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

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

Kim Bouillon,¹ G David Batty,¹,² Mark Hamer,¹ Severine Sabia,¹ Martin J Shipley,¹ Annie Britton,¹ Archana Singh-Manoux,¹,³,⁴ Mika Kivimäki¹,⁵

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 hospitalisation⁴ 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 depression⁶ 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 level¹⁰ 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 preventative measures. Evidence from randomised controlled trials suggest that exercise programmes¹² and selected drugs (eg, dehydroepiandrosterone¹³ and testosterone¹⁴) can reverse frailty.

METHODS

Study population


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

Epidemiology

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,16 coronary heart disease (CHD),19 stroke prediction models17 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).3 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.3 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 χ² 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 V9.1.

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 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.2 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 atherosclerotic processes 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

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**Figure 1** Flow of study members through the data collection phases in Whitehall II.
This study has some limitations. First, we identified frailty cases by using a measure operationalised by Fried et al., but a recent review identified that there are more than 20 alternative measures of frailty. 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 daily living disability, hospitalisation, functional performance and mortality. 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. 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>
<thead>
<tr>
<th>Table 2 Characteristics of participants in the analytical sample (n=3895)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frailty status at follow-up</strong></td>
</tr>
<tr>
<td><strong>Number</strong></td>
</tr>
<tr>
<td><strong>Age, years, mean (SD)</strong></td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Total cholesterol, mmol/l, mean (SD)</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Systolic blood pressure, mm Hg, mean (SD)</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Antihypertensive treatment, n (%)</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Smoking, n (%)</strong></td>
</tr>
<tr>
<td>Male</td>
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<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Diabetes, n (%)</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Atrial fibrillation, n (%)</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Left ventricular hypertrophy, n (%)</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Incident CVD at follow-up, n (%)</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Incident CHD at follow-up, n (%)</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Incident stroke at follow-up, n (%)</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
</tbody>
</table>

*p for heterogeneity.

CVD, cardiovascular disease; CHD, coronary heart disease.
Table 3  Association between individual cardiovascular disease risk factors at baseline and frailty at 10-year follow-up (n=3895)

<table>
<thead>
<tr>
<th>Predictors</th>
<th>N (%)</th>
<th>OR (95% CI) for frailty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years*</td>
<td>3895</td>
<td>1.58 (1.30 to 1.91)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl*</td>
<td>3895</td>
<td>1.05 (0.87 to 1.26)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl*</td>
<td>3895</td>
<td>0.84 (0.69 to 1.03)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg*</td>
<td>3895</td>
<td>1.15 (0.96 to 1.39)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg*</td>
<td>3895</td>
<td>1.17 (0.97 to 1.42)</td>
</tr>
</tbody>
</table>

Antihypertensive treatment

No 3515 (90.2) 1 (ref) 1 (ref) 1.56 (1.28 to 1.92) 1.22 (1.01 to 1.47)
Yes 380 (9.8) 2.42 (1.50 to 3.90) 1.77 (1.10 to 2.94) 1.62 (1.08 to 2.42)

Smoking

No 3593 (92.2) 1 (ref) 1 (ref) 1.56 (1.28 to 1.92) 1.22 (1.01 to 1.47)
Yes 302 (7.8) 1.50 (0.83 to 2.72) 1.62 (0.88 to 2.97) 1.62 (1.08 to 2.42)

Diabetes

No 3755 (96.4) 1 (ref) 1 (ref) 1.56 (1.28 to 1.92) 1.22 (1.01 to 1.47)
Yes 140 (3.6) 1.81 (0.82 to 3.99) 1.29 (0.57 to 2.91) 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) 1.56 (1.28 to 1.92) 1.22 (1.01 to 1.47)
Yes 228 (5.9) 2.09 (1.10 to 3.97) 1.66 (0.85 to 3.21) 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)

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

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

**Acknowledgements** We thank all participating men and women in the Whitehall II study; all participating Civil Service departments and their welfare, personnel and establishment officers; the Occupational Health and Safety Agency; and the Council of Civil Service Unions. The Whitehall II study team comprises research scientists, statisticians, study coordinators, nurses, data managers, administrative assistants and data entry staff, who make the study possible.

**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.

**Ethics approval** This study was approved by the University College London ethics committee, and participants provided written consent.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**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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Epidemiology


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