Web Appendix

Outcomes at follow-up

The Fried frailty measure (2007-9)

Frailty was measured using the Fried frailty scale at the end of follow-up (phase 9, 2007-9). This measure comprises the following components (cut-offs for each component are based on that of Fried and colleagues).[1]

1. *Exhaustion*: defined using two items drawn from the Center for Epidemiology Studies-Depression (CES-D) scale:[2] "I felt that everything I did was an effort in the last week" and "I could not get going in the last week". If participants answered "occasionally or moderate amount of the time (3-4 days)" or "most or all of the time (5-7 days)" to either of these items, they were categorized as exhausted.

2. *Physical activity*: based on a modified version of the Minnesota leisure-time physical activity questionnaire[3] which includes 20 items on the frequency and duration of participation in different physical activities (e.g., running, cycling, other sports, housework, and gardening activities). Total hours per week were calculated for each activity and a metabolic equivalent (MET) value was assigned to each based on a compendium of values.[4] Energy expenditure (kcal/week) was computed for each participant. Low levels of physical activity were denoted by an expenditure of <383 kcal/week (men) and 270 (women).

3. *Walking speed*: based on the duration of walking a distance of 8-foot (2.4 meters) at usual pace. Established cut-offs for this characteristic are based on results for a 15 feet (4.6 meters) walking test. Accordingly, participants were categorized as having slow walking speed when time to walk 8 feet was $\geq$ 3.73 seconds (for men with height $\leq$ 173 cm or women with height $\leq$ 159 cm) or $\geq$ 3.20 seconds (for men with height > 173 cm or women with height > 159 cm).

4. *Grip strength*: measured in kilograms using the Smedley hand grip dynamometer. Cut-offs were stratified by gender and body mass index (BMI). For men, low grip strength was denoted as: $\leq$ 29 kg

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(BMI $\leq$24 kg/m^2), $\leq$ 30 (BMI 24.1-28), and $\leq$ 32 (BMI > 28). For women, low grip strength was: $\leq$ 17 (BMI $\leq$23), $\leq$ 17.3 (BMI 23.1-26), $\leq$ 18 (BMI 26.1-29), and $\leq$ 21 (BMI > 29).

5. *Weight loss*: weight loss in the context of frailty has been defined as being either unintentional or as a proportion of body weight lost over the previous year. We used data from phases 7 and 9 to identify weight loss of greater than 10%, in accordance with that in the Women's Health Aging Study-I.[5]

A total frailty score was calculated by allocating a value of 1 to each of the above criteria if present, resulting in a range of 0 to 5. Participants were classified as "frail" if they had at least three out of five of the frailty components; as "pre-frail" if they had 1-2; and as "non-frail" if they had none of these components.[1]

CVD outcomes (1997-9 to 2007-9)

1. Non-fatal CHD events

CHD diagnoses included ischemic heart diseases (international classification of diseases version 9 (ICD-9) codes 410–414 or ICD-10 codes I20–I25)[6] which included non-fatal myocardial infarction (MI), angina pectoris, and other forms of ischemic heart disease. Information on non-fatal MI and angina was obtained from several sources. From 1989 onwards the British National Health Service (NHS) Hospital Episode Statistics (HES)[7] database has provided reports of participants' diagnoses on discharge and procedure codes for all NHS hospitals in England and Wales. Participants also self-report CHD events in our health survey questionnaires. These are then validated using the study resting electrocardiograms, the HES database, and by contacting general practitioners for confirmation when no other external source exists.

2. Non-fatal stroke events

Non-fatal stroke included first subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction, and not specified stroke (ICD-10 codes I60 – I64), and transient cerebral ischemic attacks (ICD-10 codes G45). The cases were ascertained from participants' general practitioners, information extracted from hospital medical records by study nurses, or data from the NHS HES database obtained after linking the

participants' unique NHS identification numbers to this national database. Self-reported stroke cases without clinical verification were excluded.

3. A composite of non-fatal CVD cases including the above two groups

References

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2   Radloff LS. The CES-D Scale. *Applied Psychological Measurement* 1977;1:385-401.

3   Singh-Manoux A, Hillsdon M, Brunner E, Marmot M. Effects of physical activity on cognitive functioning in middle age: evidence from the Whitehall II prospective cohort study. *Am J Public Health* 2005;95:2252-2258.

4   Ainsworth BE, Haskell WL, Leon AS, Jacobs DR, Jr., Montoye HJ, Sallis JF et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc* 1993;25:71-80.

5   Boyd CM, Xue QL, Simpson CF, Guralnik JM, Fried LP. Frailty, hospitalization, and progression of disability in a cohort of disabled older women. *Am J Med* 2005;118:1225-1231.

6   World Health Organization, Division of Health Situation and Trend Assessment. International classification of diseases translator ninth and tenth revisions : user's guide to electronic tables. Geneva: World Health Organization; 1997.

7   The NHS Information Centre for health and social care. Hospital Episode Statistics (HES) online. http://www.hesonline.nhs.uk (accessed 25 Jan 2011).

Table S1. Association between CVD risk factors mutually adjusted for CVD risk scores and frailty

CVD risk scores	Odds ratio for frailty (95% CI)
Framingham CVD score	
Unadjusted	1.42 (1.23, 1.62)
Adjusted for	
Age	1.24 (1.04, 1.48)
Total cholesterol	1.46 (1.26, 1.69)
HDL cholesterol	1.47 (1.27, 1.70)
Systolic blood pressure	1.53 (1.30, 1.80)
Antihypertensive treatment	1.33 (1.14, 1.55)
Smoking	1.40 (1.22, 1.62)
Diabetes	1.45 (1.24, 1.70)
Framingham CHD score	
Unadjusted	1.38 (1.20, 1.59)
Adjusted for	
Age	1.22 (1.03, 1.44)
Total cholesterol	1.42 (1.22, 1.65)
HDL cholesterol	1.46 (1.26, 1.71)
Systolic blood pressure	1.43 (1.22, 1.67)
Diastolic blood pressure	1.41 (1.21, 1.63)
Smoking	1.37 (1.18, 1.59)
Diabetes	1.38 (1.18, 1.61)
Framingham stroke score	
Unadjusted	1.35 (1.21, 1.51)
Adjusted for	
Age	1.23 (1.07, 1.41)
Systolic blood pressure	1.45 (1.26, 1.67)
Antihypertensive treatment	1.28 (1.13, 1.45)
Smoking	1.34 (1.20, 1.51)
Diabetes	1.35 (1.19, 1.52)
Atrial fibrillation	-
Left ventricular hypertrophy	1.43 (1.23, 1.67)
SCORE	
Unadjusted	1.36 (1.18, 1.56)
Adjusted for	
Age	1.12 (0.89, 1.39)
Total cholesterol	1.43 (1.22, 1.67)

Systolic blood pressure	1.45 (1.22, 1.73)
Smoking	1.34 (1.17, 1.55)

Table S2. Comparison of characteristics between included participants in the present analysis with not included participants but eligible at baseline (phase 5) and alive at the end of follow-up (phase 9), N=7412.

	Study participants N=3895		Not included participants N=3517		P-value*
	N	% / Mean (SD)	N	% / Mean (SD)	
Age in years	3895	55.2 (5.9)	3517	56.3 (6.0)	<0.0001
Sex					
Men	2858	73.4	2302	65.5	<0.0001
Women	1037	26.6	1215	34.5	
Ethnicity					
White	3647	93.6	3129	89.0	<0.0001
Non-White	248	6.4	388	11.0	
Employment status					
Administrative	1812	46.5	1279	36.3	<0.0001
Professional/executive	1695	43.5	1536	43.7	
Clerical/support	388	10.0	702	20.0	
Total cholesterol, mmol/L, mean (SD)	3895	5.92 (1.05)	2245	5.97 (1.08)	0.09
HDL cholesterol, mmol/L, mean (SD)	3895	1.46 (0.39)	1564	1.45 (0.40)	0.38
Systolic blood pressure, mm Hg, mean (SD)	3895	122.7 (16.0)	2306	123.3 (17.0)	0.17
Diastolic blood pressure, mm Hg, mean (SD)	3895	77.6 (10.3)	2306	77.4 (10.7)	0.44
Antihypertensive treatment, n (%)					
No	3515	90.2	2873	83.3	<0.0001
Yes	380	9.8	578	16.7	
Missing	-	-	66	-	
Smoking, n (%)					
No	3593	92.3	2560	87.2	<0.0001
Yes	302	7.7	377	12.8	
Missing	-	-	580	-	
Diabetes, n (%)					
No	3755	96.4	1936	90.1	<0.0001
Yes	140	3.6	214	9.9	
Missing	-	-	1367	-	
Atrial fibrillation, n (%)					
No	3882	99.7	2284	99.4	0.18
Yes	13	0.3	13	0.6	
Missing	-	-	1220	-	
Left ventricular hypertrophy, n (%)					

No	3667	94.10	2154	93.8	0.60
Yes	228	5.90	143	6.2	
Missing	-	-	1220	-	

[*]P for heterogeneity

Table S3. Sensitivity analyses: odds ratios (95% CIs) per one sex-specific standard deviation increment in score using four CVD risk algorithms for future frailty after excluding incident CVD

CVD risk scores	**Non-missing sample**	**Sensitivity analysis 1**	**Sensitivity analysis 2**
	Study sample: n=3895	Study sample excluding incident CVD: n=3552	Multiple imputation: n=7412
Framingham CVD risk score	1.42 (1.23, 1.62)	1.37 (1.17, 1.61)	1.43 (1.28, 1.59)
Framingham CHD risk score	1.38 (1.20, 1.59)	1.32 (1.12, 1.56)	1.34 (1.20, 1.50)
Framingham stroke risk score	1.35 (1.21, 1.51)	1.33 (1.17, 1.52)	1.28 (1.18, 1.39)
SCORE	1.36 (1.18, 1.56)	1.30 (1.10, 1.53)	1.33 (1.20, 1.47)

Abbreviations: CVD, cardiovascular disease.

Table S4. Odds ratio per one sex-specific standard deviation increment in score using four CVD risk algorithms for future pre-frailty and cardiovascular diseases (n=3787)

	Pre-frailty		CVD		
	Number of cases	Odds Ratio (95% CI)	Outcome	Number of cases	Odds ratio (95% CI)
Framingham CVD risk score	1445	1.18 (1.10, 1.26)	CVD	325	1.64 (1.49, 1.79)
Framingham CHD risk score	1445	1.15 (1.08, 1.23)	CHD	298	1.52 (1.38, 1.68)
Framingham stroke risk score	1445	1.16 (1.09, 1.24)	Stroke	35	1.40 (1.17, 1.68)
SCORE (CVD risk score)	1445	1.15 (1.08, 1.23)	CVD	325	1.55 (1.42, 1.70)

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease.