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Cardiovascular disease risk scores in identifying future frailty: the Whitehall II prospective cohort study

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ABSTRACT

Objectives To examine the capacity of existing cardiovascular disease (CVD) risk algorithms widely used in primary care, to predict frailty.
Design Prospective cohort study. Risk algorithms at baseline (1997–1999) were the Framingham CVD, coronary heart disease and stroke risk scores, and the Systematic Coronary Risk Evaluation.
Setting Civil Service departments in London, UK.
Participants 3895 participants (73% men) aged 45–69 years and free of CVD at baseline.
Main outcome measure Status of frailty at the end of follow-up (2007–2009), based on the following indicators: self-reported exhaustion, low physical activity, slow walking speed, low grip strength and weight loss.
Results At the end of the follow-up, 2.8% (n=108) of the sample was classified as frail. All four CVD risk scores were associated with future risk of developing frailty, with ORs per one SD increment in the score ranging from 1.35 (95% CI 1.21 to 1.51) for the Framingham stroke score to 1.42 (1.23 to 1.62) for the Framingham CVD score. These associations remained after excluding incident CVD cases. For comparison, the corresponding ORs for the risk scores and incident cardiovascular events varied between 1.36 (1.15 to 1.61) and 1.64 (1.50 to 1.80) depending on the risk algorithm.
Conclusions The use of CVD risk scores in clinical practice may also have utility for frailty prediction.

INTRODUCTION

Frailty is a clinically recognised geriatric syndrome characterised by declines in functioning across an array of physiological systems.[1] Common symptoms of frailty are weight loss, exhaustion, low physical activity, slow walking speed at 'usual pace' and low grip strength.[1] In the elderly, there is growing evidence that frailty predicts various adverse health outcomes such as disability,[2] institutionalisation,[2] falls,[3] fractures,[3] hospitalisation[4] and mortality.[3] In order to design interventions for preventing frailty, it is important to identify individuals at risk of developing the syndrome.

In addition to cardiovascular disease (CVD), there is increasing evidence to suggest that CVD risk factors measured in midlife predict a wide range of old-age health outcomes including cognitive decline and dementia,[5] late-life depression[6] and disability.[7] Although few large-scale prospective studies have examined the association between CVD risk factors and frailty, such a link is plausible for at least two reasons. First, several studies have shown a cross-sectional association between CVD and frailty.[2] In one cross-sectional study, subclinical CVD diagnosed using non-invasive testing (carotid ultrasound, ankle–arm index, electrocardiography, echocardiography and cerebral MRI) was related to frailty after excluding clinically diagnosed CVD.[8] Second, several individual risk factors included in multi-factorial prediction algorithms of CVD, such as the Framingham score, have been associated with frailty status: high blood pressure,[9] diabetes,[9] low high-density lipoprotein (HDL)-cholesterol level[10] and cigarette smoking.[11]

In this study, we hypothesised that CVD risk scores used to assess 10-year risk of CVD would be associated with subsequent frailty status in people who were initially CVD-free. If a strong association between CVD risk scores and frailty is confirmed, these scores, importantly already routinely administered in clinical practice, would present a convenient way to identify individuals at an increased risk of frailty later in life and in need of early preventive measures. Evidence from randomised controlled trials suggest that exercise programmes[12] and selected drugs (eg, dehydroepiandrosterone[13] and testosterone[14]) can reverse frailty.

METHODS

Study population

Data were drawn from the Whitehall II study, an ongoing longitudinal study of 10 308 (67% men) London-based British civil servants aged 35–55 years in 1985.[15] Study inception (phase 1) took place during 1985–1988 and involved a clinical examination and self-administered questionnaire. Subsequent phases of data collection have alternated between postal questionnaire alone (phases 2 (1988–1990), 4 (1995–1996), 6 (2001), 8 (2006) and 10 (2011)), and postal questionnaire accompanied by a clinical examination approximately every 5 years (phases 3 (1991–1993), 5 (1997–1999), 7 (2002–2004) and 9 (2007–2009)).

We utilised CVD risk factors measured at phase 5 ('baseline' for the purposes of our analyses) to assess the risk of developing frailty at phase 9 when the frailty components were first measured. This design provides a 10-year follow-up corresponding to that of the CVD risk prediction models we utilised.[16–19]

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CVD risk factors at baseline

Blood samples were collected following either an 8-h overnight fast or at least a 4-h fast after a light fat-free breakfast. Serum for lipid analyses was refrigerated at −4°C and assayed within 72 h. Total cholesterol was determined by an enzymatic procedure using the automated cholesterol oxidase-phenol aminophenazone (CHOD-PAP) method. Serum HDL-cholesterol concentrations were measured from the supernatant after precipitation of non-HDL-cholesterol with phosphotungstate. Systolic blood pressure was measured twice with the Hawksley random zero sphygmomanometer in the sitting position after 5 min rest. We used the average of the two readings in the present analyses. Participants reported the medications used in the previous 14 days; responses were coded using the British National Formulary codes.[20] Antihypertensive therapy was based on the use of the following drugs: diuretics, β-blockers, ACE inhibitors, calcium channel blockers and other antihypertensive drugs. Current smoking (yes/no) was ascertained by self-report. Prevalent diabetes mellitus was defined based on reported doctor-diagnosed diabetes mellitus or use of diabetes medication, or when participants had a baseline fasting plasma glucose level >126 mg/dl (>7.0 mmol/l).[21] Presence of atrial fibrillation and left ventricular hypertrophy was determined on the ECG using the Minnesota Code:[22] atrial fibrillation is coded as 8-3-1 and left ventricular hypertrophy as 3-1-0.

CVD risk scores at baseline

In addition to first relating individual CVD risk factors to later frailty risk, we also examined the predictive capacity of four established CVD risk score algorithms: the Framingham CVD,[18] coronary heart disease (CHD),[19] stroke prediction models[17] and SCORE (systematic coronary risk evaluation).[16] Table 1 summarises all components included in the models, described below.

Outcomes at follow-up

Frailty was measured using the Fried frailty scale at the end of follow-up (phase 9, 2007–2009). This measure comprises the following components: self-reported exhaustion, low physical activity, slow walking speed, low grip strength and weight loss (cut-offs for each component are based on that of Fried *et al*).[1] A total frailty score was calculated by allocating a value of 1 to each of the criteria if present, resulting in a range of 0–5. 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] Validated CVD outcomes (non-fatal CHD, non-fatal stroke, and a composite of non-fatal CVD cases including both groups) were assessed over the follow-up period (1997–1999 to 2007–2009). More details are available in the supplementary web appendix.

Statistical analyses

Each CVD risk factor at baseline was described according to the frailty status (frail, pre-frail, and non-frail) at year 10 of follow-up using the χ^2 test, Fisher's exact test or analysis of variance as appropriate. We then summarised these associations using binary logistic regression analyses with frailty status dichotomised: frail versus pre-frail/non-frail. As the mean risk scores in men were systematically higher than those in women (p values for all four scores <0.0001), we standardised these risk scores into standard scores (mean=0, SD=1) in men and women separately. The OR of being frail or pre-frail was estimated per one SD increase (higher score represents greater CVD risk) in the risk scores over the 10-year follow-up. As sex did not modify the relation of the standardised risk scores with frailty at follow-up (all p values for sex interaction >0.61), men and women were combined in the analysis.

In examining the associations between individual risk factors and later frailty, we initially produced sex-adjusted models and then adjusted for the other risk factors to explore the independent effect of individual CVD risk factors with frailty. Binary logistic regression models were then used to examine the impact of a one SD increment in the risk scores on frailty at follow-up. We also examined the association between the CVD risk scores and incident cardiovascular events (CVD, CHD and strokes) to compare the strength of their associations to that with frailty. In addition, we conducted several sensitivity analyses. (1) To examine whether the association between the risk scores and frailty was mediated by underlying CVD, we estimated the strength of this association after excluding incident CVD cases. (2) To examine whether the association between the risk scores and frailty was biased by missing data, we imputed data for missing frailty status and individual CVD risk factors included in the risk scores. This was done for participants eligible at phase 5 and alive at the end of follow-up (n=7412) using the method of multiple imputation by chained equations performed with an SAS-callable software application, IVEware.[23] (3) We tested whether the CVD risk scores also predict 'pre-frailty' in a cohort excluding the frailty cases (see supplementary web appendix). Finally, to explore the extent to which the relationship between the risk scores and frailty was driven by specific CVD risk factors included in the scores, analyses on the risk scores–frailty associations were adjusted individually for each of their risk factors (see supplementary web appendix, table S1). A greater attenuation in the association after adjustment indicates a greater contribution of that specific risk factor. All analyses were performed with SAS V.9.1.

RESULTS

Of the 7870 study members who participated at phase 5, a total of 3895 participants (1037 women) aged 45–69 years constituted the analytic sample (figure 1). Compared with participants

Table 1 Composition of the SCORE and Framingham CVD, CHD and stroke risk algorithms

Score	Country	Sex	Age	Total C	HDL-C	SBP	DBP	AHTD	Smoking	Diabetes	CVD	AF	LVH
Framingham CVD	USA	+	+	+	+	+		+	+	+			
Framingham CHD	USA	+	+	+	+	+	+		+	+			
Framingham stroke	USA	+	+			+		+	+	+	+	+	+
SCORE	Europe	+	+	+		+			+				

AHTD, antihypertensive drug; AF, atrial fibrillation; CVD, cardiovascular disease; CHD, coronary heart disease; C, cholesterol; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; SBP, systolic blood pressure; SCORE, Systematic Coronary Risk Evaluation.

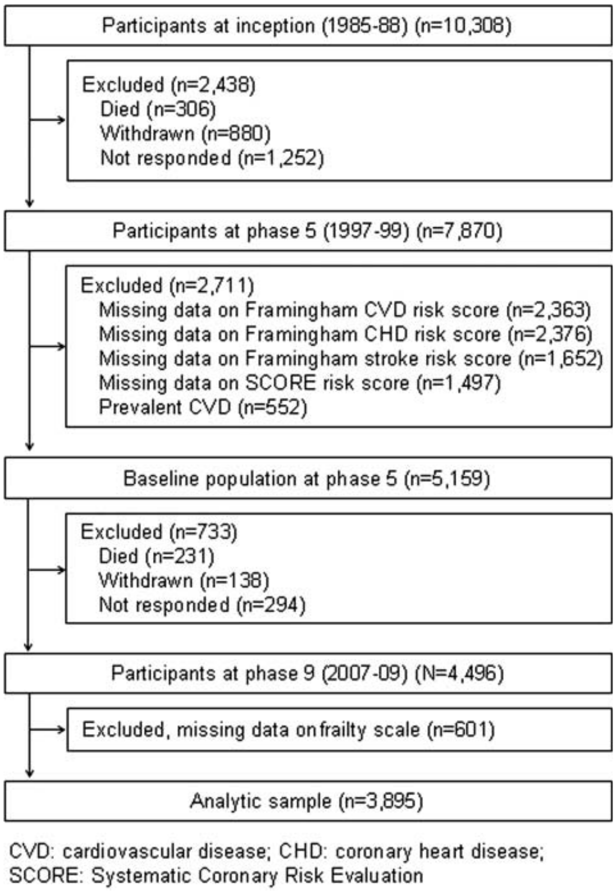

Figure 1 Flow of study members through the data collection phases in Whitehall II.

alive at phase 9 but excluded (owing to non-participation at phases 5 and 9, prior history of CVD at phase 5, and missing data on the CVD risk scores or the frailty scale, total n=3517), persons included in the analytic sample (n=3895) were 1.1 years younger (p<0.0001), less likely to be female (26.6% vs 34.5%, p<0.0001) and less likely to be from the lower socio-economic group (10.0% vs 20.0%, p<0.0001) (see supplementary web appendix, table S2).

In table 2 we present the baseline characteristics of participants according to frailty status at the end of follow-up, on average 10.5 years (SD=0.5) after the measurement of CVD risk scores. Of the 3895 participants, 2.8% were classified as frail, 37.1% as pre-frail and 60.1% as non-frail. In comparison with non-frail participants, frail participants were more likely to be older, female, use antihypertensive treatment, smoke and have diabetes. Frail participants were also more likely to have experienced a CVD event during the follow-up relative to their non-frail counterparts (incidence 16.7% vs 8.5%, p=0.01).

In table 3, we present the association between the individual CVD risk factors at baseline and frailty at follow-up. In the model including all risk factors, only two were independently associated with future frailty: increased age and use of antihypertensive treatment. Thus, a one SD increment in age (5.9 years for men and women) increased the odds of being frail by 56% (OR=1.56, 95% CI 1.28 to 1.92) and using an antihypertensive treatment increased the odds by 77% (OR=1.77, 95% CI 1.10 to 2.94).

Table 4 shows the association of a one SD increment in the CVD risk scores with future frailty and cardiovascular events. All risk scores had a similar strength of association with frailty, with the ORs ranging from 1.35 (95% CI 1.21 to 1.51) for the Framingham stroke risk score to 1.42 (95% CI 1.23 to 1.62) for the Framingham CVD risk score. As expected, the association of the CVD risk scores was stronger in relation to predicting CVD events, with ORs ranging from 1.36 (95% CI 1.15 to 1.61) for the Framingham stroke risk score to 1.64 (95% CI 1.50 to 1.80) for the Framingham CVD risk score. The strength of the association between the CVD risk scores and frailty remained essentially the same after exclusion of incident CVD cases, and in multiple imputation (see supplementary web appendix, table S3). The CVD risk scores also predicted pre-frailty although to a lesser extent than for frailty (see supplementary web appendix, table S4).

In supplementary web appendix, table S1, we present results of analyses in which the four CVD risk scores were adjusted for each of their risk factors. The association between risk scores and frailty was attenuated after adjustments for age and antihypertensive treatment, but is still statistically significant, suggesting that this association was not driven by any specific risk factor.

DISCUSSION

Our main finding from this cohort of middle aged individuals was that four different CVD risk scores were associated with an elevated risk of frailty. Thus, one sex-specific SD increment in the risk scores increased the odds of being classified as frail at the end of the 10-year follow-up by 35–42%. The strength of this association was only slightly diminished after exclusion of cases of CVD during the follow-up, suggesting that the predictive risk score-frailty associations were not driven by co-morbid CVD. Furthermore, we found that these scores stratified the risk of developing frailty. To the best of our knowledge, the link between scores from CVD risk factor engines and future frailty has not been examined.

Although initially designed to predict CVD, our results suggest that the CVD risk scores also appear to be a predictive marker of general health such as frailty status. In a previous study, the Framingham CVD risk score was also found to be associated with cognitive decline.[5] Our finding in relation to frailty is plausible given that each risk factor—age, total cholesterol, HDL-cholesterol, systolic blood pressure, smoking and diabetes—included in these scores has also been shown to be associated with various other health outcomes including cancer, which, after CVD, is the second leading cause of death in economically developed countries.[24] One plausible mechanism linking risk scores to both CVD and frailty is the presence of atherosclerosis in arteries and related chronic systemic inflammation.[25] Atherosclerotic processes can prevent blood flow through the coronary artery, causing CVD,[25] and through the muscles, causing sarcopenia, a clinical feature of frailty.[26]

We found that the proportion of frailty was higher in women than men (5.1% versus 1.9%, respectively). This is in agreement with previous findings,[27] but opposite to what one might expect for CVD, which is more common in men in late middle-age. In our study, the incidence of CVD was 9.9% in men versus 5.7% in women. A potential explanation for the higher incidence of frailty in women pertains to differences in biology between the sexes, with men having greater bone mineral density and muscle mass in old age.[28]

Table 2 Characteristics of participants in the analytical sample (n=3895)

	All	Frailty status at follow-up			p Value*
		Not frail	Pre-frail	Frail	
Number	3895	2342	1445	108	
Age, years, mean (SD)	55.2 (5.9)	54.9 (5.7)	55.5 (6.1)	57.9 (6.5)	<0.0001
Sex, n (%)					
Male	2858 (73.4)	1821 (77.8)	982 (68.0)	55 (50.9)	<0.0001
Female	1037 (26.6)	521 (22.4)	463 (32.0)	53 (49.1)	
Total cholesterol, mmol/l, mean (SD)	5.92 (1.05)	5.91 (1.02)	5.94 (1.09)	5.99 (1.03)	0.22
HDL cholesterol, mmol/l, mean (SD)	1.46 (0.39)	1.47 (0.39)	1.45 (0.38)	1.47 (0.39)	0.21
Systolic blood pressure, mm Hg, mean (SD)	122.7 (16.0)	122.3 (15.7)	123.3 (16.3)	124.5 (16.1)	0.03
Diastolic blood pressure, mm Hg, mean (SD)	77.6 (10.3)	77.5 (10.2)	77.8 (10.5)	78.4 (11.6)	0.28
Antihypertensive treatment, n (%)					
No	3515 (90.2)	2137 (91.3)	1293 (89.5)	85 (78.7)	<0.0001
Yes	380 (9.8)	205 (8.7)	152 (10.5)	23 (21.3)	
Smoking, n (%)					
No	3593 (92.3)	2185 (93.3)	1313 (90.9)	95 (88.0)	0.006
Yes	302 (7.8)	157 (6.7)	132 (9.1)	13 (12.0)	
Diabetes, n (%)					
No	3755 (96.4)	2273 (97.1)	1381 (95.6)	101 (93.5)	0.02
Yes	140 (3.6)	69 (3.0)	64 (4.4)	7 (6.5)	
Atrial fibrillation, n (%)					
No	3882 (99.7)	2335 (99.7)	1439 (99.6)	108 (100.0)	-
Yes	13 (0.3)	7 (0.3)	6 (0.4)	0	
Left ventricular hypertrophy, n (%)					
No	3667 (94.2)	2214 (94.5)	1356 (93.8)	97 (89.8)	0.10
Yes	228 (5.8)	128 (5.5)	89 (6.2)	11 (10.2)	
Incident CVD at follow-up, n (%)					
No	3552 (91.2)	2143 (91.5)	1319 (91.3)	90 (83.3)	0.01
Yes	343 (8.8)	199 (8.5)	126 (8.7)	18 (16.7)	
Incident CHD at follow-up, n (%)					
No	3582 (92.0)	2165 (92.4)	1324 (91.6)	93 (86.1)	0.05
Yes	313 (8.0)	177 (7.6)	121 (8.4)	15 (13.9)	
Incident stroke at follow-up, n (%)					
No	3856 (99.0)	2316 (98.9)	1436 (99.4)	104 (96.3)	0.01
Yes	39 (1.1)	26 (1.1)	9 (0.6)	4 (3.7)	

*p for heterogeneity.
CVD, cardiovascular disease; CHD, coronary heart disease.

This study has some limitations. First, we identified frailty cases by using a measure operationalised by Fried *et al*,[1] but a recent review identified that there are more than 20 alternative measures of frailty.[29] Although there are no gold standard measures, the measure by Fried *et al* is the most widely used. Second, we assessed CVD risk at the mean age of 55 years. It remains unclear whether our findings are generalisable to other age groups because at older ages low rather than high levels of some cardiovascular risk factors (total cholesterol, low-density lipoprotein (LDL)-cholesterol and systolic blood pressure) are associated with poor health outcome, as assessed by activity daily living disability, hospitalisation, functional performance and mortality.[30] In relation to CVD prediction, the risk scores are not recommended to be used at older ages (>75 years); the validity of these scores as risk markers of frailty should be examined in that age in future studies. Third, approximately half of the study members who participated at phase 5 were excluded from the analysis due to death, non-participation, loss to follow-up or missing data. Our sensitivity analysis suggests this is not a major source of bias because the results using the multiple multivariate imputation method were largely similar to those reported in the main analysis. However, we cannot rule out bias arising from attrition not covered by the missingness-at-random assumption. Finally, our study sample consisted of middle-aged civil servants, limiting the generalisability of our findings. These limitations can be compared to the main strength of our study, which resides in the use of prospectively collected data given that previous studies that have examined the association between CVD or its individual risk factors and frailty used cross-sectional data.[2 8 9] Our results suggest a relationship between the CVD risk scores and frailty that is independent of existing CVD. However, these findings, based on observational data, do not provide information about causality as we cannot rule out the confounding effect of unmeasured risk factors.

Besides the clinical utility of CVD risk scores—Framingham CVD, CHD, stroke or SCORE—in predicting risk of cardiovascular death and disease, our results suggest that they may also help to identify middle-aged persons who will benefit from interventions designed to prevent frailty. As such, the use of CVD risk scores in clinical practice may also have utility for frailty prediction.

Table 3 Association between individual cardiovascular disease risk factors at baseline and frailty at 10-year follow-up (n=3895)

Predictors	N (%)	OR (95% CI) for frailty: Adjusted for sex	Fully adjusted†
Age, years*	3895	1.58 (1.30 to 1.91)	1.56 (1.28 to 1.92)
Total cholesterol, mg/dl*	3895	1.05 (0.87 to 1.26)	0.96 (0.79 to 1.18)
HDL cholesterol, mg/dl*	3895	0.84 (0.69 to 1.03)	0.90 (0.73 to 1.10)
Systolic blood pressure, mm Hg*	3895	1.15 (0.96 to 1.39)	0.87 (0.65 to 1.15)
Diastolic blood pressure, mm Hg*	3895	1.17 (0.97 to 1.42)	1.20 (0.91 to 1.59)
Antihypertensive treatment			
No	3515 (90.2)	1 (ref)	1 (ref)
Yes	380 (9.8)	2.42 (1.50 to 3.90)	1.77 (1.10 to 2.94)
Smoking			
No	3593 (92.2)	1 (ref)	1 (ref)
Yes	302 (7.8)	1.50 (0.83 to 2.72)	1.62 (0.88 to 2.97)
Diabetes			
No	3755 (96.4)	1 (ref)	1 (ref)
Yes	140 (3.6)	1.81 (0.82 to 3.99)	1.29 (0.57 to 2.91)
Atrial fibrillation			
No	3882 (99.7)	–	–
Yes	13 (0.3)	–	–
Left ventricular hypertrophy			
No	3667 (94.1)	1 (ref)	1 (ref)
Yes	228 (5.9)	2.09 (1.10 to 3.97)	1.66 (0.85 to 3.21)

*OR per SD increase.
†Model includes all predictors in addition to sex.

Table 4 OR per one sex-specific SD increment in score using four CVD risk algorithms for future frailty and cardiovascular diseases (n=3895)

	Frailty		Cardiovascular disease		
	Number of cases	OR (95% CI)	Outcome	Number of cases	OR (95% CI)
Framingham CVD risk score	108	1.42 (1.23 to 1.62)	Any CVD	343	1.64 (1.50 to 1.80)
Framingham CHD risk score	108	1.38 (1.20 to 1.59)	CHD	313	1.53 (1.40 to 1.68)
Framingham stroke risk score	108	1.35 (1.21 to 1.51)	Stroke	39	1.36 (1.15 to 1.61)
SCORE (CVD risk score)	108	1.36 (1.18 to 1.56)	Any CVD	343	1.57 (1.44 to 1.71)

CVD, cardiovascular disease; CHD, coronary heart disease; SCORE, Systematic Coronary Risk Evaluation.

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Contributors MK and GDB conceived the idea for the study and along with KB developed the objectives and design of the study. KB ran the analyses and acts as guarantor of the paper. KB, MK and GDB drafted the paper. All authors contributed to the interpretation of results and revision of the paper, and approved the final version of the paper.

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Competing interests None.

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Data sharing statement Whitehall II data, protocols, and other metadata are available to the scientific community. Please refer to the Whitehall II data sharing policy at http://www.ucl.ac.uk/whitehallII/data-sharing.

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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

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

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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.