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Trajectories of the Framingham general cardiovascular risk profile in midlife and poor motor function later in life: The Whitehall II study

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A B S T R A C T
Background: Vascular risk factors are associated with increased risk of cognitive impairment and dementia, but their association with motor function, another key feature of aging, has received little research attention. We examined the association between trajectories of the Framingham general cardiovascular disease risk score (FRS) over midlife and motor function later in life.

Methods: A total of 5376 participants of the Whitehall II cohort study (29% women) who had up to four repeat measures of FRS between 1991–1993 (mean age = 48.6 years) and 2007–2009 (mean age = 65.4 years) and without history of stroke or coronary heart disease in 2007–2009 were included. Motor function was assessed in 2007–2009 through objective tests (walking speed, chair rises, balance, finger tapping, grip strength). We used age- and sex-adjusted linear mixed models.

Results: Participants with poorer performances for walking speed, chair rises, and balance in 2007–2009 had higher FRS concurrently and also in 1991–1993, on average 16 years earlier. These associations were robust to adjustment for cognitive, socio-economic status, height, and BMI, and not explained by incident mobility limitation prior to motor assessment. No association was found with finger tapping and grip strength.

Conclusions: Cardiovascular risk early in midlife is associated with poor motor performances later in life. Vascular risk factors play an important and under-recognized role in motor function, independently of their impact on cognition, and suggest that better control of vascular risk factors in midlife may prevent physical impairment and disability in the elderly.

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1. Introduction

In addition to being strong predictors of cardio- and cerebrovascular disease, vascular risk factors have been associated with aging phenotypes, including worse cognitive function [1] and dementia [2]. Motor impairment is another key aspect of the aging process and poor motor function has been linked to adverse health outcomes, including disability [3] and death [4]. However, the association of vascular risk factors with motor function has received little research attention. To date, there is some evidence linking individual risk factors (hypertension [5], diabetes [6]) or markers of subclinical atherosclerosis [7–9] to poorer motor function, but the combined effect of vascular risk factors remains unknown.

For better prediction of cardiovascular disease (CVD) risk and a more complete assessment of vascular burden, several risk algorithms encompassing multiple risk factors have been developed [10]. Scores derived from these algorithms predict the risk of CVD, stroke, dementia [11], and cognitive deficit [12,13], but to our knowledge their association with motor function has not been examined. Here, we examine the association between trajectories of the Framingham general cardiovascular disease risk score (FRS) [14] during midlife, using four assessments over 16 years, and motor function at the end of the follow-up.

Abbreviations: CVD, cardiovascular disease; FRS, Framingham general cardiovascular disease risk score; SES, socioeconomic status; BMI, body mass index; SD, standard deviation.

⁎⁎ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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2. Methods

2.1. Participants

The Whitehall II study is a longitudinal study of 10,308 civil servants [15]. All civil servants aged 35–55 years in 20 London based departments were invited to participate...
2.4. Covariates

≥ centrifugal analyzer (Roche Diagnostics System). HDL cholesterol was measured by precip-
(participants presenting in the afternoon). Cholesterol was measured using a Cobas Fara
fast (participants presenting in the morning), or at least 4 h after a light fat-free breakfast
smokers. Diabetes was de-

risk and risk of individual events (coronary, cerebrovascular, peripheral artery disease,
palm down, number; the mean of the tests was used.

the table, forearm pointing upwards, and palm of the hand facing up. Participants were

dynamometer adjusted to suit participants’ hands with participants seated, their elbow on

higher scores correspond to better function. Participants had 10 min to do this test.

Finger tapping test

The FRS was developed as part of the Framingham Heart study to assess general CVD

1993 and 2007–2009 were exclud-

of 10,308 participants of Whitehall II at inception (1985–1988), 8104 participated in the clinical 1991–1993 examination, 954 died be-

and their association with motor tests in 2007–2009. Correlations between z-scores of motor tests were examined through age- and sex-adjusted partial Spearman correlations.

The association between the FRS and motor tests was examined separately for each test to establish whether motor function was associated with FRS concurrently and with FRS trajectories over 16 years prior to motor testing. We defined age- and sex-specific quartiles (supplementary Table 2) for all tests with continuous measures (walking speed, grip strength, finger tapping, chair rises), given that motor performances decreased with age (p < 10⁻⁴) and were higher in men than women (p < 10⁻⁴) [20], for balance (binary measure), models were age- and sex-adjusted.

2.2. Motor function

Motor function was assessed in 2007–2009 through measures of walking speed, chair rises, balance, grip strength, and finger tapping: while the first three tests involve several systems and represent global measures, the last two are taken at the upper limbs and represent more specific measures (muscle strength, psychomotor speed). A practice session was allowed for all. Correlations between tests were weak to moderate (supplementary Table 1).

Walking speed was measured at usual pace over a marked 8- (2.44 m) course. The starting position was standing at the start of the course. A trained nurse walked behind the participant and stopped timing when the participant’s foot hit the floor after the end of the course. Three tests were conducted; walking speed was computed as 2.44 m divided by the mean of three measures (in seconds).

Time to complete 5 chair rises: participants sat on an armless chair with feet resting on the floor and arms folded across their chest. They stood up without using their arms and sat down five times as quickly as possible. Time needed to complete the five chair rises was recorded. Participants (n = 6) not to stand up five times were excluded.

Balance was assessed through a series of tests of varying difficulty (full- and semi-
tandem stands, one-leg balance with eyes open or closed). For the present analyses, we used the full-tandem stand and one-leg balance test with eyes open. Particip-

Grip strength (in kilograms; dominant hand) was measured using a Smedley hand grip dynamometer adjusted to suit participants’ hands with participants seated, their elbow on the table, forearm pointing upwards, and palm of the hand facing up. Participants were asked to squeeze the dynamometer as hard as possible for 2 s. Three tests were performed with a one minute rest between each. Readings were rounded up to the nearest whole number; the mean of the tests was used.

Finger tapping test: the number of taps during 10 s was recorded using an electronic device (WPS Electronic tapping test) [16] with participants holding their dominant hand palm down, fingers extended, keeping their hand and arm stationary, and tapping on the lever using their index.

2.3. Framingham general cardiovascular disease risk score

FRS [21]. Poorer cognitive function is also associated with higher FRS [13] and worse motor function [22,23]. We examined whether our findings were explained by confound-

Lower SES, weight, and height are strongly associated with motor performances and FR

0.05) interactions with time: non-linear differences in change were allowed by including interac-
tions between the quadratic time term and quartiles of motor tests.

Lower SES, weight, and height are strongly associated with motor performances and FRS [21]. Poorer cognitive function is also associated with higher FRS [13] and worse motor function [22,23]. We examined whether our findings were explained by confound-

In sensitivity analyses, we examined the influence of incident mobility limitations be-

FRS [21]. Poorer cognitive function is also associated with higher FRS [13] and worse motor function [22,23]. We examined whether our findings were explained by confound-

In sensitivity analyses, we examined the influence of incident mobility limitations (limited to climb several flights of stairs or to walk more than 1 mile) at least once between 1991–1993 and 2002–2004.

As FRS is higher in men than women [13], and men perform better than women on motor tests [20], we examined whether sex modified cross-sectional associations between the FRS and motor tests. We also investigated whether age modified their association.

Two-tailed p-values ≤ 0.05 were considered to be statistically significant. Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, North Carolina, USA).

3. Results

Of 10,308 participants of Whitehall II at inception (1985–1988), 8104 participated in the clinical 1991–1993 examination, 954 died before 2007, and 6225 participated in the 2007–2009 clinical examination; compared to those who participated in 2007–2009, those who did not were older (p < 0.001), more often women (p < 0.001), and had higher FRS (p < 0.001) in 1991–1993. We excluded 725 participants with a history of CHD/stroke, and 124 participants who did not have FRS or motor data. Our analyses are based on 5376 participants. The chair rise test was missing for 7.2% of the participants due to more stringent exclusion criteria than for other tests.

Participants’ characteristics at four waves are shown in Table 1; 3250 (60%) participants had four FRS measurements, 1225 (23%) three, 633 (12%) two, and 268 (5%) one. Mean (SD) FRS increased from 8.6 (6.3) in 1991–1993 to 16.9% (10.6) in 2007–2009 (on average 16.8 years later) with the prevalence of vascular risk factors, besides smoking, also rising over this period. Higher age, male sex, and vascular risk factors were strongly associated with higher cardiovascular risk (Table 2); after adjustment for age and sex, higher BMI, smaller height, lower SES, and worse cognitive function remained associated with higher risk. Participants who developed mobility limitations between 1991–1993 and 2002–2004 had higher FRS than those who did not.

Geometric FRS means from 1991–1993 to 2007–2009 according to quartiles of motor tests are presented in Table 3. Differences between the top and bottom quartiles were larger for walking speed, chair
rises, and balance than for grip strength and finger tapping, and these differences increased somewhat over time. The results of modeling FRS trajectories are presented in Table 4 and Fig. 1. There was good agreement between observed (Table 3) and predicted differences (Fig. 1) in FRS between top and bottom quartiles of motor tests. For participants with poor perfor-
izations between FRS and walking speed, chair rises, and balance were explained by a single covariate; note that the weaker association between low total cholesterol and slow walking speed disappeared (p = 0.19) after adjustment for HDL-cholesterol. Finger tapping and grip strength were not associated with most FRS components.

Supplementary Tables 3–7 describe associations between participants’ characteristics, including FRS components, and motor tests. Associations between FRS and walking speed, chair rises, and balance were explained by a single covariate; note that the weaker association between low total cholesterol and slow walking speed disappeared (p = 0.19) after adjustment for HDL-cholesterol. Finger tapping and grip strength were not associated with most FRS components.

Adjustment for cognitive status in 2007–2009 had little influence (supplementary Fig. 1, panel a). After adjustment for SES, BMI, and height, the association between FRS and motor tests decreased but remained statistically significant, except for balance in 2007–2009 (supplementary Fig. 1, panel b); analyses using time-dependent covariates yielded similar conclusions (data not shown). After exclusion of

Table 2

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Framingham general cardiovascular risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Women, % (95% CI)</td>
<td>74 (72–76)</td>
</tr>
<tr>
<td>Mean age (SE)</td>
<td>62.2 (0.1)</td>
</tr>
<tr>
<td>High grade, % (95% CI)</td>
<td>51 (46–57)</td>
</tr>
<tr>
<td>Mean BMI (SE), kg/m²</td>
<td>24.7 (0.1)</td>
</tr>
<tr>
<td>Mean height (SE), cm</td>
<td>168.7 (0.2)</td>
</tr>
<tr>
<td>Mean SBP (SE), mm Hg</td>
<td>121.4 (0.4)</td>
</tr>
<tr>
<td>Mean DBP (SE), mm Hg</td>
<td>64.4 (0.3)</td>
</tr>
<tr>
<td>Antihypertensive drugs, % (95% CI)</td>
<td>12 (9–16)</td>
</tr>
<tr>
<td>Mean total cholesterol (SE), mmol/L</td>
<td>1.93 (0.01)</td>
</tr>
<tr>
<td>Current smokers, % (95% CI)</td>
<td>0.7 (0.4–1.0)</td>
</tr>
<tr>
<td>Diabetes, % (95% CI)</td>
<td>1.3 (0.8–1.7)</td>
</tr>
<tr>
<td>Mean cognitive score (AHA-I) (SE)</td>
<td>43.7 (0.3)</td>
</tr>
</tbody>
</table>

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.\n\( p^a \) Values computed using linear regression or analysis of covariance adjusted for age and sex with the log-transformed FRS as the dependent variable and participants’ characteristics as explanatory variables. Age- and sex-adjusted means (SE) and percentages (95% CI) are presented.

\( ^b \) Defined as no self-reported difficulty to climb several flights of stairs and to walk more than 1 mile before the motor assessment according to questionnaires from 1991–1993, 1997–1999, and 2002–2004.
participants who reported mobility limitations, associations remained statistically significant in 1991–1993 for walking speed and balance (supplementary Fig. 1, panel c). There were no sex- (p-values > 0.10) or age-related differences (p-values > 0.10) in cross-sectional associations between motor tests and FRS.

4. Discussion

Higher Framingham cardiovascular risk was associated with worse motor function assessed through measures of walking speed, chair rises, and balance. Based on repeated FRS assessments, higher risk was associated with worse motor function 16 years later. This association corresponds to a roughly 50% reduced risk of death and is clinically relevant; it was not explained by mobility limitations before motor assessment. Our findings suggest that exposure to vascular risk factors in midlife is associated with poor motor function at older ages. The corollary, that high vascular risk is associated with poorer motor function 16 years later. This association was robust to adjustments for BMI, height, SES, and cognitive function; however, our results are associated with worse cognitive performances [1], which are themselves associated with motor function [22,23]. However, our results remained unchanged in analyses adjusted for a cognitive test associated with FRS in our study [13]; the association between cardiovascular risk and motor function was not explained by cognitive status.

There was some heterogeneity across motor tests. The association with FRS was strongest for walking speed and balance, less pronounced for chair rises, and absent for finger tapping and grip strength. These differences likely reflect the fact that walking speed, balance, and chair rises represent general measures of motor function, since they involve several systems and functions, including cardiovascular function, while finger tapping and grip strength pertain to more specific functions (psychomotor speed, muscle function). Another potential explanation is that vascular risk factors increase the risk of peripheral neuropathy in diabetic patients [33], which could explain the apparent sparing of upper limbs; however, analyses excluding diabetic patients yielded similar conclusions.

The absolute difference in cardiovascular risk between quartiles of motor function is modest. For instance, for walking speed, the absolute difference in the 2007–2009 FRS between the worse and best performers was 2.0%. However, the difference in walking speed between the top and bottom quartiles is large (~0.6–0.7 m/s). A meta-analysis estimated that 0.1 m/s higher walking speed was associated with a 12% reduced risk of mortality [4]; therefore, a 0.6 m/s difference corresponds to a roughly 50% reduced risk of death and is clinically relevant as it would significantly impact cardiovascular mortality [34,35].

Previous studies that examined a vascular contribution to motor performances were performed in elderly subjects. Selection biases
Table 4

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Walking speed (N = 5336) (m/s)</th>
<th>Five chair rises (N = 4958) (time in seconds)</th>
<th>Balance test (N = 5268) (failed vs passed)</th>
<th>Finger tapping test (N = 5348) (number of taps per 10 s)</th>
<th>Grip strength (N = 5319) (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta</td>
<td>95% CI</td>
<td>p&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Beta&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Beta&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Intercept</td>
<td>−2.022</td>
<td>−2.056; −1.987</td>
<td>&lt;10&lt;sup&gt;−4&lt;/sup&gt;</td>
<td>−2.007−2.043;−1.971</td>
<td>−1.769−1.788;−1.751</td>
</tr>
<tr>
<td></td>
<td>(Reference)</td>
<td></td>
<td></td>
<td>0.000 (Reference)</td>
<td>0.000 (Reference)</td>
</tr>
<tr>
<td>MT-Q4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.000</td>
<td>0.000; 0.000</td>
<td></td>
<td>0.000 (Reference)</td>
<td>0.000 (Reference)</td>
</tr>
<tr>
<td>MT-Q3</td>
<td>0.027</td>
<td>0.022; 0.076</td>
<td>0.056; 0.006; 0.107</td>
<td>0.083; 0.056; 0.110</td>
<td>0.037−0.012; 0.086</td>
</tr>
<tr>
<td>MT-Q2</td>
<td>0.074</td>
<td>0.025; 0.123</td>
<td>0.054; 0.003; 0.105</td>
<td>0.25−0.023; 0.074</td>
<td>0.032−0.016; 0.081</td>
</tr>
<tr>
<td>MT-Q1</td>
<td>0.139</td>
<td>0.090; 0.188</td>
<td>0.062; 0.011; 0.113</td>
<td>0.123</td>
<td>0.013−0.037; 0.063</td>
</tr>
<tr>
<td>Time</td>
<td>0.200</td>
<td>0.153; 0.247</td>
<td>0.316; 0.267; 0.365</td>
<td>0.144; 0.310; 0.378</td>
<td>0.268; 0.221; 0.315</td>
</tr>
<tr>
<td>Time&lt;sup&gt;2&lt;/sup&gt;</td>
<td>−0.143</td>
<td>−0.169; −0.117</td>
<td>−0.077; −0.104; −0.050</td>
<td>−0.067; −0.086; −0.049</td>
<td>0.025; 0.016; 0.084</td>
</tr>
<tr>
<td>Time × MT-Q4</td>
<td>0.000</td>
<td>(Reference)</td>
<td>0.000 (Reference)</td>
<td>0.000 (Reference)</td>
<td>0.000 (Reference)</td>
</tr>
<tr>
<td>Time × MT-Q2</td>
<td>0.081</td>
<td>0.014; 0.148</td>
<td>−0.054; −0.124; 0.015</td>
<td>−0.047; −0.098; 0.003</td>
<td>−0.004; −0.063; 0.072</td>
</tr>
<tr>
<td>Time × MT-Q1</td>
<td>0.066</td>
<td>−0.002; 0.133</td>
<td>−0.056; −0.126; 0.014</td>
<td>−0.047; −0.098; 0.003</td>
<td>−0.032; −0.099; 0.035</td>
</tr>
<tr>
<td>Time2 × MT-Q4</td>
<td>0.076</td>
<td>0.038; 0.144</td>
<td>−0.103; −0.172; −0.033</td>
<td>−0.015; −0.082; 0.053</td>
<td>−0.015; −0.082; 0.053</td>
</tr>
<tr>
<td>Time × MT-Q4</td>
<td>0.000</td>
<td>(Reference)</td>
<td>0.000 (Reference)</td>
<td>0.000 (Reference)</td>
<td>0.010 −0.058; 0.079</td>
</tr>
<tr>
<td>Time2 × MT-Q3</td>
<td>0.045</td>
<td>0.008; 0.081</td>
<td>−0.043; −0.081; −0.005</td>
<td>−0.024; −0.052; 0.004; 0.18</td>
<td>−0.001; −0.036; 0.037</td>
</tr>
<tr>
<td>Time2 × MT-Q2</td>
<td>0.027</td>
<td>−0.009; 0.064</td>
<td>−0.038; −0.076; 0.000</td>
<td>−0.022; −0.059; 0.014</td>
<td>−0.012 −0.025; 0.048</td>
</tr>
<tr>
<td>Time2 × MT-Q1</td>
<td>0.039</td>
<td>0.001; 0.076</td>
<td>−0.058; −0.096; −0.020</td>
<td>−0.013; −0.050; 0.024; 0.47</td>
<td>0.002 −0.035; 0.039</td>
</tr>
</tbody>
</table>

*Trajectories of the log-transformed FRS were modeled using linear mixed models with random effects for the intercept and time (linear, squared) and a backwards time scale. The main effects of the quartiles of the motor tests represent the difference in the log-transformed FRS between each quartile and the reference quartile in 2007–2009, and the interactions of the quartiles of the motor tests with time and time squared examine whether trajectories of the FRS are different in each quartile compared to the reference quartile. Regression coefficients (beta) were back transformed to present these findings graphically (Fig. 1). p-Values for trend for the main effect of the quartiles of the motor tests and for their interactions with time (linear, squared) computed by including a four-level ordinal variable defined by the mean of the tests in each of the quartiles. We report a global test for the interactions of motor tests with time (linear, squared).

<sup>a</sup> MT-Q1 to -Q4: age- and sex-specific quartiles of motor tests from worse (Q1) to better function (Q4, reference); for the balance test, Q4 corresponds to those who passed the test and Q3 to those who failed the test.

<sup>b</sup> The linear mixed model was adjusted for age (centered at 65 years; p < 10<sup>−4</sup>) and sex (reference group, males; p < 10<sup>−4</sup>), the interactions of age and sex with time and time squared (all p < 10<sup>−4</sup>), the interaction between age and sex (p < 10<sup>−4</sup>), and the three-way interaction between age, sex, and time (p = 0.002).
related to competing risks of death as well as reverse causation may complicate their interpretation. Our analyses, in contrast, are based on subjects who were on average ~49 years old at baseline followed for approximately 16 years; one important finding is that differences in FRS across groups defined by motor tests were already established many years before the motor assessment and well before the start of old age. However, the main limitation of our analyses is that motor function was measured once, and we were not able to study the association between the FRS and change in motor function. This limits causal inference as we were not able to formally assess temporality and to examine when differences in motor function appeared among participants; results of analyses with exclusion of persons who developed mobility limitations are reassuring to this respect. Our analyses are based on participants who participated in 2007–2009, which raises the possibility that selection biases due to survival or other causes may impact our findings. This is however unlikely given that the association between the FRS and motor tests was not modified by age; because persons who did not participate in 2007–2009 had higher FRS in 1991–1993 and are likely to be in worse health and have worse motor function [36], our estimates of the association between motor function and FRS are likely to be conservative. Finally, Whitehall II participants are office-based civil servants and not fully representative of the British population, which may limit the generalizability of our findings; this is likely, however, to mainly affect the distribution of risk rather than the strength of associations.

Our study has several strengths, including its large size and extended follow-up with at least three FRS measures available for most participants, thus allowing modeling trajectories over time. The availability of tests assessing different aspects of motor function is also an important feature.

In conclusion, our findings are in line with research on cognitive function and dementia showing that higher vascular risk in midlife is associated with worse outcomes later in life [2]. Our study is the first to show that participants with poor motor function have higher cardiovascular risk and that this association was already present approximately 16 years before the assessment of motor function. These findings suggest that vascular risk factors play an important and under-recognized role in motor function, independently of their impact on cognition. Thus, better control of vascular risk factors in midlife may prevent physical impairment and disability in the elderly.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2013.12.051.

References