Physical and cognitive function in midlife: reciprocal effects? A 5-year follow-up of the Whitehall II study.

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Physical and cognitive function in midlife: reciprocal effects? A 5-year follow-up of the Whitehall II study

Marko Elovainio, PhD[1,3], Mika Kivimäki, PhD[1 2,] Jane E. Ferrie, PhD[1] , David Gimeno, PhD[1], Roberto De Vogli, PhD[1], Marianna Virtanen PhD[2], Jussi Vahtera, MD[2], Eric J. Brunner, PhD[1], Michael G. Marmot, MBBS, MPH, PhD[1], Archana Singh-Manoux, PhD[1, 4]

[1] International Institute for Society and Health, Department of Epidemiology and Public Health, UCL Medical School, London, England, UK.

[2] Finnish Institute of Occupational Health, Helsinki, Finland.

[3] National Research and Development Centre of Welfare and Health (STAKES), Helsinki, Finland.

[4]INSERM U687-IFR69; Hôpital Paul Brousse, Bât 15/16
16 avenue Paul Vaillant Couturier; 94807 Villejuif Cedex, France

Correspondence to: Marko Elovainio, UCL, Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London WC1E 6BT, UK. E-mail: marko.elovainio@stakes.fi

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ABSTRACT

Background: Cognitive and physical functions are closely linked in old age but less is known about this association in midlife. We assessed whether cognitive function predicts physical function and whether physical function predicts cognitive function in middle-aged men and women.

Methods: Data were from Whitehall II; an ongoing large-scale, prospective occupational cohort study of employees from 20 London-based white-collar Civil Service departments. The participants, 3446 men and 1274 women aged 45-68 years at baseline (1995-1997), had complete data on cognitive performance and physical function both at baseline and follow-up (2002-2004). A composite cognitive score was compiled from the following tests: verbal memory, inductive reasoning (Alice Heim 4-I), verbal meaning (Mill Hill), phonemic and semantic fluency. Physical function was measured using the physical composite score of the short form (SF-36) scale. Average follow-up was 5.4 years.

Results: Poor baseline cognitive performance predicted poor physical function at follow-up ($\beta=0.08$, $p<0.001$) while baseline physical function did not predict cognitive performance ($\beta=0.01$, $p=0.67$). After full adjustment for socio-demographic, behavioral and biological risk factors, baseline cognitive performance ($\beta=0.04$ $p=0.009$) remained predictive of physical function.

Conclusion: Despite previous work indicating that the association between physical and cognitive performance may be bidirectional, our findings suggest that in middle age, the direction of the association is predominantly from poor cognition to poor physical function.

What is already known on this subject?

Cognitive function and physical function are both important components of quality of life.

There is an association between cognitive and physical function among the elderly.

What this study adds?

The association between cognitive and physical function is apparent already in midlife.

In midlife the direction of the association may be predominantly from poor cognitive function to poor physical function.

INTRODUCTION

Cognitive function and physical function are both important components of quality of life and functional independence. A growing body of research suggests that there is an association between cognitive and physical function among the elderly in general [1-9] particularly among those with dementia [10-12]. Nevertheless, the dynamics between cognitive and physical function, especially in terms of direction of the association, remain unclear.

As people get older there is increasing heterogeneity in physical and cognitive functioning, [13, 14] resulting in age peers becoming more and more dissimilar from each other. This process starts early and it is increasingly evident that decline in physical and cognitive function is already present in midlife. To our best knowledge, no previous study has examined the relative importance of the influence of cognition on physical function and vice versa among middle aged individuals. Compared to the elderly, lower levels of co-morbidity and low prevalence of severe neurological diseases such as Alzheimer's and Parkinson's disease in this age-group improve opportunities to an unbiased examination of the direction of association between physical function and cognitive function.

A number of health risks as well as specific diseases may lead to declining cognitive performance. Alcohol use in middle age, for example, has been shown to have a U shaped relation with risk of cognitive impairment in old age [15]. Smoking, a sedentary life style, diabetes [16], cardiovascular heart disease [17] and depression [18, 19] all predict a decline in cognitive and physical functioning. The aim of this study is to evaluate the magnitude and direction of the association between cognitive and physical function, followed up over a 5 year period, among middle-aged men and women. The study uses data from Whitehall II, an ongoing large-scale prospective occupational cohort study of London-based civil servants, with the potential to take into account many potential confounders including socioeconomic status, health risk behaviours and health status measures, such as depressive symptoms, diabetes, cardiovascular heart disease, and hypertension.

METHODS

Design/setting and participants

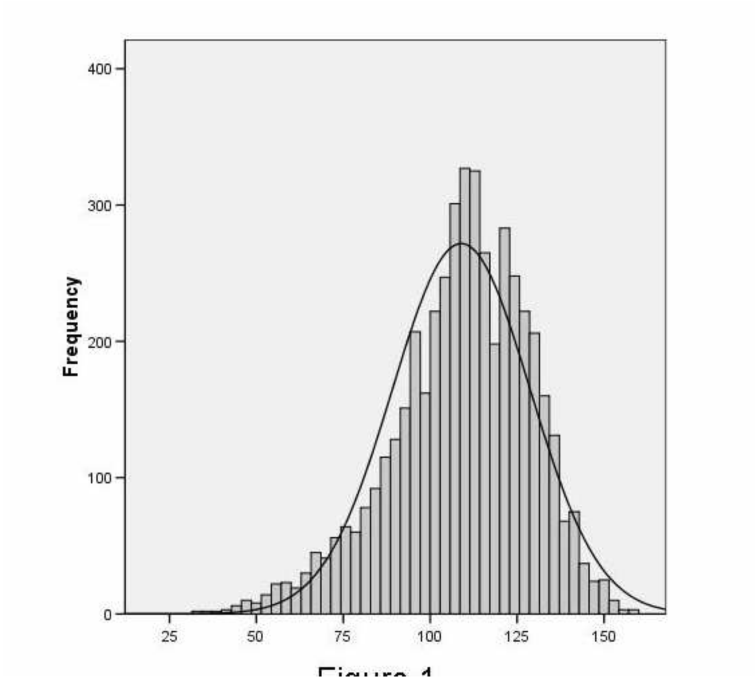
The Whitehall II study sample recruitment (Phase 1) took place between late 1985 and early 1988 among all office staff, from 20 London based Civil Service departments. The response rate was 73% (6895 men and 3413 women), although the true response rate is likely to be higher since around 4% of those invited were ineligible. Since Phase 1 there have been seven further data collection phases. Odd-numbered phases include both a self-administered questionnaire and a clinical examination (Phases 1, 3 (1991-1993), 5 (1997-1999) and 7 (2002-2004)), while even-numbered phases are questionnaire only (Phases 2 (1989-1990), 4 (1995-1996), 6 (2001) and 8 (2006)). Informed consent was gained from all participants. The University College London Medical School Committee on the Ethics of Human Research approved the protocol.

Cognitive function and physical function were both assessed at Phase 5 and again at Phase 7. Thus Phase 5 is used as the baseline for the present study and Phase 7 as the follow-up. Mean age of the participants at Phase 5 was 55.4 years (range 44.8 to 68.2 years) and mean follow-up was 5.4 years (range 3.7 to 7.3 years).

Cognitive function

Cognitive function was measured as a composite score compiled from the results of five standard tests: (1) Verbal memory test was assessed by a 20-word free recall test of short-term memory. Participants were presented a list of one or two syllable words (n=20) at 2-second intervals and were then asked to recall in writing as many of the words in any order within 2 minutes; (2) The AH 4-I [20] is composed of a series of 65 items (32 verbal and 33 mathematical reasoning items) of increasing difficulty. This is a test of inductive reasoning that measures the ability to identify patterns and infer principles and rules. Participants had 10 minutes to complete this section; (3) The Mill Hill vocabulary test [21] assesses knowledge of verbal meaning and encompasses the ability to recognize and comprehend words. We used the test in its multiple-choice format which consists of a list of 33 stimulus words ordered by increasing difficulty, and six response choices per word. In addition, two measures of verbal fluency: phonemic and semantic, were used [22] (4) Phonemic fluency was assessed via ‘‘S’’ words and (5) semantic fluency via ‘‘animal’’ words. Subjects were asked to recall in writing as many words beginning with ‘‘S’’ and as many animal names as they could. One minute was allowed for each test. The distribution of the cognitive function composite score at Phase 7 is presented in Figure 1.

Figure 1

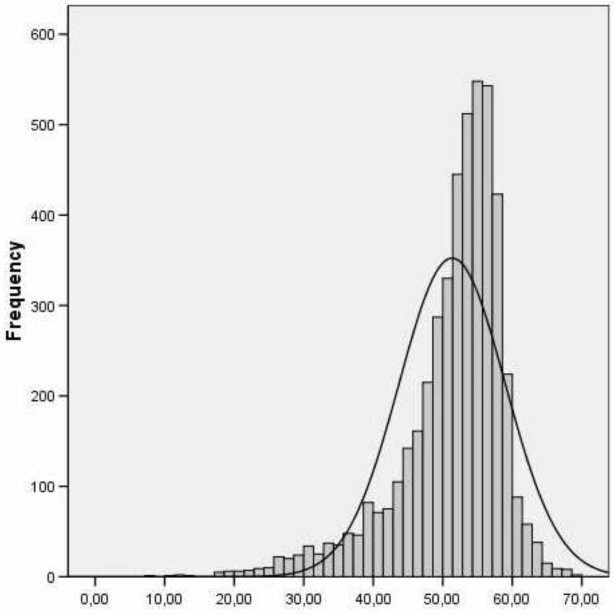


Physical function

Physical function was measured using the physical composite score of the short form 36 health survey (SF-36).The SF-36 is a 36 item questionnaire which measures functioning on eight scales and is among the most widely used measure of quality of life in studies of patients and the general population (for a review, see [23]). Cross-sectional data from population studies have shown that the SF-36 is reliable and able to detect differences between groups defined by age, sex, socioeconomic status, geographical region, and clinical conditions [23].

We used the SF–36 Physical Component Score (PCS) as the measure of physical function. It has greater sensitivity to change over the original eight scales of the SF–36, involves fewer statistical comparisons and eliminates floor and ceiling effects. The PCS is standardized to the general population (mean score, 50: standard deviation, 10), with high scores representing higher levels of functioning. A change on the PCS of between three and five points (equivalent to 0.3 to 0.5 of the standard deviation) is considered to be clinically significant. The distribution of the physical function score at Phase 7 is presented in Figure 2.

Figure 2



Covariates

All covariates were measured at Phase 5 and included socio-demographic characteristics, health behaviors and measures of mental (depressive symptoms) and physical health (diabetes, coronary heart disease (CHD) and hypertension).

Socio-demographic data included age, sex and socioeconomic position collapsed into high (administrators, the top 7 unified grades), intermediate (executives, professionals and technical staff) and low (clerical and office support staff) employment grades. Health behaviours included smoking (self-reported cigarette smoking classified as never or former smoker and current smoker), alcohol consumption (units/week, classified as: none, 1–14 units, 15–21 units, 22 + units with the highest two categories being combined in women), and physical activity. Physical activity was assessed via a questionnaire on the frequency and duration of participation in "mildly energetic" (e.g., weeding, general housework, bicycle repair), "moderately energetic" (e.g., dancing, cycling, leisurely swimming), and "vigorous" (e.g., running, hard swimming, playing squash) physical activity. The frequency and duration measures were combined to compute hours per week of activity at the 3 intensity levels. A compendium of activity energy costs was then used to assign each of the 20 physical activities assessed a metabolic equivalent (MET), which reflects the intensity of each physical activity [24]. Amount of time spent in activities with MET values ranging from 0 to 6 or above was summed to allow calculation of total number of hours per week of physical activity and divided into three categories low, moderate and high.

To examine depressive symptoms in the Whitehall II study, a four item depression subscale (Cronbach α=0.88) was derived from the 30-item General Health Questionnaire (GHQ-30). These items requested whether the participant has recently: been thinking of him/herself as a worthless person; felt that life is entirely hopeless; felt that life isn't worth living; and, found at times he/she couldn't do anything because his/her nerves were too bad. Response options were "not at all", "no more than usual", "rather more than usual", and "much more than usual" [25]. Those with more than 2 symptoms were classified as having depressive symptoms.

Diagnosis of type 2 diabetes was made according to the WHO definition and used self-reports from phases 1, 2, 3, 4, and 5 and an oral glucose tolerance test at Phases 1, 3 and

5. Thus, diabetes was defined by a blood glucose 2 hours after a glucose tolerance test >11.1 g/L (or if the 2- hours post load value was missing, a fasting glucose of >7.0 g/L) or by self-reported doctor diagnosed diabetes or use of diabetes medication.

CHD events from Phase 1 to Phase 5 included non-fatal myocardial infarction (MI) and definite angina. Potential cases of non-fatal MI were ascertained by questionnaire items on chest pain, and doctor's diagnosis of heart attack. Details of physician diagnoses and investigation results were sought from clinical records for all potential cases of MI. Twelve-lead resting electrocardiograms were performed at Phase 5 (Siemens Mingorec) and assigned Minnesota codes. Based on all available data (from questionnaires, study electrocardiograms, hospital records: acute ECGs and cardiac enzymes), non-fatal MI was defined according to MONICA criteria. Classification of MI was carried out blind to other study data independently by two trained coders, with adjudication by a third in the (rare) event of disagreement. Definite angina was recorded for participants who reported symptoms of angina, with corroboration in clinical records or abnormalities on a resting ECG, exercise ECG, or coronary angiogram.

Subjects with SBP≥140 mm Hg and DBP≥90 mmHg or on antihypertensive treatment were considered to be hypertensive[26].

Statistical analysis

Cross-sectional associations between cognitive performance and physical function at phases 5 and 7 were analyzed using Pearson correlations. To estimate two-way antecedent–consequence (i.e., baseline-follow-up) relationships simultaneously, we fitted structural equation models using the LISREL 8.51 software. Goodness-of-fit of the models was judged by (a) the X^2 test, where the higher the P value the better the fit of the data; and (b) the standardized root mean squared residuals (SRMR), lower values indicating better fit. In comparing alternative models, a statistically significant improvement in the X^2 value indicated a better fit of the model.

To explore the direction of the relationships, two linear models were fitted. First, the effect of baseline physical function on cognitive performance at follow-up was modeled, adjusting for cognitive performance at baseline. Second, the effect of cognitive performance on physical function at follow-up was modeled, adjusting for physical function at baseline. The contribution of the potential explanatory factors at baseline to the relationships between physical and cognitive function was explored in linear regression models by including each of the following sets of factors in turn: socioeconomic factors, behavioral and biological risk factors. Finally, the analysis was repeated with simultaneous adjustment for all the above potential explanatory factors. The regression analyses were performed using SAS 9.1.

RESULTS

There were 4720 participants with data on all covariates at baseline (Phase 5) and cognitive and physical function at baseline and follow up (Phase 7), 3446 men and 1274 women. At recruitment to the study, those excluded from the current analyses were older (45.1 years compared to 43.4 years, $p<0.001$), more likely to be women (38% vs. 27%, $p<0.001$), and from the lowest employment grade (25% vs. 11%, $p<0.001$). Baseline characteristics of the study participants are shown in Table 1. The majority of the participants worked in the highest (46%) and middle (44%) grades, most of them were non-smokers, less than one fifth had depressive symptoms, 6% suffered from diabetes, 13% had prevalent CHD and 39% were hypertensive. Mean values for both physical and cognitive scores at baseline and 5 years later and respective standard deviations are presented in Table 2.

Table 1. Sample characteristics

	N	Mean (SD) or %
Age (years)	4720	55.4 (5.9)
Sex		
Men	3446	73
Women	1274	27
Employment Grade		
Administrators (high)	2148	46
Professionals (intermediate)	2087	44
clerical /office support (low)	472	10
Smoking		
Non- smokers	4314	92
Current smokers	396	8
Physical activity		
Low	1404	31
Moderate	1505	34
High	1516	34
Alcohol consumption (units of alcohol/week)		
None	645	14
1-14 units/week	2368	51
15 –22 units/week	705	15
Over 22 units/week	953	20
Diabetes		
No	4022	94
Yes	256	6
CHD		
No	4112	87
Yes	608	13
Hypertension		
No	2827	61
Yes	1881	39
Depressive symptoms		
No	3907	83
Yes	753	17

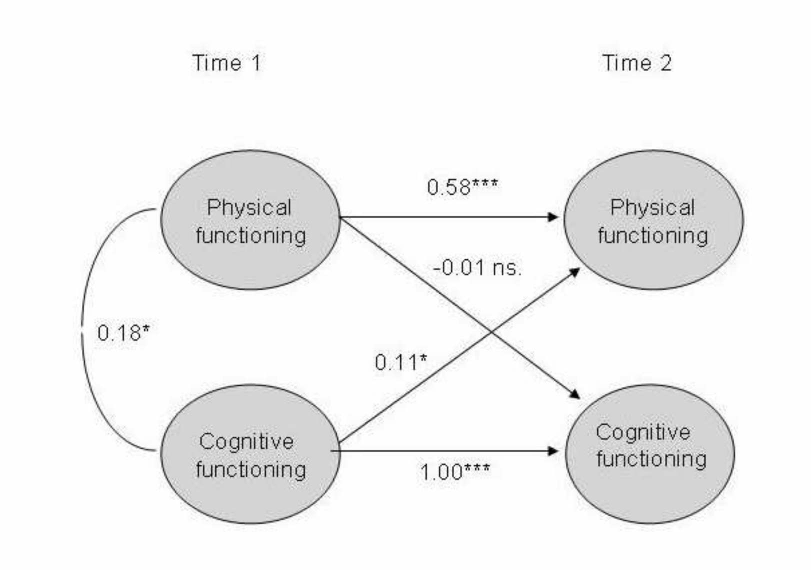
Table 2. Means and standard deviations of cognitive and physical functioning at study Phases 5 and 7

	N	**Mean (SD)**
Cognitive functions		
At Phase 5	4720	113.8 (19.7)
At Phase 7	4720	108.9 (19.8)
Physical functioning		
At phase 5	4720	51.3 (7.6)
At Phase 7	4720	49.3 (8.5)

There was a small decline in the composite cognitive function score between baseline and follow-up (from 113.8 to 108.9), but the correlation between cognitive scores at the two phases was strong ($r = 0.91 p<0.0001$). The physical function score also showed relatively strong stability ($r = 0.60$, $p<0.0001$) although the stability was weaker than that of cognitive function. There was also a slight decline, below the 3-5 point decline considered to be clinically significant, in physical function score between study phases (from 51.3 to 49.3) Cognitive and physical function (measured using summed variables) were moderately inter-correlated at Phase 5 ($r = 0.15$, $p<0.001$) and Phase 7 ($r = 0.17$, $p<0.001$).

Structural equation models (using latent variables for cognitive and physical functions) showed the following results. The models incorporating paths from baseline cognitive function to follow-up physical function and from baseline physical function to follow-up cognitive function offered the best fit for the data (χ^2 (51) = 6771.12 P = 0.000, SRMR = 0.18, NFI=0.85) compared to any other simpler model. The coefficient for the path from cognitive function at baseline to physical function at follow-up was statistically significant (0.11, z-value 8.54, $p<0.001$), while the coefficient for the path from physical function at baseline to cognitive function at follow-up was small and not statistically significant (-0.01, z-value -1.32, p=0.16). Adjusting the model for confounders (latent variable including demographics and health behaviors) produced only moderate change in the association between cognitive function at baseline and physical function at follow-up (0.06, z-value 3.58, p<0.001).

Figure 3



There was a significant, baseline adjusted association between baseline cognitive function and physical function at follow-up (β=0.08, p<0.001). Table 3 presents the age and sex adjusted longitudinal association between cognitive and physical function and the contribution of the covariates to the relationships. The association between cognitive function at baseline and the physical function at follow-up was relatively robust to adjustment for all the baseline covariates considered. None of the covariates, or their combination, accounted for more than a small part of the relationship (Table 3). We additionally adjusted the models for stroke (99 people had experienced stroke in the sample) and the use of drugs for rheumatoid arthritis at Phase 5, but that produced little change in the association between cognitive and physical functions (β=0.04, p=0.013)

On the other hand, there was no evidence of an association between baseline physical function and cognition at follow-up. The adjustments for all of the covariates did not much change this association. Similarly, repeating the analyses among participants over 65 did not change results (standardized estimate from physical function to cognitive performance was -0.01, p=0.590).

Table 3. Associations between cognitive and physical function (unstandardized (B) and standardized (β) beta regression coefficients) in men and in women (N=4720)

Cognitive function	Physical function			
	B	**β**	**t-value**	**p-value**
Adjusted for (in addition to baseline)				
Age and sex	0.02	0.05	4.38	<0.001
Age, sex and social class	0.02	0.04	2.68	0.007
Age, sex, smoking, alcohol consumption, and physical activity	0.02	0.03	2.27	0.023
Age, sex, smoking, alcohol consumption, physical activity, depressive symptoms, diabetes, hypertension and CHD	0.02	0.04	2.62	0.009
Physical function	**Cognitive function**			
	B	**β**	**t-value**	**p-value**
Adjusted for (in addition to baseline)				
Age and sex	0.01	0.00	0.43	0.67
Age, sex and social class	0.00	0.00	0.22	0.83
Age, sex, smoking, alcohol consumption, and physical activity	0.01	0.00	0.28	0.79
Age, sex, smoking, alcohol consumption, physical activity, depressive symptoms, diabetes, hypertension and CHD	0.00	0.00	0.00	0.99

DISCUSSION

The present study examined the direction of the association between cognitive and physical function in a large sample of middle aged British civil servants. Over an average period of 5 years, we found that cognitive performance at baseline predicted physical function at follow-up, while physical function at baseline did not predict cognitive performance at follow-up. Our findings suggest that the direction of any causal association is more likely to be from cognitive to physical function, rather than the reverse.

Our results indicate that poor cognitive function may play a role in the initiation and the progression of poor physical function. However, the size of the regression coefficients between baseline cognitive function and physical function at follow-up would indicate that the contribution of cognitive performance to physical performance is rather small in this middle-aged population. Our results seem not to support the possible reverse proposition that poor physical function leads to poor cognitive function.

Our findings are in agreement with earlier studies demonstrating a correlation between low cognitive function and later declines in physical functioning [2, 27]. Most of these studies were on the elderly (aged > 65 years) and physical function was assessed by asking about activities of daily living or basic/instrumental activities of daily living. Our results add to these findings by showing that there is an association already in middle age using measures of physical function appropriate for middle aged individuals. It has been shown that declines in cognitive function predict decrements in both demanding and routine physical tasks in the elderly, suggesting that cognition plays an integral role in the execution of most physical tasks and the maintenance of physical functioning [28].

The mechanisms underlying the association between cognitive function and physical function require further investigation. It is possible that factors that influence both these outcomes are driving the association observed in this study. One potential candidate is physical exercise that has repeatedly been shown to be a predictor of improved physical functioning. Similarly, many longitudinal intervention studies have shown that regular physical exercise and related physical health status predict improved mental functions and slower cognitive decline in elderly subjects (for a meta-analysis, see [29]). Positive effects of regular physical exercise for some, but not all cognitive tasks, have been found also among younger subjects [30]. It has also been found that leisure time activities is associated with cognition in middle age [31, 32]. In our study, the relationship between cognitive and physical function was, however, quite robust to adjustment for physical exercise level measured by MET hours at baseline. This suggests that physical exercise is not a major driving force for the association found in our study.

Another potential underlying factor is depression. In previous studies, depression has been shown to predict impairment in the physical components of health-related quality of life (HRQoL, [33]). However, our results did not offer support for this hypothesis because adjusting for depressive symptoms had little effect on the results. Similarly, there is evidence in the literature supporting the view that a considerable proportion of cognitive decline in the elderly population is vascular in origin even when there is no sign of specific physical symptoms. However, adjustment for prevalent CHD or hypertension had hardly any effect on our results. Finally, socioeconomic position is likely to be a potential confounder of the association observed here. However, this appeared not to be the case as adjustment for employment grade reduced the size of cognitive performance effects only slightly.

This study has a number of strengths and limitations. It benefits from data from the Whitehall II study, a well-characterized cohort with sufficient power to detect effects, and repeated measures of the key factors: cognitive and physical function. Furthermore, cognitive function was tested using a wide variety of well characterized validated tests. However, the participants were mainly white women and men from white-collar occupations, thus results may have limited applicability to other ethnic groups and occupations. Nonetheless, given the increase in the percentage of workers in affluent societies employed in white-collar occupations, our sample is largely representative, although observed associations are likely to be smaller than in the overall population because of the healthy worker effect. Future research in more diverse samples should confirm the generalizability of our findings. Similarly, our findings need to be replicated in studies with a longer follow-up time with several measures of both cognitive and physical functioning in order to draw robust conclusions on the magnitude and direction of the association. However, the five year follow-up used in the present study is comparable to those used in previous studies on cognitive function and later functional abilities among elderly populations [34]. Availability of long-term repeated data from more than two occasions would help to reduce some of the potential limitations of this study and further illuminate the longer term associations between cognitive ageing and decline in physical functioning.

In this study, physical function among adults was assessed using the SF-36, a questionnaire which measures health functioning and is among the most widely used quality of life measures in studies of patients and the general population [23]. The SF-36 physical composite score (PCS) measures capacity for performing physical activities (vigorous, moderate and light), with one question related to activities of daily living (dressing and bathing). In previous studies, physical functioning among older adults has mostly been measured using information on activities that require extremely light physical efforts, such as activities of daily living or instrumental activities of daily living[34]. Such measures can not be used as indicators of physical function in a middle-aged population due to higher mean levels of physical functioning leading to ceiling effects on instruments designed for older adults. However, the argument for a life-long view of ageing is increasing being made [35], making it important to examine the determinants of ageing earlier than has been done previously. Ageing is characterised by increasing heterogeneity [13, 14], our analysis attempts to add to the understanding of the divergence in ageing trajectories.

In summary, findings over a 5 year period from a large-scale prospective British middle-aged cohort support the view that cognitive function predicts future physical function, but that there is little evidence for the reverse. Extensive covariate adjustment did not remove the associations observed in this study. This study suggests that interventions to improve cognitive functioning in middle age can have long-term effects on physical functioning, and they may therefore constitute important, indirect tools for health promotion and the prevention of physical decline.

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Competing interests: None.

Figure legends:

Figure 1. Cognitive functions composite score distribution at Phase 7 N=4720

Figure 2. Physical functioning composite score distribution at Phase 7 N=4720

Figure 3. Temporal relationships between cognitive and physical function
Structural Equation Model (Lisrel 8.52, loadings of measured variables not shown)
***p<0.001, **0.01, *0.05, n.s. non-significance

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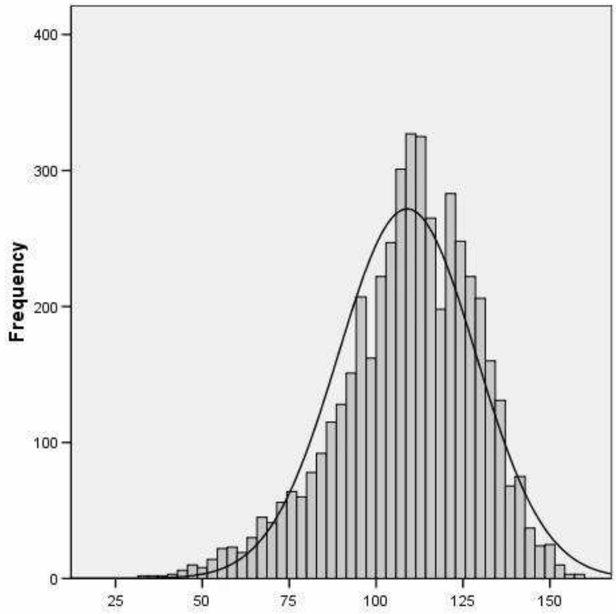

Figure 1.