INTERNAL MEDICINE JOURNAL

RACP Specialists. Together

doi:10.1111/imj.14002

Choice reaction time and grip strength as predictors of cardiovascular mortality in middle-aged and elderly Japanese: from the Radiation Effects Research Foundation Adult Health study

Masaki Shimizu,[1]† Munechika Misumi,[2] Michiko Yamada,[1] Waka Ohishi,[1] Hideya Yamamoto[3] and Yasuki Kihara[3]

Departments of [1]Clinical Studies, and [2]Statistics (Hiroshima), Radiation Effects Research Foundation, and [3]Department of Cardiovascular Medicine, Hiroshima University Graduate School of Biomedical and Health Sciences, Hiroshima, Japan

Key words
reaction time, grip strength, heart disease, stroke, mortality.

Correspondence
Masaki Shimizu, Department of Clinical Studies, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minamiku Hiroshima 732-0815, Japan.
Email: sm537f-1@ac.auone-net.jp

Received 9 January 2018; accepted 11 June 2018.

Abstract

Background: Cognitive function and physical function are important predictors of mortality.
Aim: To investigate whether or not reaction time (RT) as a cognitive function and grip strength (GS) as a physical function were associated, alone or in combination, with mortality from heart disease or stroke.
Methods: The subjects included 4901 Adult Health Study participants in Hiroshima who had undergone RT and GS measurements, were 35–74 years old at baseline (1970–1972) and were followed until the end of 2007.
Results: After adjustment for other potential risk factors, RT was positively and GS was negatively associated with mortality from both heart disease and stroke. These associations were persistent in the model when adjusting simultaneously for RT, GS and other factors, but hazard ratios were attenuated. When we evaluated the associations by baseline age and gender, we found the greater hazard ratios for RT in the younger cohort, but no clear modification by age for GS. The interaction between RT and GS was statistically significant ($P = 0.012$) for stroke mortality. In the stratified analyses divided using the age-specific median value of RT or GS, the estimated hazard ratio of stroke mortality for RT was significant in participants with weak or strong GS but greater in the former, and for GS, it was only significant in participants with slow RT.
Conclusion: RT and GS, alone and in combination, predicted heart disease and stroke mortalities. Interventions for both cognitive function and physical function may be beneficial for the prevention of cardiovascular disease mortality.

Introduction

Cognitive function and physical function are important predictors of mortality. Reaction time (RT) is a measure of processing speed,[1] and processing speed reflects cognitive function.[2] Using the Radiation Effects Research Foundation (RERF) Adult Health Study (AHS), which covered a wide age range of men and women over a period of 30 years, our previous study showed RT to be a strong and consistent predictor of mortality.[3] Some cohort studies found RT, including the digit symbol substitution test, to be related to cardiovascular disease (CVD) mortality[4,5] and CVD incidence.[6]

A meta-analysis by Cooper *et al.* found that grip strength (GS), which is a measure of physical function, is associated with all-cause mortality in younger, as well as older, community-dwelling populations.[7] The prospective Urban–Rural Epidemiology study, a large, longitudinal population study, showed that GS was inversely associated with all-cause mortality, cardiovascular

†Present address: Working Hours and Welfare Division, Employee Welfare Bureau, National Personnel Authority.
Funding: The Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan, is a public interest foundation funded by the Japanese Ministry of Health, Labour and Welfare (MHLW) and the US Department of Energy (DOE). This publication was supported by RERF Research Protocol RP-A6-12 and, in part, by a Grant-in-Aid from the MHLW, Health and Labor Sciences Research Grants, Japan (H26-Junkankitou [Seisaku]-Ippann-001 and H29-Junkankitou-Ippan-003). The views of the authors do not necessarily reflect those of the two governments.
Conflict of interest: None.

mortality, myocardial infarction incidence and stroke incidence.[8] Our previous study found that GS was significantly associated with heart disease and stroke mortality,[9] in accordance with the Hisayama Study in Japan.[10]

Although the relationship between cognitive function and physical function suggests both separate and shared processes of ageing,[11,12] only a few studies have reported the simultaneous potential of cognitive and physical function on mortality.[13,14] Here, we investigated the independent and combined effects of RT and GS as predictors of heart disease mortality and stroke mortality to determine whether cognitive function and physical function are modifiable predictors of CVD mortality.

Methods

General procedure

The AHS, a population-based longitudinal clinical study of atomic bomb survivors and unexposed controls of approximately a similar number, has conducted biennial health examinations and mortality surveys continuously since 1958.[15] The subjects of the present study were 4901 AHS participants living in Hiroshima, who underwent RT and handgrip measurements and were 35–74 years old between July 1970 and June 1972. The AHS biennial clinical examination included medical history (diabetes mellitus (DM)), physical examination (blood pressure and body mass index (BMI) calculated as body weight (kg)/height^2 (m)), measurements (serum cholesterol) and questionnaire (smoking habit and alcohol intake). The RERF institutional review boards approved this study, and all participants provided informed consent and confirmed their anonymity.

Measurement of reaction time and handgrip

RT was defined as the length of time for extinction of 10 lights mounted on a rectangular board.[3] The test was repeated after practice, and that time was used for analysis. Handgrip strength was measured twice for each hand with participants in a standing position. The maximum GS among all measurements was used in the analysis.[9]

Mortality follow up

Mortality was followed for all study participants from the baseline measurements in 1970–1972 to the end of 2007. We identified 3338 deaths not due to external causes. The primary cause of death was assessed from death certificates and classified according to the International Classification of Diseases (ICD) (ICD, 8–10th revision, WHO, Geneva). We analysed deaths caused by heart disease (390–429 in ICD 8 and 9, I01-I51 in ICD 10) and stroke (430–438 in ICD 8 and 9, I60–I69 in ICD 10).

Statistical analysis

We used multivariate Cox proportional hazards models to investigate the association of RT and GS with mortality. We treated age as the timescale in the Cox regression models, instead of follow-up time.[16] We also handled adjustments for age effects non-parametrically based on this approach. First, we evaluated the association between the mortality of each disease and either RT or GS, adjusting for gender and other potential confounding factors (systolic blood pressure (SBP), BMI, DM, smoking and drinking habits, total cholesterol and radiation dose). We then investigated the associations by including both RT and GS with the same multivariate adjustments. Considering the wide age range, we conducted the Cox regression analysis by age categories of 35–54, 55–64 and over 65 years at the time of measurement for each gender. In addition, we tested two-way interaction effects of RT and GS. If a significant interaction was shown, we examined the association between RT and mortality after stratifying for GS and the association between GS and mortality after stratifying for RS. To prevent contamination caused by latent diseases, we excluded participants who died within 2 years of the baseline examination or were diseased at baseline. All statistical tests were two-sided and conducted using the R survival package R 3.0.1 (http://www.cran.r-project.org/).

Results

Table 1 shows the characteristics of the study participants. After the exclusion of participants who died within 2 years of the baseline examination or were diseased at baseline (80 cases of heart disease and 85 of stroke), 4821 participants remained in the analysis of heart disease and 4816 in the analysis of stroke. By the end of 2007, 616 participants had died of heart disease and 512 of stroke. At baseline, Spearman's correlation coefficient between RT and GS was −0.33.

Table 2 shows the hazard ratio (HR) per unit increment for mortality due to each disease associated with RT and GS in the gender-adjusted model, the multivariate (gender and other factors)-adjusted (a) model and the multivariate (gender, other factors and RT or GS)-adjusted (b) model. In all models, RT was positively and significantly associated with mortality from heart disease and stroke, and GS was negatively and significantly

Table 1 Baseline characteristics of the study participants

Variable	Total	Men	Women
Number of participants	4901	1689	3212
Age at baseline (years)	54.4	55.5	53.8
	(10.9)	(11.1)	(10.7)
Systolic blood pressure (mm Hg)	127.4	131.0	125.5
	(23.6)	(23.6)	(23.3)
Total cholesterol (mg/dL)	192.2	183.7	200.4
	(36.3)	(34.3)	(36.2)
Body mass index (kg/m^2)	22.3	21.6	22.6
	(3.5)	(3.1)	(3.6)
Current smokers (%)	32.7	68.4	13.9
Current alcohol drinkers (%)	34.3	70.0	15.7
Diabetes mellitus (%)	8.7	14.3	5.7
Reaction time (s)			
Mean	7.53	7.48	7.56
	(1.69)	(1.69)	(1.70)
Median	7.2	7.1	7.2
First, third quartile	6.5, 8.2	6.4, 8.2	6.5, 8.1
Minimum, maximum	4.5, 27.2	4.5, 27.2	4.6, 27.0
Grip strength (kg)			
Mean	35.1	46.4	29.2
	(11.0)	(9.0)	(6.3)
Median	33	46	30
First, third quartile	27, 42	41, 52	25, 34
Minimum, maximum	7, 73	14, 73	7, 50
Unexposed subjects (dose <0.001 Gy) (%)	47.2	48.8	46.3
Dose (Gy) among exposed subjects	0.43	0.47	0.41
	(0.58)	(0.62)	(0.55)

Continuous variables are shown as means (SD). SD, standard deviation.

associated with mortality from heart disease and stroke, although the HR were slightly attenuated in the latter model. Additional calculations per 1 SD of deterioration in RT and/or GS showed that the range of the HR of mortality for heart disease or stroke for a 1 SD increase of RT alone or a 1 SD decrease in GS alone is 1.17–1.31, and the range of the HR of mortality for 1 SD of simultaneous change in both variables is 1.27–1.43. (Table 3) Significant predictive values were detected for factors other than RT and GS in the (b) model. An SBP increase of 10 mmHg was associated with heart disease mortality (HR = 1.10, 95% confidence interval (CI) = 1.07–1.14) and stroke mortality (HR = 1.16, 95% CI = 1.12–1.20), DM with heart disease mortality (HR = 1.80, 95% CI = 1.41–2.30) and stroke mortality (HR = 1.43, 95% CI = 1.08–1.90), current smoking with heart disease mortality (HR = 1.62, 95% CI = 1.30–2.02) and a 10 mg/dL increase of total cholesterol with stroke mortality (HR = 0.95, 95% CI = 0.92–0.98). Radiation dose was not associated with either mortality. When we evaluated the association of RT or GS with mortality in the stratified model by gender and baseline age categories (35–54, 55–64 and over 65 years old), we found an association of RT with CVD mortality in more than half the age and gender categories with greater HR in younger birth cohorts and an association of GS with CVD mortality in fewer age and gender categories (Table 4).

In the model including the interaction between RT and GS, the interaction showed a significant effect on only stroke mortality (P = 0.012), showing a better fit than the model that included only main effects. In the stratified analyses divided by the median value of RT or GS of each gender and age category, RT was significantly associated with stroke mortality for participants with weak GS (HR = 1.17, 95% CI = 1.11–1.25) and for participants with strong GS (HR = 1.09, 95% CI = 1.03–1.15), and GS was significantly associated with stoke mortality for participants with slow RT (HR = 0.98, 95% CI = 0.96–0.99) but not for subject with fast RT (HR = 1.00, 95% CI = 0.98–1.03) (Fig. 1).

Discussion

Our results showing the association between CVD mortality and RT or GS suggest that RT and GS are associated with vascular ageing. RT, a measure of processing speed,[1] may reflect vascular function in the whole body

Table 2 Hazard ratio (HR) for death per one unit increment of reaction time and grip strength

	Gender-adjusted model	Multivariate-adjusted model	
	HR (95% CI)	Model A, HR (95% CI)	Model B, HR (95% CI)
Reaction time (1 s)			
Heart disease	1.13 (1.10–1.17)**	1.10 (1.06–1.14)**	1.08 (1.04–1.13)**
Stroke	1.16 (1.12–1.19)**	1.12 (1.09–1.16)**	1.11 (1.07–1.15)**
Grip strength (1 kg)			
Heart disease	0.97 (0.96–0.98)**	0.97 (0.96–0.98)**	0.98 (0.97–0.99)*
Stroke	0.97 (0.96–0.98)**	0.97 (0.96–0.99)**	0.98 (0.97–0.99)*

*P < 0.01. **P < 0.001. In all models, adjustment for the effect of age was handled non-parametrically using age as the timescale of the Cox regression. We used a gender-adjusted model with gender as a covariate. Multivariate model A was adjusted for gender, systolic blood pressure, diabetes mellitus, smoking habit, alcohol consumption, radiation dose and total cholesterol. Model B was adjusted for factors in model A and reaction time or grip strength. CI, confidence interval.

Table 3 Hazard ratio (HR) for death per 1 SD deterioration in reaction time and grip strength

	Gender-adjusted model	Multivariate-adjusted model	
	HR (95% CI)	Model A, HR (95% CI)	Model B, HR (95% CI)
Reaction time (1 SD)			
Heart disease	1.23 (1.17–1.30)***	1.17 (1.10–1.24)***	1.14 (1.07–1.22)***
Stroke	1.29 (1.22–1.36)***	1.21 (1.15–1.29)***	1.19 (1.12–1.27)***
Grip strength (1 SD)			
Men			
Heart disease	1.32 (1.13–1.53)***	1.31 (1.12–1.53)***	1.25 (1.07–1.47) ***
Stroke	1.23 (1.06–1.43)***	1.19 (1.02–1.40)**	1.15 (0.99–1.34)*
Women			
Heart disease	1.32 (1.13–1.53)***	1.17 (1.05–1.30)***	1.11 (1.00–1.24)*
Stroke	1.31 (1.16–1.48)***	1.25 (1.11–1.41)***	1.14 (1.01–1.29)**

*P < 0.05. **P < 0.01. ***P < 0.001. The HR for death per 1 SD decrease in grip strength was analysed by gender due to differences in grip strength between the genders. In all models, adjustment for effect of age was handled non-parametrically by using age as the timescale of the Cox regression. The multivariate model A was adjusted for gender, systolic blood pressure, diabetes mellitus, smoking habit, alcohol consumption, radiation dose and total cholesterol. Model B was adjusted for factors in model A and reaction time or grip strength. CI, confidence interval; SD, standard deviation.

Table 4 Multivariate-adjusted hazard ratio (HR) for reaction time (1 s) and grip strength (1 kg) by gender and baseline age

Gender	Age (years)	Reaction time (1 s)		Grip strength (1 kg)	
		Heart disease *n* (subjects) HR (95% CI)	Stroke *n* (subjects) HR (95% CI)	Heart *n* (subjects) HR (95% CI)	Stroke *n* (subjects) HR (95% CI)
Men	35–54	54 (750)	50 (750)	54 (750)	50 (750)
		1.23 (1.00–1.51)	1.24 (1.01–1.52)*	0.97 (0.93–1.00)	0.98 (0.95–1.02)
	55–64	66 (485)	65 (485)	66 (485)	65 (485)
		1.13 (0.97–1.31)	1.19 (1.06–1.34)**	0.98 (0.95–1.02)	0.98 (0.94–1.01)
	65–74	72 (411)	76 (410)	72 (411)	76 (410)
		1.10 (1.03–1.18)**	1.05 (0.96–1.14)	0.94 (0.91–0.98)***	0.99 (0.96–1.02)
Women	35–54	103 (1740)	67 (1740)	103 (1740)	67 (1740)
		1.22 (1.08–1.39)***	1.28 (1.11–1.47)***	0.95 (0.92–0.99)*	1.00 (0.96–1.05)
	55–64	163 (771)	120 (771)	163 (771)	120 (771)
		1.08 (0.96–1.22)	1.19 (1.08–1.31)***	0.99 (0.97–1.02)	0.99 (0.96–1.02)
	65–74	158 (664)	134 (660)	158 (664)	134 (660)
		1.10 (1.02–1.19)*	1.12 (1.03–1.21)**	0.97 (0.94–1.01)	0.96 (0.93–1.00)*

*P < 0.05. **P < 0.01. ***P < 0.001. In all models, adjustment for the effect of age was handled non-parametrically by using age as the timescale of the Cox regression. The multivariate model was adjusted for systolic blood pressure, diabetes mellitus, smoking habit, alcohol consumption, radiation dose, total cholesterol and reaction time/grip strength. CI, confidence interval.

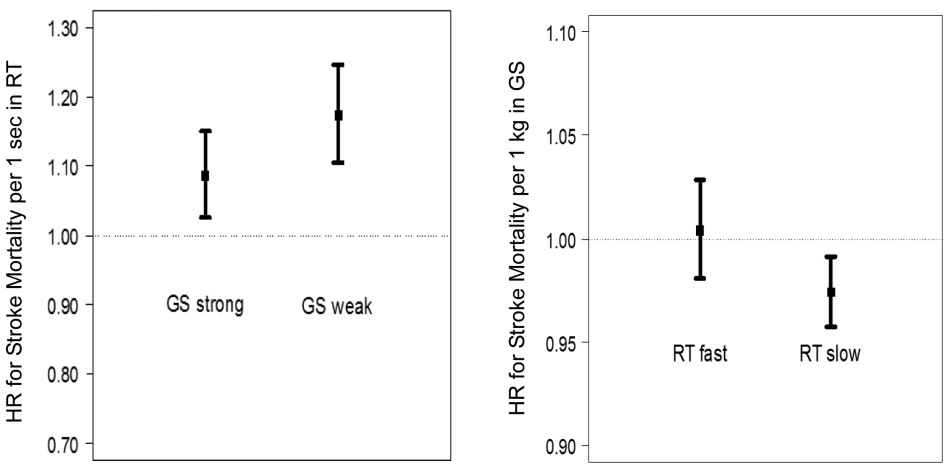

Figure 1 Hazard ratio (HR) for stroke mortality per unit increase in reaction time (RT) or grip strength (GS). The left graph showed HR for Stroke Mortality per unit increase in RT among participants with strong and weak GS. The right graph showed HR for Stroke Mortality per unit increase in GS among participants with fast and slow RT.

as well as in the brain as white matter brain changes reflecting vascular brain function are associated with changes in processing speed,[17] and such morphological changes in brain are thought to reflect aortic atherosclerosis and microvascular disease in the whole body.[18] Regarding the effect of GS, the role of skeletal muscle as a secretory organ might be involved. Inflammatory processes or secreted myokines associated with a lack of exercise may favour the development of CVD,[19] linking CVD mortality with GS. Another possible mechanism is through a genetic factor, such as Apolipoprotein E (*APOE*) genotype, that is related not only to CVD but also to RT or GS.[20]

Although studies investigating an association of RT or GS with CVD mortality across different age and gender groups are limited, the Health and Lifestyle Survey showed the effect of different ages on associations between RT and all CVD and stroke mortalities,[5] and the Cooperative Health Research in the Region of Augsburg-Age study showed the effect of different genders on association between GS and CVD mortality.[21] In our study, RT was significantly associated with heart disease and stroke mortalities in those aged 35–74 years at baseline, with greater HR in the younger birth cohort, and no clear gender difference was shown in the association between GS and CVD mortality.

Two studies have investigated the effects of the combination of cognitive and physical functions on mortality. Rosano and colleagues reported that a low digit symbol substitution test score and slow gait were independent risk factors for mortality,[13] and Sanders and colleagues reported that slow processing speed and slow gait independently predicted mortality.[14] In our study, RT and GS were independently associated with both stroke mortality and heart disease mortality. Although the interaction between gait speed and neither the digit symbol substitution test[13] nor processing speed[14] were significantly associated with mortality, we found the interaction between RT and GS to be significantly associated with stroke mortality ($P = 0.012$), suggesting that an intervention for cognitive function may be more effective for participants with less physical function, and an intervention for physical function may be more effective for participants with less cognitive function. The association between cognitive and physical function was indicated in a cross-sectional study[12] and a longitudinal study.[11,12] The latter showed that the direction of the association between the two functions is predominantly from poor cognition to poor physical function. Intensity and direction of association between cognitive and physical function is inconsistent,[22] and the effects of cognitive function or physical function on mortality differ across study populations and measures used.[4,5,23] Further investigations of the combined effects of cognitive and physical function on CVD mortality and incidence are needed before we discuss the generalisability of this study.

The limitations of this study are that the analysis was not adjusted for relevant risk factors, such as exercise habits, education and occupation, that no validated diagnoses of death certificate information was used, that RT and GS were measured only at baseline, although a strong temporal relationship for cognitive function and for physical function was indicated in the Whitehall II study,[11] and false positive associations might be inevitable due to the large number of statistical tests.

Conclusion

Although RT as a measure of cognitive function or GS as a measure of physical function was associated with mortality from heart disease and stroke separately in previous reports,[4,5,8,9] only a few studies reported the simultaneous potential of cognitive and physical function on mortality.[13,14] In this study, RT and GS were associated with heart disease and stroke mortality alone or in combination with the adjustment of other risk factors. The interaction between RT and GS was statistically significant for stroke mortality, suggesting that physical exercise may compensate for effects related to the decline of cognitive function and vice versa. Interventions for both cognitive function and physical function may be beneficial for the prevention of CVD mortality.

References

1 Mulder MJ, van Maanen L. Are accuracy and reaction time affected via different processes? *PLoS One* 2013; **8**: e80222.

2 Deary IJ, Johnson W, Starr JM. Are processing speed tasks biomarkers of cognitive aging? *Psychol Aging* 2010; **25**: 219–28.

3 Yamada M, Shimizu M, Kasagi F, Sasaki H. Reaction time as a predictor of mortality: the radiation effects research foundation adult health study. *Psychosom Med* 2013; **75**: 154–60.

4 Pavlik VN, de Moraes SA, Szklo M, Knopman DS, Mosley TH Jr, Hyman DJ. Relation between cognitive function and mortality in middle-aged adults: the atherosclerosis risk in communities study. *Am J Epidemiol* 2003; **157**: 327–34.

5 Shipley BA, Der G, Taylor MD, Deary IJ. Cognition and mortality from the major causes of death: the health and lifestyle survey. *J Psychosom Res* 2008; **65**: 143–52.

6 Elkins JS, Knopman DS, Yaffe K, Johnston SC. Cognitive function predicts first-time stroke and heart disease. *Neurology* 2005; **64**: 1750–5.

7 Cooper R, Kuh D, Hardy R, Mortality Review Group, on behalf of the FALCon and HALCyon study teams. Objectively measured physical capability levels and mortality: systematic review and meta-analysis. *BMJ* 2010; **341**: c4467.

8 Leong DP, Teo KK, Rangarajan S, Lopez-Jaramillo P, Avezum A Jr, Orlandini A *et al*. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. *Lancet* 2015; **386**: 266–73.

9 Sasaki H, Kasagi F, Yamada M, Fujita S. Grip strength predicts cause-specific mortality in middle-aged and elderly persons. *Am J Med* 2007; **120**: 337–42.

10 Kishimoto H, Hata J, Ninomiya T, Nemeth H, Hirakawa Y, Yoshida D *et al*. Midlife and late-life handgrip strength and risk of cause-specific death in a general Japanese population: the Hisayama study. *J Epidemiol Community Health* 2014; **68**: 663–8.

11 Elovainio M, Kivimaki M, Ferrie JE, Gimeno D, de Vogli R, Virtanen M *et al*. Physical and cognitive function in midlife: reciprocal effects? A 5-year follow-up of the Whitehall II study. *J Epidemiol Community Health* 2009; **63**: 468–73.

12 McGough EL, Kelly VE, Logsdon RG, SM MC, Cochrane BB, Engel JM *et al*. Associations between physical performance and executive function in older adults with mild cognitive impairment: gait speed and the timed 'up & go' test. *Phys Ther* 2011; **91**: 1198–207.

13 Rosano C, Newman AB, Katz R, Hirsch CH, Kuller LH. Association between lower digit symbol substitution test score and slower gait and greater risk of mortality and of developing incident disability in well-functioning older adults. *J Am Geriatr Soc* 2008; **56**: 1618–25.

14 Sanders JB, Bremmer MA, Comijs HC, van de Ven PM, Deeg DJH, Beekman ATF. Gait speed and processing speed as clinical markers for geriatric health outcomes. *Am J Geriatr Psychiatry* 2017; **25**: 374–85.

15 Yamada M, Lennie Wong F, Fujiwara S, Akahoshi M, Suzuki G. Noncancer disease incidence in atomic bomb survivors, 1958-1998. *Radiat Res* 2004; **161**: 622–32.

16 Cologne J, Hsu WL, Abbott RD, Ohishi W, Grant EJ, Fujiwara S *et al*. Proportional hazards regression in epidemiologic follow-up studies: an intuitive consideration of primary time scale. *Epidemiology* 2012; **23**: 565–73.

17 Gunning-Dixon FM, Brickman AM, Cheng JC, Alexopoulos GS. Aging of cerebral white matter: a review of MRI findings. *Int J Geriatr Psychiatry* 2009; **24**: 109–17.

18 de Leeuw FE, Cees de Groot J, Oudkerk M, Witteman JCM, Hofman A, van Gijn J *et al*. Aortic atherosclerosis at middle age predicts cerebral white matter lesions in the elderly. *Stroke* 2000; **31**: 425–9.

19 Pratesi A, Tarantini F, di Bari M. Skeletal muscle: an endocrine organ. *Clin Cases Miner Bone Metab* 2013; **10**: 11–14.

20 Batterham PJ, Bunce D, Cherbuin N, Christensen H. Apolipoprotein E ε4 and later-life decline in cognitive function and grip strength. *Am J Geriatr Psychiatry* 2013; **21**: 1010–19.

21 Arvandi M, Strasser B, Meisinger C, Volaklis K, Gothe RM, Siebert U *et al*. Gender differences in the association between grip strength and mortality in older adults: results from the KORA-age study. *BMC Geriatr* 2016; **16**: 201.

22 Kuh D, Cooper R, Hardy R, Guralnik J, Richards M, Musculoskeletal Study Team. Lifetime cognitive performance is associated with midlife physical performance in a prospective national birth cohort study. *Psychosom Med* 2009; **71**: 38–48.

23 Cooper R, Kuh D, Cooper C, Gale CR, Lawlor DA, Matthews F *et al*. Objective measures of physical capability and subsequent health: a systematic review. *Age Ageing* 2011; **40**: 14–23.