	FAST questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do = 1
Difficulty using the telephone	FAST questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do = 1
Difficulty with financial management	FAST questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do = 1

Health deficit	Source	Scoring & cut-offs
Difficulty visiting relatives/friends	FAST questionnaire	None = 0; a little = 0.25; some = 0.5; a lot = 0.75; unable to do = 1
Downhearted and depressed	SF-12 questionnaire	None = 0; a little = 0.25; some = 0.50; most = 0.75; always = 1
Less careful in work/activities	SF-12 questionnaire	None = 0; a little = 0.25; some = 0.50; most = 0.75; always = 1
Social activities impacted by health	SF-12 questionnaire	None = 0; a little = 0.25; some = 0.50; most = 0.75; always = 1
Cognition & Performance (6)		
Episodic memory, delayed recall	HVLT-R questionnaire	No = 0, Yes=1 [≤4 at baseline or >1.5SD decline over follow-up]
Low Global cognition	3MS questionnaire	No = 0, Yes=1 [< 78 or decline >10-point decline over follow-up]
Low Psychomotor Speed	SDMT questionnaire	No = 0, Yes=1 [≤14 at baseline or >1.5SD decline over follow-up]
Low Language and Executive Function	COWAT questionnaire	No = 0, Yes=1 [≤7 at baseline or >1.5SD decline over follow-up]
Slow Gait speed over 3 meters	Clinical measure	No = 0; Yes = 1 [Lowest quintile defined at baseline according to sex and height]
Weak handgrip strength	Clinical measure	No = 0; Yes = 1 [Lowest quintile defined at baseline according to sex and BMI]

Notes: 3MS: Modified Mini-Mental State Examination; ADL: Activity of Daily Living; BMI: Body mass index, calculated based on measured weight (kg) and height (m^2); CES-D: Center for the Epidemiologic Studies Depression scale; COWAT: Controlled Oral Word Association Test; HVLT-R: Hopkins Verbal Learning Test Revised; SBP: Systolic Blood Pressure; SDMT: Symbol Digit Modalities Test; SF-12: 12-item short-form questionnaire

eTable 2. Summary statistics of the ASPREE Frailty Index score across follow-up, for men (top) and women separately.

MEN	**Baseline**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
N	8,331	7,922	7,595	6,598	4,910	3,075	1,092
Mean (SD)	0.10 (0.06)	0.10 (0.07)	0.11 (0.07)	0.11 (0.07)	0.12 (0.08)	0.12 (0.08)	0.13 (0.08)
Median (25-75%)	0.09 (0.06-0.13)	0.09 (0.06-0.13)	0.09 (0.06-0.13)	0.09 (0.06-0.14)	0.10 (0.06-0.15)	0.10 (0.06-0.15)	0.10 (0.06-0.16)
99% submaximal	0.29	0.34	0.38	0.37	0.40	0.43	0.43
FI pre-frail[1] (%)	35.6%	31.8%	34.6%	35.0%	35.7%	35.7%	38.3%
FI frail[2] (%)	4.7%	6.5%	8.4%	9.0%	11.5%	12.2%	12.9%
WOMEN							
N	10,779	10,168	9,706	8,501	6,451	4,107	1,591
Mean (SD)	0.12 (0.07)	0.13 (0.08)	0.14 (0.09)	0.14 (0.09)	0.15 (0.10)	0.15 (0.09)	0.15 (0.10)
Median (25-75%)	0.11 (0.07-0.16)	0.11 (0.07-0.16)	0.12 (0.08-0.18)	0.11 (0.08-0.18)	0.12 (0.08-0.20)	0.13 (0.08-0.20)	0.13 (0.08-0.19)
99% submaximal	0.34	0.39	0.42	0.41	0.46	0.45	0.48
FI pre-frail[1] (%)	35.6%	40.5%	41.2%	41.0%	40.9%	41.5%	43.1%
FI frail[2] (%)	4.7%	13.5%	17.1%	17.4%	21.1%	21.5%	20.6%

[1]An FI score > 0.1 and ≤ 0.21.

[2]An FI score >0.21.

eTable 3: The comparison between participants classified as pre-frail and frail defined using the FI and the Fried phenotype.

Fried frailty phenotype[1]		**Frailty Index (FI)**		
		Not frail (≤ 0.10)	Pre-frail (>0.10 & <0.21)	Frail (≥ 0.21)
Not frail (0 components)	n; %	7236; 66.2%	3541; 32.4%	159; 1.4%
Pre-frail (1-2 components)	n; %	2337; 32.1%	3862; 53.1%	1078; 14.8%
Frail (3+ components)	n; %	19; 4.6%	149; 35.8%	248; 59.6%

[1]Cut-offs were used to define pre-frail and frail according to modified Fried frailty phenotype, as previously [1].
Chi-square p<0.0001

eTable 4. Cox proportional hazards regression for the association between ASPREE Frailty Index score and persistent physical disability endpoint over a median 4.7 years, when FI scores were grouped into seven categories (n=19,110).

Frailty Index score	Events n (%)	HR per 0.01 (95% CI), p
FI = 0	14 (3.4)	1.00 [Ref]
0 < FI ≤ 0.05	44 (10.7)	1.11 (0.61-2.03, p=0.73)
0.05 < FI ≤ 0.10	76 (18.5)	2.64 (1.49-4.67), p=0.001
0.10 < FI ≤ 0.15	82 (19.9)	5.89 (3.33-10.40), p<0.001
0.15< FI ≤ 0.25	84 (20.4)	14.10 (7.97-24.95), p<0.001
0.25 < FI ≤ 0.30	45 (10.9)	17.15 (9.38-31.37), p<0.001
FI > 0.30	67 (16.3)	48.23 (26.96-86.27), p<0.001

Notes: Models were adjusted for age and gender.

eTable 5. Cox proportional hazards regression for the association between Frailty Index score at baseline and the ASPREE composite primary endpoint (DFS)[1] and persistent physical disability endpoint over a median 4.7 years (n=19,110).

	Primary Composite Endpoint (1,835 events) HR (95% CI), p value	**Persistent Disability (412 events)** HR (95% CI), p value
Univariate		
Frailty Index[2]	1.08 (1.07 to 1.08), p<0.001	1.15 (1.14 to 1.16), p<0.001
Multivariable		
Frailty Index[2]	1.07 (1.06 to 1.08), p<0.001	1.15 (1.13 to 1.16), p<0.001
Age, years	1.10 (1.10 to 1.11), p<0.001	1.09 (1.07 to 1.10), p<0.001
Male	1.70 (1.56 to 1.88), p<0.001	1.61 (1.31 to 1.97), p<0.001
Ethno-racial group		
White Australian	1 (reference)	1 (reference)
White U.S.	0.99 (0.82-1.18), p=0.88	0.73 (0.49-1.11), p=0.14
African-American	1.45 (1.18-1.79), p<0.001	0.92 (0.58-1.44), p=0.69
Hispanic/Latino	1.09 (0.79-1.51), p=0.60	1.04 (0.52-2.11), p=0.91
Other	0.90 (0.60-1.35), p=0.62	0.15 (0.02-1.06), p=0.06

[1]The primary endpoint was a composite of death, dementia or physical disability.
[2]HR is per 0.01-unit

eTable 6. Hazard ratios (95% confidence intervals) from multivariable Cox proportional hazards regression for the association between Frailty index and the ASPREE composite primary endpoint (DFS)[1] across different ethno-racial groups.

	Australian white N=16,360 HR (95% CI)	U.S. white N=1088 HR (95% CI)	U.S. African-American N=899 HR (95% CI)	U.S. Hispanic-Latino N=488 HR (95% CI)	Other N=275 HR (95% CI)
Frailty Index, per 0.01-unit	1.07 (1.06-1.08)	1.06 (1.03-1.08)	1.06 (1.03-1.09)	1.07 (1.02-1.12)	1.07 (1.06-1.08)
Age, year	1.11 (1.10-1.12)	1.12 (1.08-1.15)	1.07 (1.04-1.11)	1.10 (1.03-1.17)	1.11 (1.10-1.12)
Male	1.66 (1.50-1.84)	1.64 (1.14-2.37)	2.23 (1.46-3.41)	2.20 (1.13-4.27)	1.71 (1.56-1.88)

[1]The primary endpoint was a composite of death, dementia or physical disability.

eTable7: The risk of the composite DFS[1], and persistent physical disability endpoints associated with Frailty Index and Fried phenotype, when considered together in adjusted multivariate models (n=18,629[2]).

Combined	**DFS (1,776 events)**	**Disability (394 events)**
	HR per 0.1 unit (95% CI), p value	HR per 0.1 unit (95% CI), p value
Frailty Index	1.72 (1.59 to 1.85), p<0.001	3.72 (3.27 to 4.23), p<0.001
Fried phenotype	1.11 (1.08 to 1.15), p<0.001	1.07 (1.00 to 1.14), p=0.04
	HR (95% CI), p value	HR (95% CI), p value
Frailty Index		
Not Frail	1.00 (Reference)	1.00 (Reference)
Pre-frail	1.54 (1.38-1.73), <0.001	3.47 (2.52-4.79), <0.001
Frail	3.01 (2.58-3.52), <0.001	16.4 (11.5-23.4), <0.001
Fried phenotype		
Not Frail	1.00 (Reference)	1.00 (Reference)
Pre-frail	1.46 (1.31-1.63), <0.001	1.70 (1.30-2.20), <0.001
Frail	2.05 (1.65-2.54), <0.001	2.39 (1.60-3.56), <0.001

[1]The primary endpoint was a composite of death, dementia or physical disability.

[2]481 participants were missing one of the components of the Fried frailty phenotype, and are thus not included here.

eTable8. Separate multivariate[a] Cox proportional hazards regression for the association between Frailty Index and Fried phenotype at baseline and the ASPREE composite primary endpoint (DFS)[1], and persistent physical disability endpoints over a median 4.7 years (n=19,110).

	Frailty Index (n=19,110)	Fried phenotype (n=18,629[4])
DFS[2]	HR[3] (95% CI), p value	HR[3] (95% CI), p value
Continuous measure[3]	1.95 (1.84 to 2.07), p<0.001	1.25 (1.22 to 1.29), p<0.001
Categorical measure		
Not Frail	1.00 (Reference)	1.00 (Reference)
Pre-frail	1.73 (1.56 to 1.93), p<0.001	1.88 (1.68 to 2.06), p<0.001
Frail	3.91 (3.41 to 4.48), p<0.001	3.74 (3.07 to 4.55), p<0.001
DISABILITY	HR[3] (95% CI), p value	HR[3] (95% CI), p value
Continuous measure[3]	3.88 (3.52-4.28), <0.001	1.49 (1.42-1.56), <0.001
Categorical measure		
Not Frail	1.00 (Reference)	1.00 (Reference)
Pre-frail	3.85 (2.85-5.19), <0.001	3.51 (2.78-4.45), <0.001
Frail	21.15 (15.5-28.8), <0.001	11.3 (7.84-16.2), <0.001

[1]The models were adjusted for age, sex and ethno-racial group.

[2]The primary endpoint was a composite of death, dementia or physical disability.

[3]HR is per 0.1-unit increase.

[4]481 participants were missing one of the components of the Fried frailty phenotype, and are thus not included here.

eTable 9. Cox proportional hazards regression[1] for the association between composite frailty category[2] and the ASPREE composite primary endpoint (DFS) over a median 4.7 years (n=18,629).

Composite Frailty Category	Events n (%)	HR (95% CI), p
Not Frail both	369 (11.2)	1.00 [Ref]
Not Frail Index, Pre-Frail Fried	203 (18.6)	1.43 (1.20-1.70), p<0.001
Pre-Frail Index, Not Frail Fried	270 (17.2)	1.55 (1.32-1.81), p<0.001
Pre-Frail both	530 (30.6)	2.20 (1.92-2.53), p<0.001
Not Frail Index, Frail Fried[3]	2 (24.8)	1.46 (0.36-5.87), p=0.60
Frail Index, Not Frail Fried[3]	16 (23.4)	2.23 (1.35-3.68), p=0.002
Pre-Frail Index, Frail Fried	42 (65.7)	3.59 (2.59-4.97), p<0.001
Frail Index, Pre-Frail Fried	259 (58.5)	4.53 (3.84-5.35), p<0.001
Frail both	85 (87.9)	5.82 (4.57-7.41), p<0.001

[1]Models were adjusted for age, gender and ethno-racial category.

[2] The composite frailty score considered categorization of participants into frailty status groups, based on both the FI and the Fried phenotype.

[3]The numbers of events in these discordant groups are very small, and the estimates are thus less likely to be reliable. These curves are thus not shown in Figure 3b.