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Research Article

A Coordinated Multi-study Analysis of the Longitudinal Association Between Handgrip Strength and Cognitive Function in Older Adults

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Abstract

Objective: Handgrip strength, an indicator of overall muscle strength, has been found to be associated with slower rate of cognitive decline and decreased risk for cognitive impairment and dementia. However, evaluating the replicability of associations between aging-related changes in physical and cognitive functioning is challenging due to differences in study designs and analytical models. A multiple-study coordinated analysis approach was used to generate new longitudinal results based on comparable construct-level measurements and identical statistical models and to facilitate replication and research synthesis.

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Methods: We performed coordinated analysis on 9 cohort studies affiliated with the Integrative Analysis of Longitudinal Studies of Aging and Dementia (IALSA) research network. Bivariate linear mixed models were used to examine associations among individual differences in baseline level, rate of change, and occasion-specific variation across grip strength and indicators of cognitive function, including mental status, processing speed, attention and working memory, perceptual reasoning, verbal ability, and learning and memory. Results were summarized using meta-analysis.

Results: After adjustment for covariates, we found an overall moderate association between change in grip strength and change in each cognitive domain for both males and females: Average correlation coefficient was 0.55 (95% CI = 0.44–0.56). We also found a high level of heterogeneity in this association across studies.

Discussion: Meta-analytic results from nine longitudinal studies showed consistently positive associations between linear rates of change in grip strength and changes in cognitive functioning. Future work will benefit from the examination of individual patterns of change to understand the heterogeneity in rates of aging and health-related changes across physical and cognitive biomarkers.

Keywords: Cognitive function, Coordinated analysis, Grip strength, Harmonization, Integrative data analysis, Longitudinal studies

Understanding the patterns, associations, causes, and consequences of aging and health-related changes in physical function and cognitive function has been of longstanding interest and priority in gerontological research. Numerous studies over the decades, based on a variety of study designs and analytical models, have reported associations, some very strong, between age-related differences and aging-related changes across indicators of physical (e.g., pulmonary function, handgrip strength, gait), sensory (e.g., auditory and visual acuity), and cognitive functioning (Hofer, Berg, & Era, 2003; Wayne & Johnsrude, 2015). However, a majority of the studies examining associations between handgrip strength and cognitive functioning have either relied on cross-sectional designs, or utilized analytical models that evaluate the effects of baseline function in one domain on change in another domain of functioning. Relatively few studies have examined the dynamics of change across indicators of both physical and cognitive domains (Clouston et al., 2013; Duggan et al., 2019; Fritz, McCarthy, & Adamo, 2017). In this article, we provide new results on the association between rates of change, as well as between baseline levels and time-specific variation, between handgrip strength and cognitive functioning.

Implications of Handgrip Strength in Cognitive Aging

Handgrip strength is a valid and reliable measure of the total force from the upper limb muscles (Neumann, Kwisda, Krettek, & Gaulke, 2017). Handgrip strength is an indicator of global muscle strength, overall body strength, and is an important determinant of healthy aging (Fritz et al., 2017; Wearing, Konings, Stokes, & de Bruin, 2018). Handgrip strength is also a key indicator of frailty, and is associated with disability and mortality, particularly mortality related to cardiovascular disease (Buchman et al., 2014; Fried et al., 2001; Leong et al., 2015; Ritchie, Tucker-Drob, Starr, & Deary, 2016; Sternäng et al., 2016; Wilson et al., 2000, 2012; Wilson, Leurgans, Boyle, & Bennett, 2011). Muscle deterioration in older adults is usually due to age-related muscular decline, malnutrition, physical inactivity, and/or disease (McLeod, Breen, Hamilton, & Philp, 2016). At lower levels of functioning, handgrip strength impacts the ability to perform functional activities of daily living, such as dressing, holding small items (brushing teeth, eating with a fork), and performing tasks such as rising from a chair.

Results from cross-sectional analysis of between-person age-related differences have generally reported very high amounts of shared age-related variance across physical functioning (e.g., handgrip strength), sensory acuity, and cognitive functions (e.g., executive function, attention, working memory, language, and semantic memory; Anstey & Smith, 1999; Camargo et al., 2012; Hofer et al., 2003; Takata et al., 2008). Several underlying mechanisms (lifestyle, diet, white matter integrity, brain aging, central nervous system) have been proposed to explain this association. However, since most of the research supporting a common-cause hypothesis have been based on cross-sectional analysis of between-person age differences (Baltes & Lindenberger, 1997; Lindenberger & Baltes, 1994), such inferences are limited to age-related differences and not to within-person aging-related changes over time. We have shown how such associations can arise from average between-person age-related differences and identified this as a major confound of cross-sectional design and analysis for understanding aging-related change (Hofer et al., 2003; Hofer, Flaherty, & Hoffman, 2006; Hofer & Sliwinski, 2001).

Handgrip strength at baseline has been shown to predict future cognitive function, functional status, mobility, and mortality (Boyle, Buchman, Wilson, Leurgans, & Bennett, 2009; Narazaki et al., 2014; Rijk, Roos, Deckx, van den Akker, & Buntinx, 2016; Viscogliosi, Di Bernardo, Ettorre, & Chiriac, 2017). Although this type of analysis considers change in cognitive performance, it does not consider whether the individuals changing more rapidly in handgrip strength also tend to be the ones changing more rapidly in cognition, unless one assumes that individuals with lower grip strength are those who are declining more rapidly (Piccinin, Muniz, Sparks, & Bontempo, 2011). The focus

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on baseline also ignores any changes experienced after that point in time. This becomes more likely and more problematic with longer follow-up. For situations where two processes are both assumed to be changing over time, and interest is in the association between these changes, a bivariate growth model is the appropriate analysis (Piccinin et al., 2011).

In our recent systematic qualitative review of longitudinal studies, we focused on previously published articles investigating the association between change in cognitive function and change in grip strength over time (Zammit, Robitaille, Piccinin, Muniz-Terrera, & Hofer, 2018). We did not find conclusive evidence to support a high commonality among individual differences in rates of aging. While all six eligible studies (Christensen et al., 2000, 2004; Deary et al., 2011; MacDonald, DeCarlo, & Dixon, 2011; Ritchie et al., 2016; Sternäng et al., 2016) reported declining trends, results were mixed for associations among rates of change across grip strength and cognitive function. One of the studies went further to suggest a "decoupling" of physical (including grip strength) and cognitive change in later life (Ritchie et al., 2016). This review (Zammit et al., 2018) highlighted the need for further evidence regarding rates of within-person change and the pattern of associations among rates of change across physical and cognitive functioning over time.

The Coordinated Multi-study Approach

Direct comparison of results across results from longitudinal studies can be challenging due to study differences in research design, sample composition, measurements, statistical analysis, and the practical limits on full reporting of results. Coordinated multi-study analysis is a rigorous approach for achieving new results from independent longitudinal studies based identical statistical models and comparable construct-level outcome and predictor variables and provides the basis for research synthesis and examination of study heterogeneity (Hofer & Piccinin, 2009). This is an especially useful approach when evaluating questions where published research has shown inconsistent patterns of results or where the effects are considered to be relatively small or potentially null (Piccinin et al., 2013).

In our previous review, we synthesized results from already published articles investigating the longitudinal association between grip strength and cognition; in this study, we used a coordinated and integrative data analysis approach (Hofer & Piccinin, 2009) to analyze raw data in nine longitudinal studies to evaluate associations between longitudinal changes in grip strength and concomitant linear changes in cognitive function (mental status, processing speed, attention and working memory, perceptual reasoning, verbal ability, and learning and memory) in older adults. Results from this multi-study analysis and synthesis will contribute to basic research on the influence of aging and health on the dynamics of physical and cognitive changes.

Method

Data

Data were from nine longitudinal aging studies affiliated with the Integrative Analysis of Longitudinal Studies on Aging and Dementia (IALSA) network. All studies obtained institutional ethics approval and all participants across studies provided written consent. This coordinated analytic study was approved by the University of Victoria Human Ethics Board (Protocol 09-227).

All studies in this report included participants who had at least three waves of data. Only assessment waves with cognitive and grip strength data were included in this analysis. The participating studies were the *Einstein Aging Study* (EAS; Katz et al., 2012); the *English Longitudinal Study of Ageing* (ELSA; Steptoe, Breeze, Banks, & Nazroo, 2013); the *Health and Retirement Study* (HRS; Sonnega et al., 2014); the *Interdisciplinary Longitudinal Study of Adult Development* (Sattler et al., 2015); the *Longitudinal Aging Study Amsterdam* (LASA; Huisman et al., 2011); the *Origins of Variance in the Old-Old: Octogenarian Twin* (OCTO-Twin; Lichtenstein et al., 2002; Pedersen, Lichtenstein, & Svedberg, 2012); the *Memory and Aging Project* (MAP; Bennett et al., 2005, 2012); the *Quebec Longitudinal Study on Nutrition and Successful Aging* (NuAge; Gaudreau et al., 2007); and the *Swedish Adoption Twin Study of Aging* (SATSA; Finkel & Pedersen, 2004; Lichtenstein et al., 2002; Pedersen et al., 2012). Further study details are provided in Supplementary Table S1. Individuals with a diagnosis of dementia at baseline were excluded from analyses.

Measures

Handgrip strength

Handgrip strength was measured using either a dynamometer (EAS, ELSA, HRS, LASA, MAP, SATSA) or a vigorimeter (ILSA NuAge, OCTO). The dynamometer is a hydraulic instrument that measures isometric strength in kilograms, while the vigorimeter is a compressible rubber ball that measures the force of compression in kilo pascal. A high correlation between these instruments has been previously found (Neumann et al., 2017). Some studies used the mean average performance across two (HRS, LSA), three (ELSA, NuAge), or four (ILSA, MAP) trials per hand, while other used maximum force out of three trials (EAS, OCTO, and SATSA; see Supplementary Table S2) per occasion.

Cognitive function

Each study provided between 2 (NuAge) and 18 (MAP) cognitive measures per occasion, all administered per protocol, the details of which are provided in the published documentation for each study. To ease interpretation of the

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data across studies, we grouped the cognitive measures into mental status and the five domains of processing speed, attention and working memory, perceptual reasoning, verbal ability, and learning and memory (Strauss, Sherman, & Spreen, 2006; Supplementary Table S2).

Covariates

We centered baseline age at 70 years (75 in HRS; 80 in OCTO-Twin), education at 7 years (dichotomized in ELSA as having or not having educational qualifications; dichotomized in ILSE as basic and further education; and on a four-point scale in SATSA using elementary school as reference point), and standing height at 1.72 m for male and 1.60 m for females. Smoking history was dichotomized (nonsmoker reference); cardiovascular disease was dichotomized (no symptoms as reference); and diabetes was dichotomized (not diabetic as reference; except ILSE, for which this information was not available). All covariates included in the model were measured at baseline.

Statistical Approach

We applied bivariate linear mixed models to examine the association between rates of linear change in handgrip strength and indicators of cognitive function. Bivariate linear mixed models provide estimates of (a) baseline associations (between intercepts); (b) associations between linear rates of change (between slopes); and (c) occasion-specific residual associations. Within-person correlations among occasion-specific residuals provide information about state-like variation after adjustment for individual differences in level and rate of change. We specified the models using time in years since first observation, with varying times for each participant to account for variation in time of measurement across individuals. We stratified the models by male/female to adjust for body size differences across the sexes. Each cognitive measure was modeled separately.

Meta-analytic Summary

We combined results from all nine participating studies to obtain a variance-weighted average effect. We calculated meta-analytic average correlations using estimated covariances and transformed results to correlation coefficients for display in forest plots because prior work has shown that meta-analyses relying on covariances are less biased than those derived from correlation coefficients (Silver & Dunlap, 1987). Given the differences in type and number of measures representing the various cognitive constructs in the participating studies, we did not harmonize or pool the data.

Statistical Software

Descriptive statistics were calculated using software available to researchers for each study, including R version 3.5.1 (R Core Team, 2017) and SPSS version 24 (SPSS, Inc., Released 2016). We fit linear mixed models using MPlus version 7 (Muthén & Muthén, 1998–2016) and extracted output using R. We addressed missing data using full information maximum likelihood estimation under the missing at random assumption. Parameter estimates were obtained using maximum likelihood robust estimation. Model estimation results were stored in a dedicated GitHub repository, a public cloud location that facilitates transparency, version control, and reproducibility. Summary statistics and forest plots were produced using Microsoft Excel. Syntax and output for all models is available online at https://github.com/IALSA/ialsa-2017-portland.

Results

Descriptive Characteristics

General characteristics of the nine participating studies are provided in Table 1. Briefly, sample size for particular analyses ranged from 166 for males in OCTO to 3,404 for females in ELSA, with a total combined *N* across studies of 15,054 participants at baseline. Percentage of males ranged from 25.3% in MAP to 52.8% in ILSE, with most studies having a majority of females. Average number of years of education ranged from 7 years in OCTO-twin to 14 years in MAP. History of smoking across studies ranged from 25.5% in LASA to 53.4% in EAS, while cardiovascular disease ranged from 11.1% in ELSA to 48.3% in OCTO-twin, and diabetes ranged from 3.4% in SATSA to 20.9% in MAP. Supplementary Table S3 provides the baseline means of the cognitive measures in each of the studies.

Coordinated Analyses Across Individual Studies

Each study provided between 4 (NuAge) and 38 (MAP) analyses. Supplementary Table S4 provides the resulting correlations for each of these analyses.

Meta-analytic Summary of Results

We found consistent moderate associations between change in handgrip strength and change in each cognitive domain for both males and females. The overall average correlation was 0.55 (95% CI = 0.44–0.56). We summarized the slope–slope associations between handgrip strength and each cognitive function across all studies using forest plots (Figure 1). Average slope–slope correlations were significant for all cognitive domains (Figure 1): mental status r = .62, 95% CI = 0.42–0.66; processing speed r = .62, 95% CI = 0.32–0.72; attention and working memory r = .60, 95% CI = 0.43–0.63; perceptual reasoning r = .60, 95% CI = 0.18–0.77; verbal abilities r = .58, 95% CI = 0.37–0.64); and learning and memory r = .42, 95% CI = 0.27–0.51.

The baseline and residual correlation forest plots are in Supplementary Figures 1 and 2. The overall correlations

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Table 1. Baseline Characteristics of Each of the Nine Participating Studies

	EAS	ELSA	HRS	ILSE	LASA	MAP	NuAge	OCTO-twin	SATSA
N	585	6,473	1,148	500	1,687	1,641	1,781	529	710
Study inception date	1993	2002	2006	1993	1992	1997	2003	1991	1984
N occasions modeled	6	3	4	3	5-Jan	5	4	5	7
Intervals between study visits (years)	1	4	2, 4	4, 8	3	1	1	2	3
Total follow-up (years)	5	8	10	12	12	4	3	8	19
	Mean								
Age, years (*SD*)	78.3 (5.4)	65.0 (10.0)	67.9 (10.0)	63.0 (0.9)	72.9 (2.2)	78.8 (7.7)	74.4 (4.2)	83.6 (3.2)	65.6 (8.5)
Sex, male (%)	38.20	46.80	42.80	52	50.60	25.30	47.60	33.40	38.40
Education, years[a] (*SD*)	13.0 (3.7)	57.20%	12.6 (3.1)	78.60%	8.8 (3.3)	14.6 (3.2)	11.6 (4.5)	7.1 (2.3)	34.7%[1]
Height, M, cm (*SD*)	172.4 (7.3)	172.7 (0.9)	174.8 (7.3)	174.1 (6.7)	176.1 (7.2)	174.4 (7.8)	168.1 (6.8)	171.0 (6.5)	175.9 (6.5)
Height, F, cm (*SD*)	159.2 (7.7)	159.2 (6.7)	160.2 (6.7)	162.1 (6.3)	165.9 (6.8)	160.0 (7.5)	155.4 (5.9)	157.0 (5.9)	162.1 (6.1)
Grip strength,[b] M, (*SD*)	26.7 (7.8)	36.1 (9.6)	40.0 (9.5)	86.1 (25.5)	33.8 (8.5)	69.2 (19.1)	73.7 (17.1)	11.0 (3.0)	40.4 (9.9)
Grip strength,[b] F, (*SD*)	17.1 (5.8)	20.8 (6.4)	24.1 (6.2)	68.9 (27.5)	19.6 (5.3)	41.3 (12.5)	56.8 (15.1)	7.9 (2.4)	21.8 (6.5)
Smoking history (%)	53.4	63.7	53.8	78	25.5	43.1	48	39.9	46
Cardiovascular disease (%)	16.8	11.1	26.2	28.8	29	14.7	22	48.3	13.2
Diabetes (%)	16.8	6.3	17.8	NA	7.9	20.9	11	8.6	3.4

Note. EAS = Einstein Aging Study; ELSA = English Longitudinal Study of Aging; HRS = Health Retirement Study; ILSE = Interdisciplinary Longitudinal Study of Adult Development; LASA = Longitudinal Aging Study Amsterdam; MAP = Memory and Aging Project; NuAge = Quebec Longitudinal Study on Nutrition and Successful Aging; OCTO-twin = Octogenarian Twin Study; SATSA = Swedish Adoption Twin Study of Aging; M = Males; F = Females.

[a] Education was dichotomized in these studies. % for ELSA show proportion of participants with educational qualifications; in ILSE proportions of having basic education; and in SATSA as having attended elementary school.

[b] EAS, OCTO-twin, and STATA used the maximum out of three trials; the rest of the studies used the average (more detail in Supplementary Table 1).

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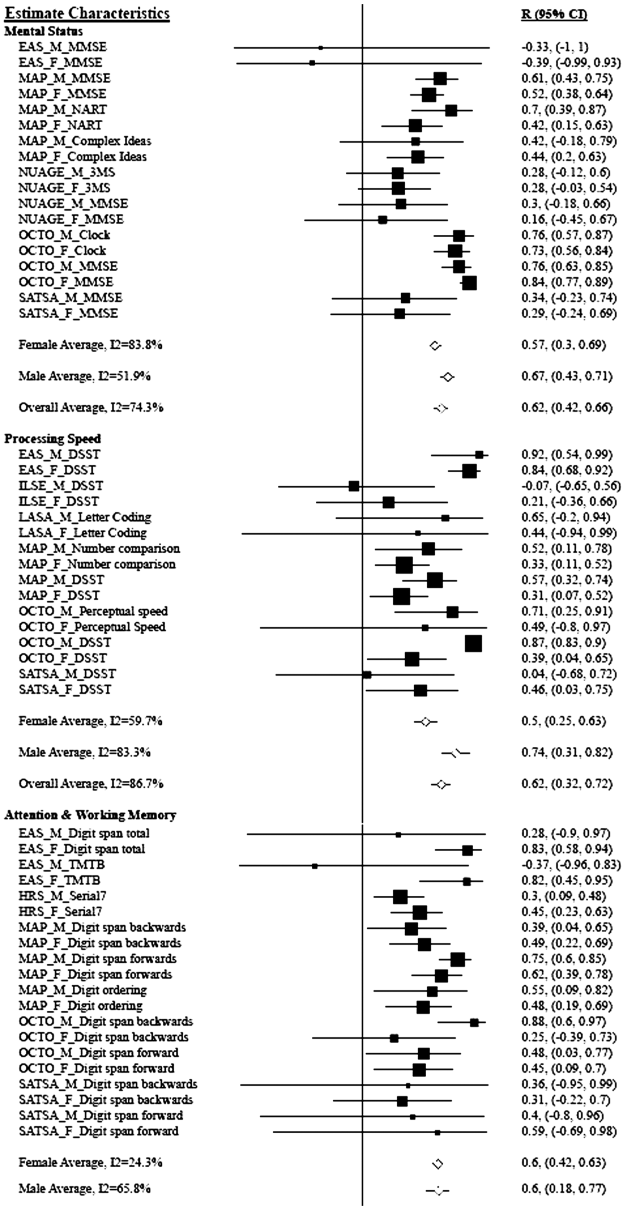

Figure 1. Forest plot of longitudinal (slope–slope) associations of grip strength and domains of cognitive function. This figure provides estimated slope correlations from the 9 studies (N = 15,054) for males and females by domain. Sex-specific and total aggregate correlations are provided for all domains and the overall total, as well as 95% confidence intervals (CIs) for all estimates.

are r = .14 (95% CI = 0.12–0.16) for baseline, and r = .05 (95% CI = 0.04–0.06) for the residuals.

Summary of Individual Study Results, Grouped by Cognitive Domain, Sex, and Cohort Study

Supplementary Table S5 provides the results from each analysis, organized by cognitive domain, by sex, and by study (136 total analyses). The most frequently significant longitudinal (i.e., slope–slope) associations were between handgrip strength and mental status, perceptual reasoning, and attention and working memory (25%, 20%, and 20% of all analyses). The fewest statistically significant associations with handgrip strength were with indicators of learning and memory (8.3%). A majority of these associations were in females, accounting for 72% of all significant associations.

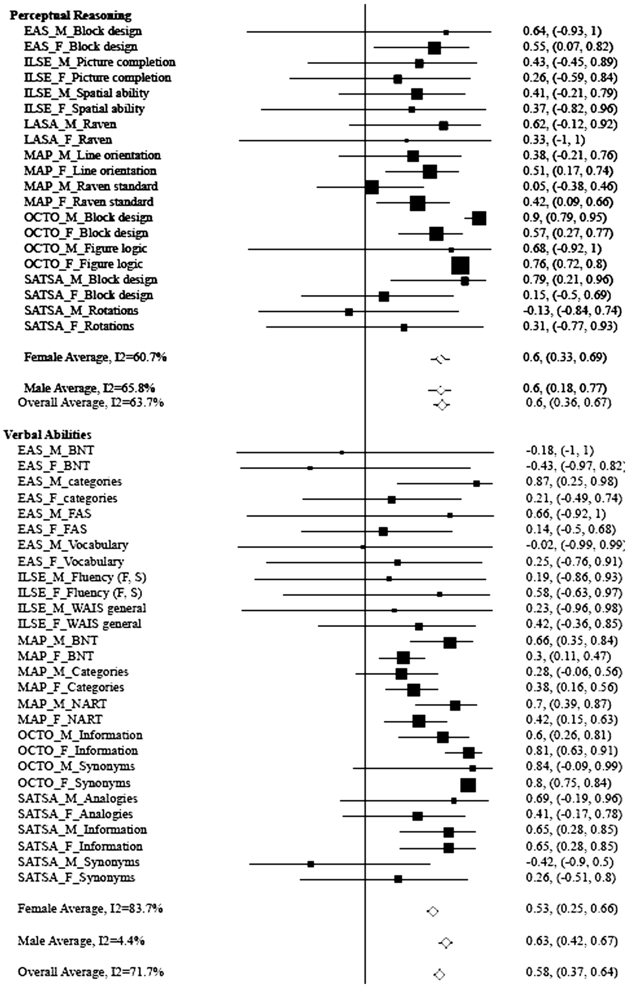

Figure 1. *Continued*

Attrition

While rate of missing data or attrition varied somewhat across each subsample (e.g., males and females) and outcome (e.g., cognitive and physical measures), retention to Wave 3 ranged between 57% (NAS) and 85% (NuAge) for the cognitive outcomes, and between 18% (EAS) and 85% (NuAge), for the handgrip outcomes. For studies with five or more waves, retention to Wave 5 ranged between 9% and 39%. Retention tended to be somewhat lower for men than for women.

Heterogeneity Within and Across Studies

Heterogeneity in individual study results was observed in both the statistical significance and magnitude of

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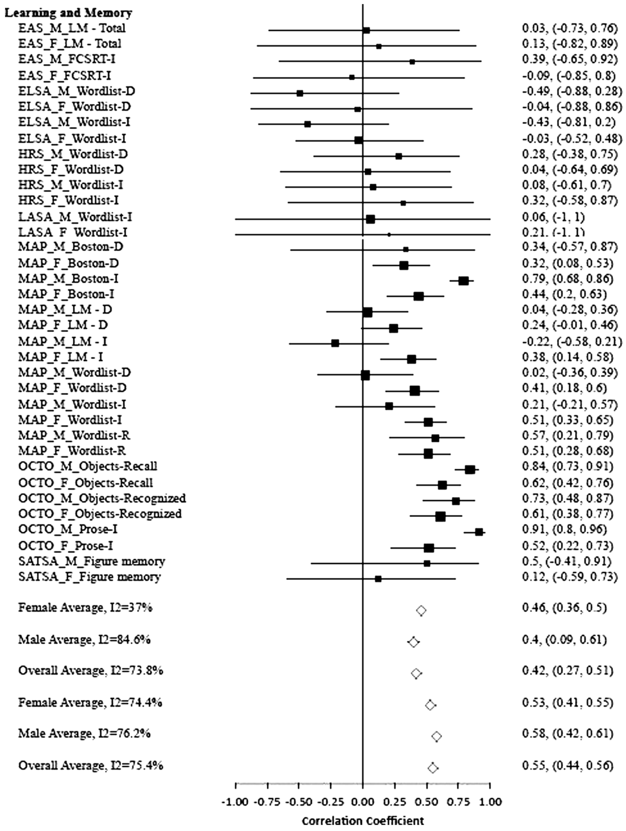

Figure 1. ***Continued***

associations among baseline level, slope, and time-specific residuals. For example, 8% to 25% of within-study associations between decline in handgrip strength and decline in available cognitive tests were statistically significant (Supplementary Table S5), a result similar in pattern to previously reported results from individual studies (Zammit et al., 2018). Statistically significant slope associations were more often present in females (23.5% relative to 8.8% of associations that were significant in males). In females, associations were also related to a wider number of domains that included working memory (Digit Span), perceptual speed (Digit Symbol Coding), attention and working memory (Digit Ordering), learning and memory (word-list measures), perceptual reasoning (Block Design and Line Orientation), and verbal knowledge (Categories).

Additional findings from this multi-study analysis were that studies with older participants showed a greater number of cross-domain associations (e.g., OCTO and EAS), similar to previous results (Sternäng et al., 2016). However, almost one-third of the longitudinal grip-cognitive associations were significant in the somewhat younger HRS cohort (mean baseline age 67.9 years). Study follow-up was also associated with the number of statistically significant associations. Studies reporting the most longitudinal associations (EAS, MAP, OCTO, SATSA) were those with at least 5 waves of follow-up data, indicative of greater statistical power (Rast & Hofer, 2014). Further, all but two studies (ILSE and LASA) had a higher number of females and can explain the pattern of more statistically significant results in the female subsamples.

Discussion

In this study, we undertook a coordinated analysis across nine studies affiliated with the IALSA network (Hofer & Piccinin, 2010) to examine the association between rates of change in handgrip strength and change in indicators of different domains of cognitive function in older adults assessed over a period of 3–19 years. Overall, results from the meta-analysis show consistent and moderate correlations between linear slope changes in handgrip strength and changes in each cognitive domain. A previously unreported association between handgrip strength and measures of perceptual reasoning was found. However, associations between baseline level and time-specific variation in handgrip strength and measures of cognitive function were very weak. However, such associations among time-specific residuals can be considered lower bound estimates of within-person variation across relatively shorter time scales (e.g., at the time of testing, daily, weekly) and be related to many potential internal and external factors (e.g., stress, fatigue, illness).

Potential Brain Mechanisms Linking Muscle Strength to Cognitive Function

The consistency of the longitudinal association between handgrip strength and cognitive performance across studies in this report is indicative of underlying brain mechanisms at play. Studies investigating muscle strength in relation to volumetric brain parameters have reported associations between decreases in handgrip strength and markers of brain aging, that is, brain atrophy and white matter hyperintensity (WMH) accumulation (Aribisala et al., 2013; Doi et al., 2012; Sachdev, Wen, Christensen, & Jorm, 2005). WMHs have been associated with decreased handgrip strength for both total brain and specific regions, including frontal, temporal, parietal, anterior, and periventricular regions (Sachdev et al., 2005). Upon stratifying analyses by sex, white matter hyperintensities have been associated with poorer handgrip strength in males but not in females (Sachdev, Parslow, Wen, Anstey, & Easteal, 2009). An association between handgrip strength and midbody corpus callosum (but not with anterior or posterior corpus callosum), has also been reported, which may be explained via associations between motor cortices and midbody corpus callosum (Anstey et al., 2007). Better handgrip strength has also been associated with less brain atrophy, as measured by ventricular volume; however this association did not hold longitudinally, implying that while handgrip strength and cerebral atrophy may be associated at the between person level, within-person decline in handgrip strength does not seem to predict progression of cerebral atrophy (Aribisala

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et al., 2013). In a systematic review (Kilgour, Todd, & Starr, 2014), exploring whether muscle strength (mainly handgrip strength and gait speed) is linked to brain volumetrics and WMHs, three main conclusions were reached with respect to handgrip strength specifically: (a) although muscle function is reflective of the aging brain (WMH and cerebral atrophy), decline over time in muscle strength does not appear to be predictive of brain atrophy; (b) the relationship between handgrip strength and WMH only becomes significant once a volumetric threshold has been reached; and (c) regional, rather than total brain volume seem to be driving associations. Indeed, the more consistent results in older age samples in our results is evidence for increasingly critical periods of within-person changes in later ages. Initial studies advocating the common-cause hypothesis either focused on individuals more than 70 years of age (Anstey, Luszcz, & Sanchez, 2001; Christensen, Mackinnon, Korten, & Jorm, 2001) or reported that the association between sensory and cognitive function strengthens with older age (Baltes & Lindenberger, 1997; Lindenberger & Baltes, 1994). However, these are also periods of increasing multimorbidity and frailty, with concomitant changes in both physical and cognitive functioning.

Physical Fitness and Brain Integrity

Results from our coordinated analysis carry implications to further understand how physical strength and performance (e.g., exercise) may affect cognition in the brain (e.g., by improving executive function tasks), and whether the wide-spread availability of treatment for physical ailments (as opposed to cognitive ones) leads to a discordance of associations between physical and cognitive function. This includes studying potential causal markers of developmental change (e.g., lifestyle, diet, and physical activity) that reflect the integrity of underlying biological and cognitive processes, and that consequently affect or are affected by brain structural and functional changes.

Associations between physical fitness (mostly involving aerobic activities, as opposed to strength training) and brain integrity have been previously explained: Higher fitness levels are associated with larger brain volume (Burns et al., 2008), larger hippocampal volume (Erickson et al., 2009), hippocampal neurogenesis (Pereira et al., 2007), and frontal, parietal, and temporal cortical integrity (Colcombe et al., 2003). Research in both childhood (Chaddock et al., 2010) and old age (Erickson et al., 2009) has examined brain morphology as a mechanism through which physical fitness influences cognition. Links in which physical fitness mediates the association between hippocampal volume and spatial memory performance have been reported (Erickson et al., 2009). Studies have also shown that hippocampal volume is larger in physically fitter children, and that bigger hippocampal volumes are associated with superior relational memory performance (Chaddock et al., 2010). In light of our association between handgrip strength and perceptual memory performance, the implication of these findings is that the hippocampus may have a mediating role in handgrip strength and cognitive function, although associations have also been reported between hippocampal structures and working memory performance and speeded tasks (Park et al., 2003).

Clinically, our study does not address causal influences of handgrip strength on cognition or vice-versa; nor does it address any health implications. However, intervention studies aiming to reduce cognitive decline by increasing physical exercise, such as weight-training and strengthening exercises, report promising results in that physical interventions appear to aid cognition (Young, Angevaren, Rusted, & Tabet, 2015). Maintaining physical fitness may be one method of preventing neural decline, building synaptic plasticity, and maintaining energy levels. Temporal and prefrontal white matter integrity and memory have been positively associated with improved physical fitness (Voss et al., 2013). Most studies investigating the brain–fitness associations in terms of cognitive outcomes address aerobic fitness, which is more in line with lung function, although multiple reports (Colcombe et al., 2004; Voss et al., 2010) indicate that exercise (both aerobic and nonaerobic) has global effects on the efficiency and flexibility of brain networks in older adults, resulting in preserved cognitive function. However, it is also possible that individuals with healthier brains are able to continue to keep their bodies physically healthy (Rosano et al., 2010).

The dimensionality and pattern of aging-related changes across functional biomarkers are of interest for basic science and are of clinical value given that these biomarkers are linked to overall health, central nervous system integrity, brain plasticity, reserve and resilience, and mortality. Overall, there is a dearth of studies that investigate longitudinal associations between physical strength and structural and functional brain parameters; indeed in their systematic review, Kilgour and colleagues (2014) only found one longitudinal association. Longitudinal studies that directly investigate brain mechanisms as possible mediators between physical strength and cognitive function would help elucidate longstanding hypotheses underlying physical–cognitive associations.

Strengths and Limitations

Strengths

The range of cognitive tests within and across studies permitted evaluation of the heterogeneity of results both within and across cognitive domains. Although different tests may reflect performance within specific cognitive domains, differences in test administration (e.g., verbal, written, or physical response) may drive associations with motor functioning. For example, written administration of cognitive tests may increase their correlation with handgrip strength and dexterity: in this study, Digit Symbol Coding and Trail-Making A and B require physical use of hands to

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complete the task successfully, whereas matrix reasoning, rotations, and line orientation require a verbal response. In the current study, no evidence was found for this potential source of methods bias.

The most notable strength of this study is the coordinated approach we used to simultaneously evaluate independent longitudinal studies to test, replicate, and extend prior findings on physical–cognitive associations. Each dataset in this study permitted the evaluation of associations among baseline level, linear change, and time-specific variations between grip strength and cognition. Meta-analysis of these results permitted the comprehensive evaluation of these associations and examination of the heterogeneity within and across studies. In this project, we did not formally harmonize any outcome variables, given the differences in the particular tests used in each study, though we did specify the covariates as similarly as possible. We encourage researchers to utilize and expand on this coordinated analysis approach to longitudinal observational research and to investigate moderators of these cross-domain associations within a coordinated analysis framework.

Limitations

The first limitation is inherent in longitudinal studies—each differs in terms of follow-up number and duration, intervals between follow-ups, nature and number of measures used, and the sample population's characteristics; it is thus impossible to have strict or exact replication of design across datasets. However, given these limitations, a coordinated approach permits a rigorous method for study comparison and for assessing the generalizability of results.

Secondly, instead of extracting cognitive factors, we used individual cognitive measures to evaluate cognitive function and change, which meant a large number of measures to evaluate within and across studies. We dealt with this complexity by grouping the different measures within cognitive domains. Although extracting cognitive factors before running analyses might appear to ease comparisons across studies by reducing the number of outcomes, it would have also ignored differences across studies in the composition of these factors. In addition, considering multiple measures within a domain for a particular study provides a useful index of the consistency of findings related to that domain within a study. For these reasons, we studied individual measures of cognition, which helped in identifying measures that seem to be more related than others; for example, within perceptual reasoning, Block Design was significantly correlated with grip strength at cross-section for OCTO and SATSA in both sexes, but not in EAS, whereas the same measure was significantly related longitudinally, for females only, in EAS and OCTO. Other correlations with grip strength, such as those for Figure Logic in OCTO and Rotations in SATSA, were not statistically significant. The differences in results across studies may also be due to the use of different measurement instruments (e.g., dynamometers ranged from Jamar, to Smedley, and Vigorimeter), different measurement protocols (e.g., maximum force of three trials or average across trials) or differences in study design, sample characteristics. However, the combination of individual study-measure combinations and meta-analytic summary provides a more comprehensive examination of these associations than have been reported previously.

A potential methodological limitation is that we excluded participants who had already been diagnosed with dementia at baseline, which is a conservative, but typical approach in the cognitive aging literature (Christensen et al., 2000, 2004; Deary et al., 2011; Ritchie et al., 2016; Sternäng et al., 2016). Inclusion of participants with dementia at baseline, or excluding dementia at all occasions may have produced different results. Despite excluding dementia at baseline, we did not exclude participants with mild cognitive impairment, and who may have the same underlying processes that eventually lead to dementia; relatedly, some individuals may have been diagnosed with dementia after end of study. Furthermore, our cohorts were reflective of a physically healthier sample than typical of this age group, as witnessed by the low proportions of cardiovascular disease and diabetes, which is likely why some scores increased (rather than decreased) over time.

Conclusion

In conclusion, these new analytic results and research synthesis confirm consistent and moderate associations between changes in grip strength and changes in multiple cognitive domains. Previous literature has been scarce and somewhat mixed due to inconsistencies in analytic models as well as due to lack of statistical power. The coordinated analysis followed by meta-analysis of comparable results was used to rigorously examine the extent to which aging-related changes in handgrip strength are related to changes in different domains of cognitive function. While this approach is demanding and is highly collaborative, thus requiring time and effort of many researchers, in the long run it will lead to a more comprehensive understanding of complex scientific questions and advance gerontological science and permit the evaluation of differences across country, birth cohort, study design, and measurement differences.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences* online.

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Conflict of Interest

None reported.

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