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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 ☆☆

Alexis Elbaz [a,b,c,*], Martin J. Shipley [b], Hermann Nabi [a,b,c], Eric J. Brunner [b], Mika Kivimaki [b], Archana Singh-Manoux [a,b,c,d]

[a] INSERM, Centre for Research in Epidemiology and Population Health, U1018, Social and Occupational Determinants of Health, F-94807, Villejuif, France
[b] Department of Epidemiology and Public Health, University College London, UK
[c] Univ Versailles St-Quentin, UMRS 1018, F-94807, Villejuif, France
[d] Centre de Gérontologie, Hôpital Ste Périne, AP-HP, France

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ABSTRACT

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 cognition, 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.

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.

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

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.

* Corresponding author at: INSERM, Centre for Research in Epidemiology and Population Health, U1018, Hôpital Paul Brousse, Bât 15/16, 16 Avenue Paul Vaillant Couturier, 94807 Villejuif Cedex, France.
E-mail address: alexis.elbaz@inserm.fr (A. Elbaz).

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(participation rate, 73%). The baseline examination took place over 1985–1988. Subsequent phases including clinical examinations and questionnaires were in 1991–1993, 1997–1999, 2002–2004, and 2007–2009. Participants gave written consent; the University College London ethics committee approved the study.

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-ft (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 able 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 data from the full-tandem stand and one-leg balance test with eyes open. Participants were first asked to perform a full-tandem stand (10 s). If they passed this test, they proceeded to perform a one-leg balance test (30 s). Participants who failed either test were deemed to have failed the balance test.

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

The FRS was developed as part of the Framingham Heart study to assess general CVD risk and risk of individual events (coronary, cerebrovascular, peripheral artery disease, heart failure) [14]. It includes measures of age, HDL- and total cholesterol, systolic blood pressure, cigarette smoking, and diabetes, and provides an estimate of the 10-year risk of CVD.

Risk score components were drawn from questionnaires and clinical examination data at four waves: 1991–1993, 1997–1999, 2002–2004, and 2007–2009. Total cholesterol and HDL cholesterol (mg/dL) were measured from blood collected after either an 8 h fast (participants presenting in the morning), or at least 4 h after a light fat-free breakfast (participants presenting in the afternoon). Cholesterol was measured using a Cobas Fara centrifugal analyzer (Roche Diagnostics System). HDL cholesterol was measured by precipitating non-HDL cholesterol with dextran sulfate-magnesium chloride and measuring cholesterol in the supernatant fluid. Systolic blood pressure (mm Hg) was taken as the average of two measurements in the sitting position after a 5 min rest with the Hawksley random-zero sphygmomanometer. Treated hypertension was determined according to antihypertensive medication use. Participants were categorized as current smokers, ex- or non-smokers. Diabetes was defined by fasting glucose $\geq$7.0 mmol/L, 2 h post-load glucose $\geq$11.1 mmol/L, doctor diagnosed diabetes, or use of diabetes medication [17].

2.4. Covariates

Individuals with prevalent or incident stroke or coronary heart disease (non-fatal myocardial infarction, definite angina) between 1991–1993 and 2007–2009 were excluded as these conditions are known to affect motor performances. Myocardial infarction was diagnosed based on clinical examination data, electrocardiograms, and medical records [18]. Angina was assessed based on reports of symptoms and nitrate medication, with corroboration in medical records or abnormalities on a resting electrocardiogram, exercise electrocardiogram, or coronary angiogram. Classification was carried out independently by two trained coders, with adjudication by a third party in the event of disagreement. Stroke was self-reported and included history of stroke or transient ischemic attack.

At all waves, mobility limitations were assessed using questions on the ability to climb several flights of stairs or walk more than 1 mile. Socioeconomic status (SES) was defined based on the highest 3-level British civil service employment grade achieved (high, administrative; intermediate, professional or executive; low, clerical or support). Weight and height were measured and body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Cognitive status was assessed using the Alice Heim 4-I (AH4-I) test [19], which includes 65 verbal and mathematical reasoning items assessing inductive reasoning by measuring the ability to identify patterns and infer principles and rules; higher scores correspond to better function. Participants had 10 min to do this test.

2.5. Statistical analysis

Descriptive analyses were carried out to examine participants' characteristics at each wave and their association with motor tests and FRS 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.

We used linear mixed models that take into account correlations between repeated measures on the same individual, with FRS as the dependent variable and quartiles of motor tests as independent variables; this approach allows examining FRS trajectories prior to the measurement of motor function (2007–2009) as well as their concurrent association. FRS was logarithmically transformed due to its skewed distribution; results were back-transformed for graphs. Models were implemented with a backward time scale, so that 2007–2009 corresponds to the baseline (time $= 0$) and participants are tracked back until 1991–1993, approximately 16 years earlier. Time was divided by 10, so that regression coefficients represent change in FRS over 10 years. Inspection of the data showed that FRS change over time was not linear; we therefore included a quadratic term for time. Both the intercept and slope (time) were fitted as random effects. The main effect represents the mean FRS difference in 2007–2009 between the reference quartile (best performance) and other quartiles. The interaction term between quartiles of motor tests and time allows examining whether the association between FRS and motor function changed over time; non-linear differences in change were allowed by including interaction terms 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 confounding (SES, weight, height) or mediated by cognition by including the following covariates in models as main effects together with their significant ($p < 0.05$) interactions with time: SES (high vs intermediate/low), quartiles of BMI and height, the measure of cognition (AH4-I). These analyses used time invariant covariates defined in 2007–2009, and were replicated using time-dependent covariates; they were adjusted for age in 2007–2009 and sex and their interactions with time (linear, squared).

In sensitivity analyses, we examined the influence of incident mobility limitations before the assessment of motor function by excluding participants who reported 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 $\leq$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