

## The Dynamic Relationship Between Physical Function and Cognition in Longitudinal Aging Cohorts

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On average, older people remember less and walk more slowly than do younger persons. Some researchers argue that this is due in part to a common biologic process underlying age-related declines in both physical and cognitive functioning. Only recently have longitudinal data become available for analyzing this claim. We conducted a systematic review of English-language research published between 2000 and 2011 to evaluate the relations between rates of change in physical and cognitive functioning in older cohorts. Physical functioning was assessed using objective measures: walking speed, grip strength, chair rise time, flamingo stand time, and summary measures of physical functioning. Cognition was measured using mental state examinations, fluid cognition, and diagnosis of impairment. Results depended on measurement type: Change in grip strength was more strongly correlated with mental state, while change in walking speed was more strongly correlated with change in fluid cognition. Examining physical and cognitive functioning can help clinicians and researchers to better identify individuals and groups that are aging differently and at different rates. In future research, investigators should consider the importance of identifying different patterns and rates of decline, examine relations between more diverse types of measures, and analyze the order in which age-related declines occur.

aging; cognition; correlated change; longitudinal analysis; meta-analysis; physical functioning; systematic review

Abbreviations: *APOE4*, apolipoprotein E  $\epsilon$ 4 allele; CI, confidence interval; HR, hazard ratio; MMSE, Mini-Mental State Examination; MSE, mental state examination; OR, odds ratio; SEP, socioeconomic position.

On average, older people walk more slowly, have less muscle strength, have poorer memory and reasoning abilities, and are slower to respond on speeded cognitive tasks relative to younger adults and to themselves when they were younger. Physical and cognitive functioning are both indicators of biologic aging—the progressive generalized impairment of functioning that occurs when people grow older. The aging process is often characterized by a loss of adaptive response to life challenges and an increasing vulnerability to pathology (i.e., aging-associated diseases) and functional limitations. With respect to cognition, fluid cognition (the ability to learn new processes and form new memories) has been shown to decline from midlife onwards as a result of normal aging (1, 2), while cognitive decline of functional or clinical significance (including diagnosis of dementia or Alzheimer's disease) is generally not detected until much later in life, often as a result of

significant neurologic morbidity (such as cerebrovascular disease) (3). Age-related declines in physical function are also observed even in the absence of disease from midlife onwards as a result of normative age-related changes in the musculoskeletal system and other body systems on which these measures depend (4). Given that changes in cognitive and physical functioning probably result from interactions among aging and disease, their effects may not be fully distinguishable (5). As people age, some individuals experience abnormal declines in physical and cognitive functioning that increase their risk of dependence and premature death (6–9). There are, however, remarkable individual differences in rates of age-associated decline and in the age at which these declines begin to accelerate.

Although changes in physical and cognitive functioning are almost universal in older adulthood, there is debate in the literature regarding the nature and degree of interdependency

across these domains and whether a common causal mechanism is responsible for declines in both. On the basis of cross-sectional evidence, Christensen et al. (10) found the link between age-related differences across physical and cognitive domains to be very strong, with the suggestion that declines in both domains are driven by a unifying process. A common causal account of aging has been that the process operates at various levels, from brain circuitry (11) and brain pathology (12) to the loss of molecular fidelity (13). However, as noted, evidence for this “common cause” hypothesis relies primarily on cross-sectional studies, with the problematic assumption that between-person age differences provide valid proxy estimates for within-person aging-related change. Highlighting the confounding created by age heterogeneity, Hofer et al. (14, 15) argued that longitudinal data are necessary for rigorously examining multivariate associations among aging-associated outcomes. To date, a relatively few studies, differing in design, measurement, and statistical analyses, have examined longitudinal associations between physical and cognitive functioning.

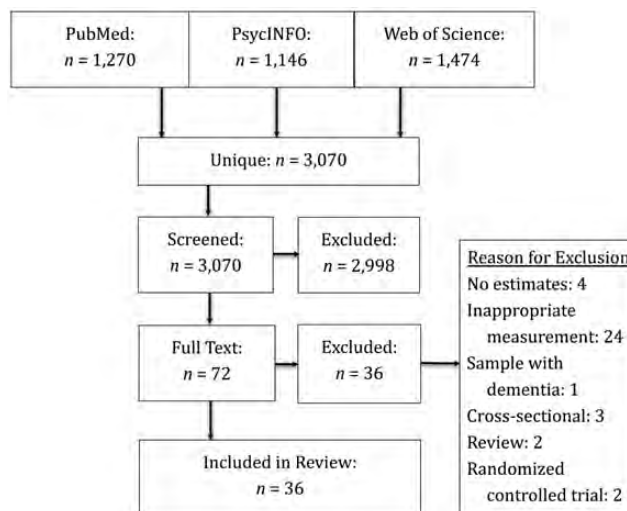
We systematically reviewed longitudinal studies that investigated the association between objective measures of physical and cognitive functioning in general community-dwelling population samples aged 40 years or older. In this paper, we focus on the relation between individual differences in physical and cognitive functioning both at baseline (intercepts) and over time (slopes). We performed random-effects meta-analyses of published data to obtain estimates of the interdependency between changes in physical and cognitive functioning. We also examined the degree to which sex, type of measurement (e.g., grip strength, walking speed, executive functioning, verbal memory), heterogeneity in samples (e.g., length of follow-up, age) or measurement, and geographic region modified these relations. To our knowledge, this is the first systematic review of the longitudinal association between changes in physical functioning and cognitive functioning.

## MATERIALS AND METHODS

We used the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) to create the protocol for this systematic review (16). A comprehensive literature search for studies that longitudinally examined the association between physical change and cognitive change in older adulthood was performed using PubMed, Web of Science, and PsycINFO from January 2000 to October 2011 (Figure 1). This study follows up on a previous literature review (published in 2003), which highlighted the need for this form of research (14). After the previous review, the number of longitudinal studies rose substantially. The search strategy focused on 3 key elements: physical functioning, cognitive functioning, and older adult populations. Only English-language papers were reviewed.

### Eligibility criteria

We included human studies that 1) used data drawn from community-dwelling population samples aged 40 years or older, 2) analyzed individual-level data, 3) included



**Figure 1.** Strategy used to select recently published articles (2000–2011) for a review of the relations between rates of change in physical functioning and cognitive functioning in community-dwelling population samples aged  $\geq 40$  years.

objective measurements of both physical and cognitive functioning, 4) measured explanatory factors coincident with or prior to the outcome factors, 5) reported effect estimates of the association between physical and cognitive functioning, and 6) included longitudinal information about physical functioning and/or cognition. We excluded studies in which 1) the outcome was assessed in childhood or early adulthood, 2) data were derived from animal models, 3) original data were not reported (e.g., review articles), and 4) data from clinical samples were reported. Finally, we excluded intervention studies (where the physical or cognitive variable was manipulated).

### Study selection and data collection

Three authors independently reviewed the resultant list of unique citations to assess eligibility for inclusion; of the original 3,070 citations, they identified 72 candidates eligible for review. Of these, 36 were included in the final analysis, with most of the excluded studies ( $n=24$ ) having failed to use appropriate (objective) measures (Figure 1). We used a standardized form to extract data from our final sample ( $n=36$ ). Included in the form was information related to study design (waves of data collection, years between measurements, total time between baseline and final follow-up, response rate, study exclusion criteria, variables used); sample characteristics (mean sample age, sex distribution, community vs. institutional setting, geographic region); measurements (tools employed for objective measurement of physical and cognitive functioning); and statistical methods (analytical approach, covariates, effects, and fully adjusted estimates of the statistical significance and reliability of study estimates). We did not formally assess

study quality because, unlike the case with randomized controlled trials, validated quality criteria were not available (17). However, in meeting our inclusion criteria, all included studies were considered to be adequately methodologically rigorous. Information was gathered from tables and figures as well as the text of manuscripts. When the reviewers disagreed with regard to the extracted models and details of performance (approximately 5% of studies at each stage of analysis), consensus was reached through discussion.

### Data analysis

Three types of associations characterize most relations examined in these studies: 1) cross-sectional (between-person differences), 2) effects of baseline characteristics in one outcome on change in another (baseline effects on within-person change), and 3) change in one form of functioning regressed or correlated with change in the other (correlated within-person change). Studies not conforming to one of these 3 types tended to be unique and are discussed at greater length in the Results section. In studies modeling the relation of baseline characteristics with change (point 2 above), we employed 2 approaches: 1) using follow-up observations indicating observed declines (for which we present beta coefficients) and 2) using later diagnosis (of dementia or physical impairment) to infer decline (with results presented as hazard ratios).

A pooled estimate of the association between each measure of physical functioning and cognitive functioning was calculated using meta-analytic techniques for regression coefficients, odds ratios, and risk ratios. Estimates and 95% confidence intervals are presented.  $I^2$  was used to evaluate the percentage of total variation that was due to between-study heterogeneity. Because of small sample sizes, we used  $\alpha = 0.10$  to designate statistical significance. To maintain sample comparability, we reduced heterogeneity in 2 ways: first by separating fundamentally different types of analysis and then by standardizing the estimates (for which we present standardized beta coefficients).

Heterogeneity between studies may be due to variation in the explanatory or outcome measures, the age and sex of participants, the number of and time interval between follow-up assessments, geographic region, apolipoprotein E  $\epsilon 4$  allele (*APOE4*) status, and age. When possible, we analyzed the roles of these sources of heterogeneity in explaining differences in results by means of subgroup analysis. We analyzed publication bias using funnel plots, which showed no evidence for publication bias in any of the risk estimates, intercepts, or slope estimates. All analyses were performed using Stata 11/IC (StataCorp LP, College Station, Texas); graphics were created using Excel (Microsoft Corporation, Seattle, Washington).

## RESULTS

### Study characteristics

The samples included in these analyses (see Table 1) varied substantially from studies with small numbers of homogeneous participants (minimum  $n = 60$ ) to larger samples

that were heterogeneous in terms of age, geography, genetics, and culture (maximum  $n = 17,333$ ). The shortest follow-up time was 1 year, the longest 20; and the ages of the subjects ranged from 41 years to over 100 years. The samples were concentrated in the United States ( $n = 20$ ) and continental Europe ( $n = 9$ ), with the remaining studies observing respondents in the United Kingdom ( $n = 3$ ), Canada ( $n = 2$ ), Australia ( $n = 1$ ), and Hong Kong ( $n = 1$ ). One-fifth of the studies were sex-homogeneous, and four-fifths were age-heterogeneous (defined as an age range greater than 9 years or a standard deviation greater than 3 years). Baseline response rates ranged from 47% to 91%; however, only 41% of the published articles reported this statistic. When it was reported, retention was good, with 46% to 80% of the sample being retained between waves; however, only 24% of the articles reported this statistic. Only 22% of study investigators used methods to reduce bias from missing data; the rest either did not report how they dealt with missing data or excluded persons with missing data from the analysis. When it was discussed, most of the attrition tended to be due to mortality.

Physical and cognitive functioning were examined as study outcomes and main independent variables. Most studies (78%) used cognition as the main outcome; fewer (35%) used physical functioning as an outcome of interest (14% estimated both directions). Forty-three percent of studies included some estimate of the risk of cognitive impairment (including Alzheimer's disease), while 68% estimated changes in cognition or physical functioning.

### Measures of physical and cognitive functioning

Physical functioning was measured using a variety of indicators, including grip strength (51% of studies), walking speed (54%), chair stands (22%), flamingo stand times (22%), and lung function (14%). Eleven percent used composite scores, and 41% analyzed more than one measure of physical functioning—for example, muscle strength (axial strength; arm and leg abduction, flexion, and extension; grip and pinch strength (18)) or lower extremity function (flamingo stands, chair stands, and walking speed (19)). Three studies used these objective measures to code physical impairment, defined alternatively as loss of ambulation, mobility impairment, and motor performance decline.

In assessing cognition, researchers used measures of fluid cognition, measures of crystallized cognition, and mental state examinations (MSEs). In some cases, MSEs were further used in combination with administrative data to indicate mild cognitive impairment and other clinical diagnostic outcomes, including dementia or Alzheimer's disease (3). Cognition was measured using MSEs 46% of the time, fluid cognition 43% of the time, and diagnostic measures of cognition 27% of the time. A variety of tests were used as indicators of fluid cognition, including verbal recall, letter cancellation, Raven's Progressive Matrices (Harcourt Assessment, Inc., San Antonio, Texas), processing speed, executive function, etc. When measuring fluid cognition, researchers used a vast array of measures; these were included either as single indicators or as part of a global measure of cognition. Most studies included only 1

**Table 1.** Characteristics of Studies<sup>a</sup> Included in a Review of the Relations Between Rates of Change in Physical and Cognitive Functioning in Older Adults

First Author, Year (Reference No.)	Region	Study	No. of Participants	% Male	Length of Follow-up, years	Baseline Age Range, years	Cognitive Measure	Physical Measure	Main Result
Abbott, 2004 (49)	Hawaii, United States	Honolulu Heart Program	2,257	100	7	71–93	Diagnostic criteria	Walking speed	Incidence of dementia was higher in persons who walked 10 feet (3 m) in 6 seconds or more relative to those who walked 10 feet in 3 seconds or less.
Aichberger, 2010 (25)	Europe (EU countries)	Survey of Health, Ageing, and Retirement in Europe	17,333	46	2.5	≥50	Fluid cognition	Grip strength	Grip strength at baseline was correlated with baseline fluid cognition but not change in fluid cognition.
Alfaro-Acha, 2006 (37)	Southwestern United States	Hispanic EPESE	2,160	43	7	≥65	MSEs	Grip strength	Lower grip strength predicted significant declines in mental state.
Alfaro-Acha, 2007 (52)	Southwestern United States	Hispanic EPESE	2,070	43	8	≥65	MSEs	Walking speed	Slow walkers were more likely to experience greater decline in mental state over 7 years, but walking speed was not correlated with mental state at baseline.
Atkinson, 2007 (54)	Southeastern United States	Health ABC Study	2,341	48	3	65–80	MSEs	Walking speed, grip strength, chair stands	Mental state was correlated with increased decline in walking speed. The effect was much reduced when vascular risk factors were included in the model.
Atkinson, 2010 (32)	United States	Women's Health Initiative Memory Study	1,793	0	6	70–79	MSEs, fluid cognition	Walking speed	Mental state and fluid cognition at baseline were associated with changes in physical functioning. Physical function at baseline was not associated with changes in cognition. Changes in cognition were associated with changes in physical functioning.
Auyeung, 2011 (31)	Hong Kong	Chinese University of Hong Kong Study	2,737	55	4	≥65	MSEs, diagnostic criteria	Grip strength	Weaker grip strength was correlated with declines in mental state. Muscle strength was associated with slowed global cognitive decline and decreased diagnostic risk.
Boyle, 2009 (18)	Midwestern United States	Rush Memory and Aging Study	970	25	3.6	54–100	Fluid cognition, diagnostic criteria	Grip strength, muscle strength	Muscle strength was associated with risk of mild cognitive impairment.

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Region	Study	No. of Participants	% Male	Length of Follow-up, years	Baseline Age Range, years	Cognitive Measure	Physical Measure	Main Result
Buchman, 2011 (44)	Midwestern United States	Rush Memory and Aging Study	836	26	4.5	54–100	Fluid cognition	Walking speed	Fluid cognition at baseline was associated with incident mobility impairment and mobility decline.
Buracchio, 2010 (34)	Northwestern United States	Oregon Brain Aging Study	204	42	19	≥65	MSEs	Walking speed	Persons with incident mild cognitive impairment experienced a more rapid decline in gait speed up to 12 years prior. In contrast, declines in finger-tapping occurred after the incidence of mild cognitive impairment.
Charles, 2006 (28)	Hawaii, United States	Honolulu-Asia Aging Study	3,519	100	20	46–68	MSEs	Grip strength	Decline in grip strength was related to mental state at baseline.
Christensen, 2000 (55)	Australia	Queanbeyan Community Study	425	48	3.5	70–93	Fluid cognition, crystallized cognition	Grip strength	Grip strength at baseline did not predict rate of change in fluid cognition. Changes in grip strength did correlate moderately.
Deary, 2011 (30)	United Kingdom	Lothian Birth Cohort 1921	550	43	8	79	Fluid cognition	Grip strength	Baseline fluid cognition and grip strength were correlated, but no evidence emerged regarding correlations with changes in either grip strength or cognition.
Deshpande, 2009 (47)	Italy	Invecchiare in Chianti Study	660	47	3	≥65	MSEs	Walking speed	Walking speed (especially "walks as fast as possible") was correlated with declines in mental state, though walking at a usual pace was not.
Gatz, 2010 (35)	Sweden	Swedish Adoption/Twin Study of Aging	60	23	9	57–88	Diagnostic criteria	Grip strength	Persons who developed preclinical dementia in 3 years performed worse on grip strength measures at baseline than did their twins who did not develop preclinical dementia.
Giltay, 2009 (24)	Europe (EU countries)	Seven Countries Study	857	100	10	45–64	Diagnostic criteria	Lung function	Midlife lung function was associated with the risk of dementia in <i>APOE4</i> noncarriers but not in <i>APOE4</i> carriers, where it was inversely related to risk of dementia. Lowered lung function predicted increased risk of dementia.

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Region	Study	No. of Participants	% Male	Length of Follow-up, years	Baseline Age Range, years	Cognitive Measure	Physical Measure	Main Result
Guo, 2007 (51)	Sweden	Swedish Adoption/Twin Study of Aging	1,291	0	29	44–66	Diagnostic criteria	Lung function	Better respiratory function was associated with lower risk of dementia.
Inzitari, 2007 (71)	Northeastern United States	Health ABC Study	2,276	47	5	70–79	Fluid cognition	Walking speed	Gait speed at baseline predicted changes in fluid cognition.
Inzitari, 2007 (45)	Italy	Italian Longitudinal Study of Aging	1,052	67	3	70–79	MSE, fluid cognition	Walking speed	Fluid cognition predicted 3-year risk of decline in motor performance.
Kuh, 2009 (48)	United Kingdom	National Survey of Health and Development	2,135	49	10	53	Fluid cognition, crystallized cognition	Grip strength, chair stands, flamingo stands	Higher childhood cognition at age 11 years and fewer declines in fluid cognition between ages 43 and 53 years were associated with balance and chair rising speed at age 53 years. The association between fluid cognition and grip strength was inconsistent.
Larson, 2006 (27)	Northwestern United States	Adult Changes in Thought Study	1,740	38	6.2	≥65	Diagnostic criteria	Grip strength, walking speed, chair stands, flamingo stands	In sedentary older adults, baseline physical functioning reduced risk of subsequent dementia. The association was nonsignificant among persons who exercised more.
MacDonald, 2011 (72)	Canada	Victoria Longitudinal Study	1,043	34	6	55–85	Fluid cognition	Grip strength, lung function	Higher grip strength and lung function ameliorated the risk of declines in fluid cognition.
Marquis, 2002 (73)	Northwestern United States	Oregon Brain Aging Study	108	37	6	≥65	Diagnostic criteria	Walking speed	Walking speed predicted the onset of cognitive impairment.
Payette, 2011 (46)	Canada	Nutrition and Successful Aging Cohort Study	1,741	48	3	68–82	MSEs	Walking speed, flamingo stands, chair stands	Physical function declined over the years more than did mental state. Although the 2 factors declined contemporaneously, they did not accelerate together within individuals.
Pugh, 2007 (19)	Southwestern United States	Hispanic EPESE	1,682	42	6	≥65	MSEs	Walking speed, chair stands	Mental state at baseline predicted changes in lower extremity functioning.
Raji, 2002 (33)	Southwestern United States	Hispanic EPESE	2,068	41	2	≥65	MSEs	Grip strength	Mental state at baseline predicted later grip strength.

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Region	Study	No. of Participants	% Male	Length of Follow-up, years	Baseline Age Range, years	Cognitive Measure	Physical Measure	Main Result
Raji, 2005 (21)	Southwestern United States	Hispanic EPESE	2,381	43	8.25	≥65	MSEs	Walking speed, flamingo stands, chair stands	Mental state at baseline predicted steeper declines in grip strength.
Richards, 2005 (29)	United Kingdom	National Survey of Health and Development	1,778	50	10	53	Fluid cognition, crystallized cognition	Lung function	Fluid cognition was correlated with baseline lung function.
Rivera, 2008 (22)	Northeastern United States	Women's Health and Aging Study	474	0	1	≥65	MSEs	Grip strength, walking speed	Cognitive impairment (MSE) predicted incidence of severe mobility difficulties.
Sattler, 2011 (26)	Germany	Interdisziplinäre Längsschnittstudie des Erwachsenenalters	381	51	12	41–44; 61–64	Fluid cognition	Grip strength, flamingo stands	Flamingo stands were correlated with baseline fluid cognition but did not predict changes in fluid cognition.
Soumare, 2009 (23)	France	Three-City Study	3,769	38	7	65–85	MSEs, fluid cognition	Walking speed	Baseline walking speed was correlated with cognition at baseline. Changes in walking speed were correlated with baseline cognition.
Tabbarah, 2002 (20)	Northeastern United States	MacArthur Research Network on Successful Aging Community Study	488	42	7	70–80	Fluid cognition	Grip strength, walking speed, chair stands, flamingo stands	Physical functioning at baseline and changes in physical functioning were correlated with fluid cognition, regardless of how fluid cognition was measured.
Taekema, 2010 (74)	Netherlands	Leiden 85+ Study	555	35	4	85	MSEs	Grip strength	MSE at baseline predicted baseline grip strength and changes in grip strength.
Wang, 2006 (50)	Northwestern United States	Adult Changes in Thought Study	2,288	40	9	≥65	Diagnostic criteria	Grip strength, walking speed, chair stands, flamingo stands	Lower levels of physical function were correlated with increases in risk of dementia and Alzheimer's disease.
Watson, 2010 (53)	Northeastern United States	Health ABC Study	865	50	5	70–79	Fluid cognition	Walking speed	Fluid cognition was associated with decline in gait speed.
Weuve, 2011 (36)	Northeastern United States	Normative Aging Study	864	100	12	≥50	MSEs, fluid cognition	Lung function	Lung function did not correlate with declines in fluid cognition or MSEs.
Mean value			1,857	45	7.41				

Abbreviations: *APOE4*, apolipoprotein E ε4 allele; EPESE, Established Populations for the Epidemiologic Study of the Elderly; EU, European Union; Health ABC, Health, Aging and Body Composition; MSE, mental state examination.

<sup>a</sup> English-language articles published between 2000 and 2011.

measure of fluid cognition, sometimes accompanied by a measure of mental state. Our analyses were separated by domain but not by measure within domain; thus, in cases where multiple measures were presented, we used estimates based on global measures of fluid cognition. In the single study that tested the differences between multiple indicators of fluid cognition, the authors suggested that the choice of indicator had little bearing on the associations presented (20). Studies using MSEs employed a number of tests to measure mental state, including, most often (88% of studies), the Mini-Mental State Examination (MMSE) or its modified version (the 3MS). Of studies that used diagnostic measures of cognition, 44% were based on diagnoses of Alzheimer's disease and 33% were based on clinical or research-based diagnoses of mild cognitive impairment. Clinical outcomes were often retrieved from clinical reports and administrative data. When researchers created a diagnostic measure of cognition, they used arbitrary cutpoints (e.g., MMSE score <21 (21) or MMSE score <24 (22)). Because crystallized cognition is relatively stable across the life span, we excluded it from our analysis. Studies using MSEs identified these measures as alternatively indicating global cognition (23) or cognitive impairment (24). Because of the wide range of different measures of cognition and physical functioning used in different studies and the differences between these measures, we do not provide overall estimates of physical functioning or cognition but rather provide summary estimates for the association between each measure of physical function and each measure of cognition.

### Adjustment for confounding variables

The included studies adjusted their statistical models using covariates that fall broadly within 8 domains: health status (body mass, self-assessed health, depressive symptoms, blood pressure, cholesterol), behavior (smoking, alcohol intake, physical activity), clinical conditions (cardiovascular disease, diabetes, hypertension, chronic obstructive pulmonary disease), social factors (education, socioeconomic status, marital status), functioning (visual acuity, ability to stand for 15 minutes), demographic factors (age, sex), and genetic factors (*APOE4* status).

Researchers highlighted a number of potential covariates with varying degrees of impact. Physical activity or exercise was significantly associated with both physical and cognitive functioning (25, 26), and it attenuated the relation between physical and cognitive functioning in one study (27). However, exposure to pesticides, solvents, and metals (28) and polypharmacy or suboptimal prescribing (19) did not attenuate the relation between grip strength and cognitive function. Two studies adjusted for childhood intelligence (measured at age 8 years in one study, using the Alice Heim general ability test (29), and at age 11 years in the other study, using the Moray House test (30)), and both found that this adjustment attenuated the association between physical and cognitive functioning in adulthood. Though results for socioeconomic position (SEP) were not often reported, adjusting for SEP attenuated estimates when it was analyzed (21, 29). Finally, including measurements of body size often attenuated the results.

### Relations between physical and cognitive functioning

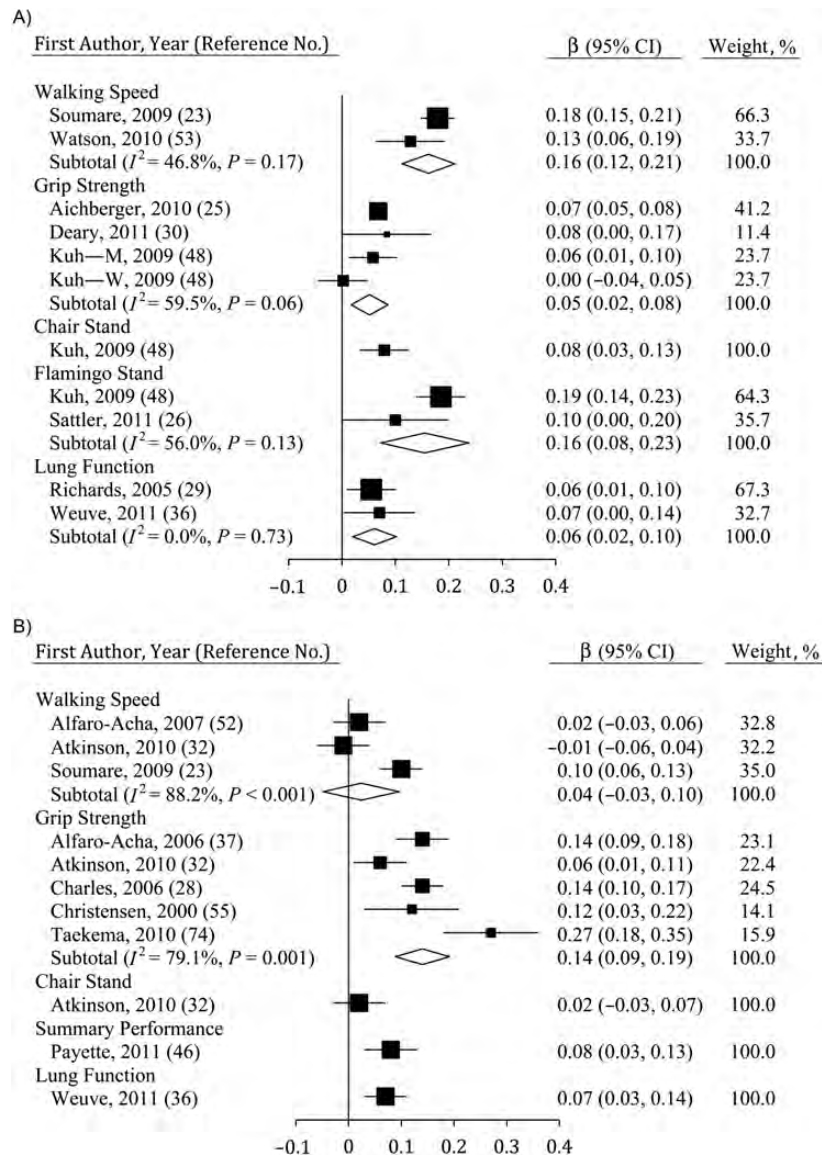
*Cross-sectional correlations (intercepts).* In the studies evaluated here, cross-sectional, between-person associations were evident between measures of physical function and both fluid cognition (Figure 2A) and MSE (Figure 2B). Grip strength (estimate size ( $\beta$ ) = 0.05, 95% confidence interval (CI): 0.02, 0.08;  $n$  = 4), walking speed ( $\beta$  = 0.16, 95% CI: 0.12, 0.21;  $n$  = 2), flamingo stands ( $\beta$  = 0.16, 95% CI: 0.08, 0.23;  $n$  = 2), chair stands ( $\beta$  = 0.08, 95% CI: 0.03, 0.13;  $n$  = 1), and lung function ( $\beta$  = 0.06, 95% CI: 0.02, 0.10;  $n$  = 2) were all significantly correlated with fluid cognition at baseline. However, results for walking speed were significantly stronger than were estimates for grip strength ( $P$  < 0.05). Study heterogeneity was observed when linking grip strength to fluid cognition at baseline ( $I^2$  = 59.5%,  $P$  < 0.10), due largely to nonsignificant estimates among women in 1 study. In contrast, for MSE, a consistent relation was observed only for grip strength ( $\beta$  = 0.14, 95% CI: 0.09, 0.19;  $n$  = 5). Limited evidence did show a significant relation using a summary performance measure ( $\beta$  = 0.08, 95% CI: 0.03, 0.13;  $n$  = 1) and lung function ( $\beta$  = 0.07, 95% CI: 0.03, 0.14;  $n$  = 1). Study heterogeneity was significant for relations between MSE and both grip strength and walking speed ( $P$  ≤ 0.001).

*Effect of baseline status on within-person change.* Change in cognition. Some measures of physical function at baseline were correlated with changes in fluid cognition (Figure 3A) and MSE (Figure 3B). For fluid cognition, only walking speed ( $\beta$  = 0.05, 95% CI: 0.02, 0.08;  $n$  = 2) and summary performance measures ( $\beta$  = 0.15, 95% CI: 0.07, 0.22;  $n$  = 2) yielded a significant association. Indeed, the relation between summary performance measures and change in cognition was stronger than was any other measure of physical function ( $P$  < 0.10), though there was substantial heterogeneity in this estimate ( $I^2$  = 65.9%,  $P$  < 0.10). In contrast, effects were consistently null for grip strength, for lung function, and for flamingo stands, which were only used in 1 study (26). One study additionally showed that changes in fluid cognition were correlated with between-person differences in flamingo stands and chair stands at follow-up (31).

Baseline grip strength ( $\beta$  = 0.06, 95% CI: 0.03, 0.09;  $n$  = 5) and walking speed ( $\beta$  = 0.04, 95% CI: 0.02, 0.07;  $n$  = 6) were associated with declines in MSE score, though the relation with grip strength was slightly stronger (not significant). Baseline measures of chair stands, flamingo stands, summary performance measures, and lung function were not significant predictors of change in cognition over time, though small samples resulted in limited statistical power.

Change in physical functioning. Fewer studies reported analysis of the relation between baseline cognition and changes in physical function (see Figure 4A for fluid cognition, Figure 4B for MSE). However, fluid cognition was correlated with changes in walking speed ( $\beta$  = 0.09, 95% CI: 0.02, 0.15;  $n$  = 2) in 2 studies (20, 32). In contrast, no significant relation emerged for fluid cognition and grip strength, flamingo stands, or chair stands. Results were also mixed for MSE, which produced the sole significant result with change in a summary performance measure (33).

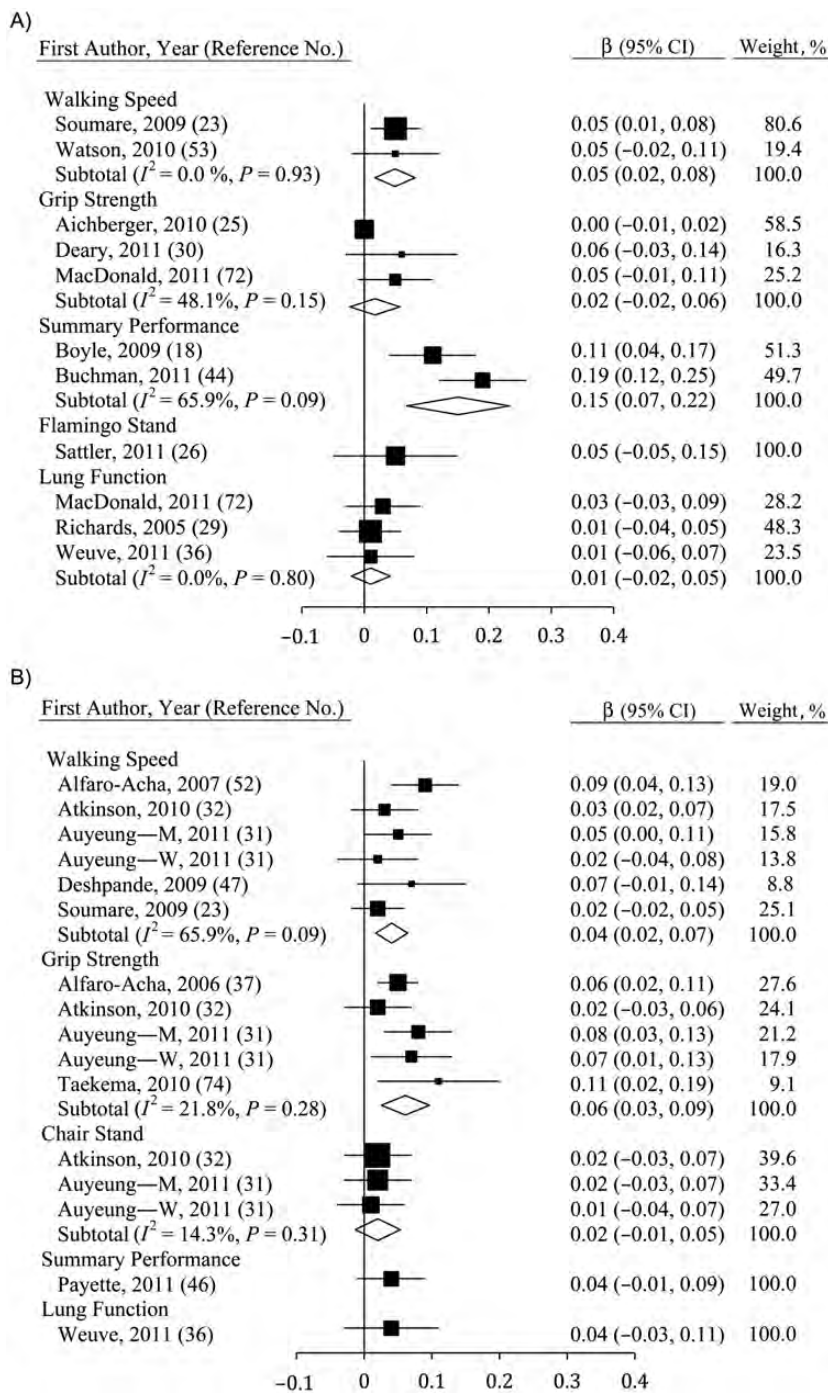




**Figure 2.** Average standardized regression coefficients ( $\beta$ ) obtained when baseline physical function was regressed on cognition at baseline using A) fluid cognition and B) mental state examinations among persons aged  $\geq 40$  years, 2000–2011. Data from the study by Kuh et al. (48) were separated by sex (M, men; W, women). Individual studies are represented by squares; subtotals provide within-group variance-weighted averages and are represented by diamonds. Bars, 95% confidence interval (CI).

**Models of risk at follow-up.** The risk of cognitive impairment (Figure 5A) was associated with walking speed (hazard ratio (HR) = 1.20, 95% CI: 1.10, 1.31;  $n = 3$ ), grip strength (HR = 1.64, 95% CI: 1.26, 2.13;  $n = 5$ ), a summary performance measure (HR = 1.61, 95% CI: 1.27, 2.04;  $n = 1$ ), and lung function (HR = 1.30, 95% CI: 1.10, 1.54;  $n = 1$ ). However, some results were not included in Figure 5A due to a lack of comparability in measures used. Analyses using the risk of impaired scores on MSE at follow-up showed much stronger relations with baseline walking speed (odds ratio (OR) = 2.32, 95% CI: 1.15, 4.90) than those described

above (34). Sattler et al. (26) used odds ratios to estimate risk and found that grip strength was not related to cognitive impairment (OR = 1.00, 95% CI: 0.99, 1.01), while relations between flamingo stands and cognitive impairment were substantial (OR = 2.86, 95% CI: 1.56, 5.26). Results from Giltay et al. (24), who stratified their analyses by *APOE4* status, showed that lung function predicted the onset of dementia among persons with the *APOE4* allele but not among noncarriers. Finally, Gatz et al. (35), whose study was unique in its capability to control for heritability by using the Swedish Twin Registry and assessments of both monozygotic and

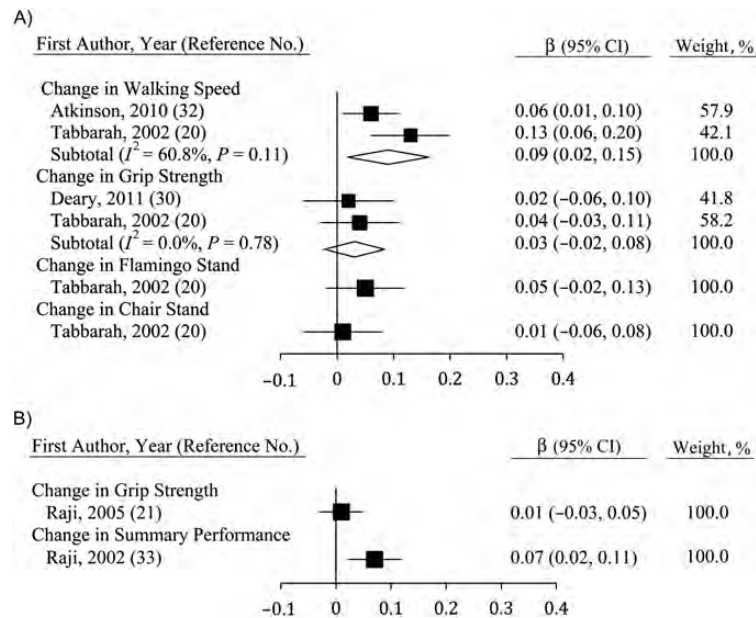


**Figure 3.** Average standardized regression coefficients ( $\beta$ ) for the association between change in cognition and baseline physical functioning derived using A) fluid cognition and B) mental state examinations among persons aged  $\geq 40$  years, 2000–2011. Data from the study by Ayeung et al. (32) were separated by sex (M, men; W, women). Individual studies are represented by squares; subtotals provide within-group variance-weighted averages and are represented by diamonds. Bars, 95% confidence interval (CI).

dizygotic twins, found support for an increased risk by showing that persons with lowered grip strength developed dementia faster than their twins did.

The risk of physical impairment (Figure 5B) was significantly related to lowered fluid cognition when mobility

impairment (HR = 1.96, 95% CI: 1.54, 2.50) or loss of ambulation (HR = 2.56, 95% CI: 1.90, 3.45) was used to indicate physical impairment, though not when motor performance declines were used. Modifying risk factors were not assessed because of the small number of samples included.



**Figure 4.** Average standardized regression coefficients ( $\beta$ ) for the association between change in physical function and baseline cognition derived using A) fluid cognition and B) mental state examinations among persons aged  $\geq 40$  years, 2000–2011. Individual studies are represented by squares; subtotals provide within-group variance-weighted averages and are represented by diamonds. Bars, 95% confidence interval (CI).

*Correlating changes in physical functioning with changes in cognition.* Studies correlating changes in physical function and changes in fluid cognition (Figure 6) were few but showed consistent and significant relations for walking speed ( $\beta = 0.09$ , 95% CI: 0.03, 0.15;  $n = 2$ ) and grip strength ( $\beta = 0.05$ , 95% CI: 0.01, 0.12;  $n = 2$ ). Single-study estimates for flamingo stands and chair stands were also significant (20), though this was not true for lung function (36). The sole study to correlate changes in lung function with changes in MSE found no significant association (36).

### Modifying factors

Two studies in our review analyzed data from male and female participants separately, noting that their associations were sufficiently different for this to be necessary (31, 37). We found that percent male, number of follow-ups, years observed, and age were not significant modifiers of any relations presented. This may have been partly due to small sample size. The one study to stratify analyses by *APOE4* status revealed an interaction between *APOE4* status and lung function when modeling cognitive decline (24).

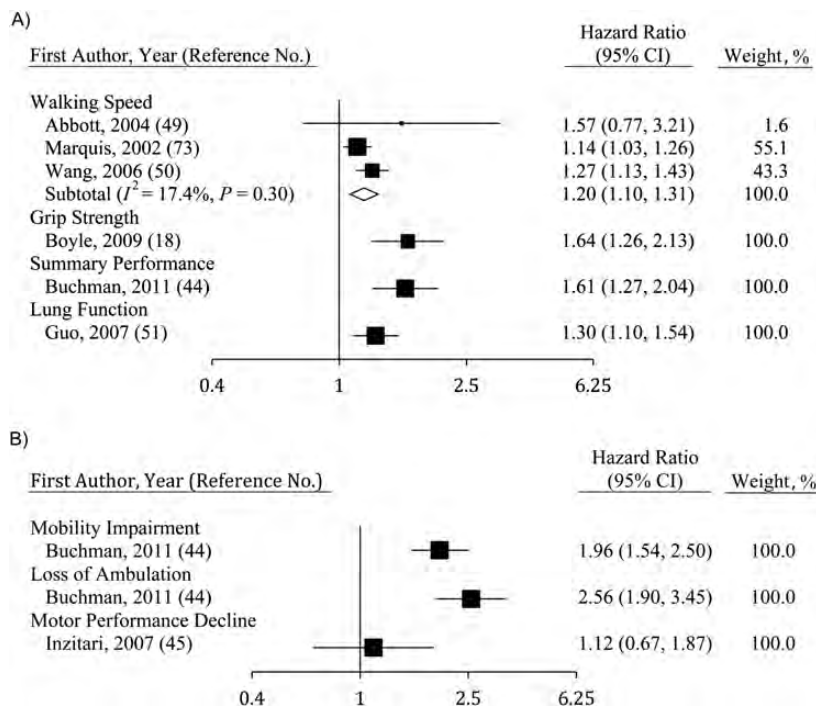
## DISCUSSION

In this study, we reviewed an emerging body of literature that uses longitudinal data to examine the relation between objective measures of physical and cognitive functioning in later life. Consistent with cross-sectional research, we found an association between baseline physical functioning and cognitive functioning. Physical functioning at baseline was also correlated

with longitudinal changes in cognition, but the inverse correlation of baseline cognition with longitudinal changes in physical functioning was only marginally significant, perhaps because of the limited number of studies examining this association. Further, all but one of the studies reporting correlations among slopes of change in physical functioning and change in cognition found a significant association. However, we also found that the degree of change depended on the particular measures of physical and cognitive functioning: Grip strength was associated with changes in MSE, while walking speed was correlated with changes in fluid cognition. Here we highlight areas for further development and critique the methodological approaches used to date.

### Possible common-cause mechanisms

There has been an increasing push to understand and identify persons at risk of decline prior to the onset of significant forms of disease (38). We found that baseline physical and cognitive functioning were correlated with poorer cognitive and physical functioning at follow-up, respectively; other researchers have suggested that both are predictors of health and mortality in later life (6–9). As such, understanding the link between physical and cognitive functioning is of substantive interest. However, we also found that not all measures of physical and cognitive functioning were equally associated. Walking requires motor coordination and balance, which are regulated by the cerebellum and are also linked to loss of strength and impaired coordination (11). Importantly, the cerebellum also connects to cortical associative areas supporting higher mental function,



**Figure 5.** Hazard ratios for development of physical and cognitive impairment over time, estimated using baseline indicators of functioning, among persons aged  $\geq 40$  years, 2000–2011. A) Impact of physical functioning at baseline on the risk of cognitive impairment; B) impact of baseline cognition on the risk of physical impairment. Individual studies are represented by squares; the subtotal provides a within-group variance-weighted average and is represented by a diamond. Bars, 95% confidence interval (CI).

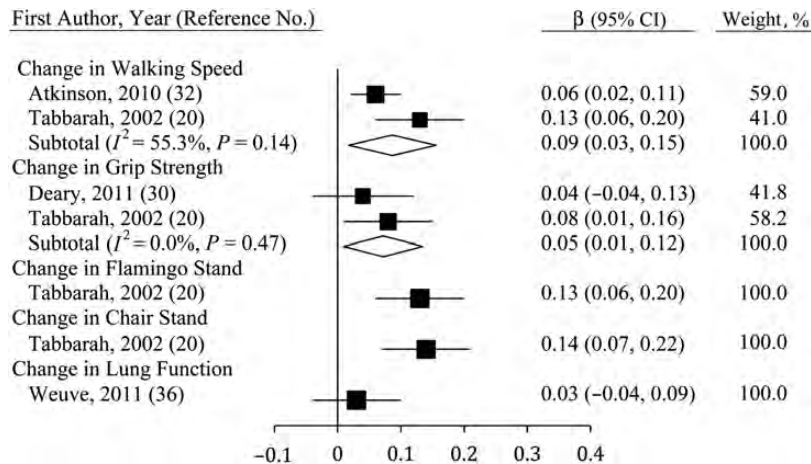
including the prefrontal cortex, which regulates several aspects of fluid cognitive skills. Consistent with this, evidence suggests that brain white-matter integrity, which affects connectivity between brain systems, is associated with information processing speed (12) and with balance and gait speed (39). Variations in this more general state of brain integrity may also underlie the association observed here between strength and mental state, in a manner consistent with our findings regarding the order of decline, and the clinical severity of measures. In their influential paper on the common-cause hypothesis of cognitive aging, Christensen et al. (10) focused on such “brain-aging” mechanisms and noted possible candidates, including white-matter changes and telomere shortening. Our summary results provide some support for such theses, suggesting that such commonalities may be important for some outcomes. However, our findings were not sufficiently strong (standardized beta coefficients on the order of 0.05–0.15) or consistent (some measures were associated, while others were not) to support a common-cause argument (40).

### Operationalization and measurement

There were differences between studies in the way that measures of physical functioning were used and in the theoretical constructs they were thought to measure. For example, we excluded some studies that used measures of physical

functioning in combination with self-reported measures of perceived frailty (e.g., weight loss, exhaustion, weakness) as indicators of “frailty” (41–43). There were also inconsistencies in how objective measures of physical functioning were operationalized. Different measures of physical functioning were combined to create scales that indicated lower extremity functioning (19), muscular strength (18), mobility (42, 44, 45), or overall performance (33, 46). This is potentially problematic, because our findings suggested that measures of physical functioning differ in their sensitivity to cognitive change, a result that many investigators acknowledged. For instance, Deshpande et al. (47) argued that walking as quickly as possible is more strongly correlated with cognition than is walking at a usual or comfortable speed. Kuh et al. provided a possible explanation for differences in the associations of cognition with different measures of physical functioning, by suggesting that the “differential patterns of association found are consistent with the degree to which each is dependent on central nervous system function” (48, p. 38).

The included studies used a heterogeneous set of cognitive tests that bridged different cognitive domains. For the majority of studies (89%), measures of absolute decline were used, although for a substantial minority, rates of onset of postdecline diagnosis (for instance, a diagnosis of dementia for a sample of nondemented persons) were used in conjunction with or instead of cognition (27%). These



**Figure 6.** Average standardized regression coefficients ( $\beta$ ) for change in fluid cognition derived using change in physical function among persons aged  $\geq 40$  years, 2000–2011. Individual studies are represented by squares; subtotals provide within-group variance-weighted averages and are represented by diamonds. Bars, 95% confidence interval (CI).

usually included risk of mild cognitive impairment (18, 26), dementia (24, 49, 50), and Alzheimer's disease (18, 42, 51), though some studies used hazard models to predict risk of poor functioning defined as lower scores for fluid cognition (36) or MSE (34).

In all cases, measures of physical and cognitive functioning were correlated, though the strength and consistency of those relations depended on the particular measures used. Many studies used an indicator of MSE, such as the MMSE (21, 37, 45, 47, 52), while some provided estimates for general fluid cognition (41, 44, 53) and in some cases for cognitive domains, including memory (25, 29, 41, 53), fluency (23, 25), and executive functioning (23, 53, 54). In a few cases, analyses included a measure of crystallized intelligence (29, 31, 55). While we were unable to differentiate between different domains of fluid cognition, Tabbarah et al. (20) made a convincing argument that different domains of fluid cognition are not substantively distinct.

### Potential limitations

This review had some potential limitations that may affect the generalizability of our results. For example, we limited our review to studies published between January 2000 and October 2011. We did not review studies published prior to 2000 to avoid redundancy, as this literature has been examined previously (14) and because the number of studies examining the longitudinal relation between physical and cognitive change, virtually nonexistent prior to 2003, increased substantially after 2005. We also included only studies written in English. By replicating our searches without this language restriction, we estimated that this restriction was unlikely to have reduced the total number of studies identified by more than 5%. While this is likely to have been a conservative estimate (since removing the language restriction enabled us to identify papers in

other languages only if they gave key words or an abstract in English, given that our search terms were in English), we do not believe that this restriction will have introduced significant bias.

We used fluid cognition, MSE, and diagnostic measures of cognition to characterize different measures of cognition, although measures used to indicate any of these varied between studies. At least one study characterizing the differences between specific indicators noted no difference in the estimates using various indicators of fluid cognition (20). Moreover, others alternatively called MSE an indicator of global cognition (23) and an indicator of impairment (24). Finally, our use of diagnostic measures of cognition as an outcome for cognitive change involved collapsing across several distinct diagnostic outcomes (e.g., unspecified dementia, mild cognitive impairment, Alzheimer's disease) that were used in the reviewed studies. This heterogeneity may have introduced some error into our estimates for studies using diagnostic measures of cognition as their outcome; however, our results did not depend on which diagnosis was used. Despite these potential limitations, analyses by subtype of measures within the general cognitive concepts (diagnostic measures of cognition, MSE, and fluid cognition) provided substantively similar results, and thus we felt that these groupings were acceptable for our purposes.

We were unable to examine whether physical functioning declined first or cognition declined first, because of insufficient data. In our review, most studies viewed cognition as the outcome, while others used physical functioning. However, Kuh et al. (48) found that midlife changes in fluid cognition predicted levels of physical performance 10 years after onset of cognitive impairment, and Buracchio et al. (34) found that walking speed declined 12 years before onset of cognitive impairment. We found that walking speed was more strongly and consistently correlated with fluid

cognition (which declines as early as midlife (1, 2)) than with MSE (which declines much later (3)), while grip strength was more strongly and consistently correlated with MSE than with fluid cognition. Such a result might suggest that measures are differently susceptible to change in a way that might depend on age. Further longitudinal analysis using repeat measurements of physical and cognitive functioning is necessary to unravel such complex relations.

Finally, the relatively small number of studies investigating any one specific relation, due in part to the diversity of measures used, was a limitation of our analyses. Thus, we were often unable to pursue analysis of potential modifying factors because of limited statistical power. This highlights the importance of trying to standardize the analyses undertaken in future studies so that results are more comparable.

### Relevance to public health

There is a growing body of literature examining the impact of physical exercise interventions on ameliorating cognitive decline in persons with cognitive impairment and examining the impact of cognitive training for reducing fall risk (56). The results of this literature broadly support the effectiveness of physical intervention for improving cognitive function and the effectiveness of cognitive intervention for improving aspects of physical functioning. However, in addition to confirming the longitudinal interrelation of physical and cognitive change, our results suggest that interventions may vary in their capacity to effect change depending on the outcomes used to measure effectiveness. Some authors support this differential view, noting that involvement in resistance training may provide stronger benefit to fluid cognition than involvement in balance interventions (57).

### Methodological considerations

The majority of studies used age-heterogeneous samples, which can be problematic for a number of reasons. In particular, when not carefully analyzed, age-heterogeneous samples can increase bias in results by conflating between-person age differences with within-person change when models are misspecified (58, 59). Additionally, because of systemic changes related to morbidity and mortality, it is important to consider health and terminal decline processes in understanding the effects of particular biologic and health-related changes on physical and cognitive functioning. With measures of physical functioning, such as grip strength, there are additional problems because grip strength varies interactively by age and sex (4, 60, 61); thus, simply adjusting for age and sex may not be sufficient. Similarly, the secular increases in both height and childhood cognition across birth cohorts are likely to cause substantial bias in the intercepts and possibly in the slopes. Since the findings on within-person change presented here were significant on average, this is unlikely to have modified the results shown. However, in future research, investigators should consider the role of secular differences in birth cohorts when considering the relations between physical and cognitive functioning.

### Mediating factors

Many of the reviewed studies included adjustment for SEP, along with demographic and health factors that are strongly correlated with SEP at baseline. There were sex differences in the relation between grip strength and fluid cognition at midlife in one case where it was explicitly analyzed (31). When indicators of individual SEP were included, relations were often not reported, though when reported the addition of SEP to models attenuated results. Parental SEP is known to predict both physical and cognitive development (62). Moreover, a person's own SEP is strongly correlated with cognitive reserve (63) and physical functioning in later life (64, 65). However, we also found that 2 studies including measures of childhood cognition found no results (29, 30), consistent with evidence that SEP is associated with prior cognition. Better conceptualization of the fundamental role that SEP plays in late-life physical and cognitive functioning may help us understand why some people experience faster declines in cognition and physical function than do others.

Depression is correlated with cognitive decline and cognitive impairment in later life (66) and has also been shown to be associated with physical functioning (67). In our review, 11 studies adjusted for depression. Depression was usually measured with the Centers for Epidemiologic Studies Depression Scale, which was sometimes dichotomized (37, 52). Depression was rarely considered in studies using physical function as the outcome, and when included these results were generally not discussed (53). Nevertheless, when they were included in Atkinson et al.'s analyses of cognition, "depressive symptoms had the greatest impact on reducing the association between [cognition] and gait speed decline" (54, p. 848). Depression may play a complex role in aging, acting as both an outcome of physical and cognitive aging and a cause of declines in capability. Future research should include investigation of the role that depression plays in linking physical functioning to cognition and in hastening age-related decline.

Risky health behaviors (excessive alcohol intake, low physical activity, high body mass, and smoking) provide a mechanism through which individuals may modify their own risk of age-related decline across multiple domains of functioning. Seventeen studies included some analysis of health behaviors and generally found mixed results. Alcohol intake was not correlated with worse performance (20, 30). Results for physical activity were mixed, though generally suggestive that physical activity plays a role in explaining the relation between cognitive functioning and physical functioning (25, 44, 46). Though body mass was examined in 17 studies, it was not found to play a consistent role in explaining associations between cognition and physical functioning. Finally, results for smoking were overwhelmingly negative (18, 36, 44, 51) or were not reported (46, 47, 54). In future research, investigators may consider the role that smoking plays in relation to physical activity and the overall role of a healthy lifestyle, combining information across multiple domains. Our results might provide support for the view that some common processes of oxidative and nitrosative stress (13) and changes in

vulnerability to pathology (40), in conjunction with external factors such as smoking (68), may increase the risk of declines in both physical and cognitive functioning.

### Recommendations for future analysis

We have identified several substantial gaps in this literature on the association between age-associated physical functioning and cognitive functioning related to measurement, gaps in analysis, reporting of results, and statistical analysis. First, few studies considered potential explanatory variables that might account for joint change in physical and cognitive functioning. Similarly, few studies included analysis of lung function, chair rises, or flamingo stands. Finally, we found little discussion of the order of declines, with only 1 study explicitly evaluating whether changes in the rate of decline in physical function preceded future cognitive impairment (34). Investigators should seek to incorporate more repeat measures of physical and cognitive functioning in order to identify which measures change first. The relations identified here were not consistent. Researchers should consider the possibility that common declines occur as a result of external factors that hasten aging (68). Finally, studies should incorporate a wider range of physical and cognitive measures. In many studies, single measures of cognition (e.g., the MMSE) or physical function (e.g., grip strength) are used; however, future research will require repeated measurement across multiple domains of physical and cognitive functioning to analyze these complex relations.

Other factors remain important when completing future research. Consistency is important when reporting information about data and their analyses. For instance, a number of studies only included *P* values or characterized their estimates as nonsignificant. Similarly, authors rarely reported estimates of their response rates at baseline or their rates of attrition from these effective samples afterwards. Better cognizance about statements detailing reporting standards for systematic reviews, including the STROBE statement (69), may be helpful when reporting results from single-sample analyses. Finally, analytic methods for understanding longitudinal data have progressed significantly. These methods can be used to correct for bias resulting from incomplete observations (due to attrition or mortality selection), permit models based on alternative temporal axes (e.g., age, birth cohort, proximity to death), and can be used for fitting alternative models of change (random change-points, mixed declines). Such methods (including mixed-effects regression and structural equation modeling) are necessary for separating between-person differences from within-person changes in the analysis of longitudinal studies, especially when data include multiple waves of age-heterogeneous data (81% of our studies) (70).

### Conclusion

Staying alert and keeping physically able are important for healthy aging and maintenance of functional independence. As the global population ages and health-care cost projections increase, there is keen interest in maximizing

years of health and minimizing years of disability for older adults. Cross-sectional evidence for a strong association between age-related differences in physical and cognitive functioning prompted a “common cause” theory of aging, positing a single aging process that manifests in joint within-individual declines in physical and cognitive ability. This systematic review provides an evaluation of the evidence from longitudinal studies, permitting testing of the link between physical and cognitive functioning without the fundamental confounds of cross-sectional studies. In general, we found evidence that changes in physical and cognitive functioning are associated, but these associations were not sufficiently strong and consistent to provide conclusive evidence for “common cause” aging. Not all declines occurred together, and not all measures had equal impact. Future studies that delineate the causal order of physical and cognitive change by examining in greater detail the individual rates of change and variation and the temporal ordering of individual changes in the acceleration of physical and cognitive change using appropriate measures will contribute to the advancement of current knowledge related to trajectories of healthy and pathologic aging.

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