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Cognitive dispersion predicts grip strength trajectories in men but not women in a sample of the oldest-old without dementia

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Abstract

Background and Objectives: Grip strength is a reliable marker of biological vitality and it typically demonstrates an expected decline in older adults. According to the common-cause hypothesis there is also a significant association between cognitive and physical function in older adults. Some specific cognitive functions have been shown to be associated with grip strength trajectories with most research solely focused on cut-off points or mean cognitive performance. In the present study we examine whether a measure of cognitive dispersion might be more informative. We therefore used an index that quantifies dispersion in cognitive scores across multiple cognitive tests, shown to be associated with detrimental outcomes in older adults.

Research Design and Methods: Using repeated grip strength measures from men and women aged 80 and older, free of dementia in the OCTO-Twin study, we estimated ageing-related grip strength trajectories. We examined the association of cognitive dispersion and mean cognitive function with grip strength level and ageing-related rate of change, accounting for known risk factors.

Results: Cognitive dispersion was associated with grip strength trajectories in men and the association varied by mean cognitive performance, whereas we found no association in women.

Discussion and Implications: Our results provide evidence of a sex-specific vitality association between cognitive dispersion and ageing-related trajectories of grip strength. Our results support the call for integration of sex and gender in health promotion and intervention research.

Keywords: Cognition, Frailty, Epidemiology, Longevity, Psychometrics

Translational Significance: Variability or inconsistency in cognitive performance is proposed as a sensitive measure of decline in cerebral integrity. Our findings suggest that this measure is associated with decline in hand-grip strength, a measure of vitality and physical status, in octogenarian men but not women, even though there were no overall differences in variability or mean cognitive performance between genders. These findings suggest different factors contribute to vitality or physical status in men and women in the oldest-old and highlights the need for targeted strategies to support health promotion and intervention between the sexes in later-life.

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Increases in life expectancy are well documented (Prince et al., 2013). As an individual's lifespan is extended, the preservation of physical and cognitive health becomes critical for functional integrity, well-being and quality of life (Paggi et al., 2016; Samy et al., 2020). Grip strength is often shown to be an indicator of physical strength and vitality and thereby a simple and overall measure of the integrity of the central nervous system that signals changes in underlying aging processes (Salthouse et al., 1998).

Grip strength is repeatedly found to be a reliable indicator of poor health in older adults. For instance, a study of the over half a million participants of the UK Biobank, reported an association of grip strength with cardiovascular, respiratory, and cancer outcomes as well as with all-cause mortality (Celis-Morales et al., 2018). Furthermore, grip strength from midlife onwards has also been shown to be associated with other detrimental events such as falls (Salthouse et al., 1998; Yang et al., 2018), hip fractures (Denk et al., 2018) and depression (Ashdown-Franks et al., 2019). As a result of these findings, grip strength has been suggested as a "vital sign" in middle-aged and older adults (Bohannon, 2008; Carson, 2020); a reliable biomarker for vitality and aging (Zammit et al., 2019). Grip strength is related to muscle mass, and as men have more muscle mass than women, the differences are reflected in grip strength too. Further, grip strength differences between men and women can be attributed to differences in behavior that result in men engaging in more manual and physical labor than women over the life course (Vianna et al., 2007). However, the evidence about differences in rate of change in grip strength between men and women is mixed (Cooper et al., 2011), with some reporting that men decline faster than women (Frederiksen et al., 2006), whilst other report the opposite (Rantanen et al., 1997).

The association between grip strength and cognition is even less understood. The common cause hypothesis suggests a relationship between the cognitive and sensory domains and that aging related changes in both reflect brain aging (Baltes & Lindenberger, 1997). Age-related loss of sensory receptors and neurons tend to produce a slowing of perceptual processing and less effective and slower encoding of new information (Anstey et al., 2001). This may directly lead to slowing of cognitive processing and hence, result in compromised cognitive performance. Most studies of the association between cognitive function and grip strength have so far only focused on single cognitive domains. For example, cross-sectional studies reviewed in 2018 by Kobayashi-Cuya et al (Kobayashi-Cuya et al., 2018) identified 22 publications that examined associations between cognition and handgrip strength in community-dwelling older adults. The majority of these studies only used the Mini Mental State Exam screening device (Folstein et al., 1975). There is currently a lack of clear evidence of the association of grip strength with more detailed measures of various cognitive

domains. Importantly, studies that have evaluated the association of multiple measures have typically considered them independently and the findings are so far mixed (Kobayashi-Cuya et al., 2018).

Longitudinally, results about the role of cognition on grip strength trajectories are scarce. As with cross sectional studies, most longitudinal investigations have focused only on measures of global cognition (Kim et al., 2019) or single tests (Viscogliosi et al., 2017). Further, studies on cognitive domains have typically only examined their independent association with changes in grip strength (see Zammit et al., 2019) ignoring functioning in other cognitive domains or looked into the correlation between changes in cognitive domains and grip strength, either in the context of ageing related decline (Zammit et al., 2021) or terminal decline (Björk et al., 2016).

Traditionally, cognitive performance is indexed by comparing an individual's performance against established cut-off criteria or a reference group mean. However, the study of an individual's inconsistency in performance across tasks or domains is gaining momentum in the neuropsychological and clinical literature (see (Costa et al., 2019). While performance inconsistency can be quantified in several ways, cognitive dispersion (CD), in which the standard deviation in an individual's performance is measured across a set of cognitive measures or domains is nowadays more commonly applied (Stawski et al., 2019). Dispersion across cognitive performance scores may signal subtle breakdowns in cognitive ability (Costa et al., 2019) and is therefore more likely to provide a more sensitive measure of early decline, relative to mean performance and/or single indicators of cognition (Cherbuin et al., 2010; Tales et al., 2012). It may also reflect subtle changes in cognition that can be detected before conventional neuropsychological thresholds for cognitive impairment are met (Koscik et al., 2016; Roalf et al., 2016). In this respect, cognitive dispersion can be conceptualized as a single representation of function across multiple domains subserved by several cortical regions and neural networks. Consequently, it may be considered a signature of decline in cerebral integrity (Holtzer et al., 2019). In fact, its association with indicators of brain pathology is well documented in studies that show associations between dispersion and smaller corpus collosum volumes (Anstey et al., 2007); global and regional white matter

degeneration (Jackson et al., 2012) and faster entorhinal and hippocampal atrophy rates (Bangen et al., 2019). In fact, in a previous study using data from the OCTO Twin Study of the oldest old, the study of Swedish Twins aged 80 and older at study entry that we also study here, we showed that cognitive dispersion was associated with increased risk of dementia (Tamlyn Watermeyer et al., 2020).

In the context of this evidence, the investigation of an association between CD and grip strength deterioration represents an opportunity to further test the common cause hypothesis and examine CD as a novel marker of decline in physical function, such as muscular strength.

To the best of our knowledge, no research has examined whether cognitive dispersion is associated with grip strength trajectories in older adults which inspired our investigation about whether cognitive dispersion is associated with trajectories of grip strength in the OCTO Twin Study of the oldest old. We hypothesize that (i) cognitive dispersion will be negatively associated with grip strength level and (ii) cognitive dispersion will be positively associated with rate of change (i.e. decline) in men and women.

METHODS

OCTO-Twin sample

The sample used in these analyses was drawn from the comprehensive longitudinal Origins of Variance in the Old-Old: Octogenarian Twins (known as the OCTO-Twin Study (McClearn et al., 1997), based on the oldest cohort of the Swedish Twin Registry. The sample includes 702 participants, with 351 complete twin pairs born in 1913 and earlier, who were or became 80 years of age during the first wave of data collection (1991-1993). Participants were tested at home or institutional settings, by medical research nurses who were specially trained and regularly supervised. Participants were re-assessed every two years with a total of eight years of follow-up. The average rate of attrition from one testing wave to the next was 20% (10% per year), primarily due to death. Due to the secondary data analysis nature of this study, power calculations were not conducted for this paper. Full details of the study population characteristics have been published previously (Cederlof & Lorch, 1978; McClearn et al., 1997; Pedersen, Lichtenstein, & Svedberg, 2002).

In order to identify cases of dementia, a multi-disciplinary team consisting of a physician and two neuropsychologists reviewed cognitive test results and medical records, including reported medical history, medication use and self-reported information about diseases. Independent classification performed by another physician produced only marginal amendment (for more information on this

procedure see Johansson and Zarit (1995)). Dementia was diagnosed by consensus according to the 3rd edition of the Diagnostic and Statistical Manual of Mental Disorders.

Ethics

The OCTO-Twin Study received approval from the Ethics Committee at the Karolinska Institute in Stockholm and from the Swedish Data Inspection Authority. Informed written consent was obtained from all participants or their relative or carer where capacity to consent was questionable, for example, due to severe cognitive impairment or dementia.

Grip Strength. A Martin vigorimeter (Elmed Inc., Addison, IL, USA; medium size bulb) to measure maximum force in pounds per square inch was used. Participants performed the task three times per hand, with the final score being the maximum force exerted.

Cognitive Battery. Cognitive tests were administered at the participants' homes by experienced registered nurses. The cognitive battery of tests for the various domains were: *Memory.* Verbal memory was assessed by a Prose Recall Test. This test is a Swedish language Prose Recall task similar to those from the Wechsler Memory Test (WMS, Wechsler (1945)). Respondents were asked for immediate free recall of a brief story.

Memory recognition and memory correspondence were assessed by four subtests of the Memory in Reality Test (Johansson, 1988/89): Naming (participant is shown and asked to name 10 objects); Recall (participant is asked to recall the 10 objects after 30 minute delay); Recognition (participant is shown objects not recalled and asked to name these) and Correspondence/Relocation (participant is asked to re-place objects in their original locations). Maximum score for each subtest is 10 (Johansson, 1988/89).

Short-term memory was assessed by the Digit Span Forward and Backward Test (WAIS, Wechsler (1991)). The participants were asked to recall orally presented digits in the same and reverse order as they were presented. Higher scores represent higher levels of short-term memory.

Visuospatial ability and Reasoning. Visuospatial ability was assessed with the Koh's Block Design Test (SRB 3, from Dureman and Sälde (1959)). Respondents were asked to reproduce with blocks a pattern shown on cards. Higher scores are indicative of a greater level of visuospatial ability. Other tasks included a Clock drawing task from The Swedish Clock Test (see, Johansson and Zarit (1991)) and the Figure Logic reasoning test, which require participants to identify one figure out of five in a row that is different in concept from the rest (SRB 2, from Dureman and Sälde (1959)).

Motor and perceptual speed. A modified version of the speeded Digit-Symbol Substitution Test (Wechsler & De Lemos, 1981) was used which measures motor speed and accuracy. The participants were given a list of symbols associated with digits from 1 to 9 and instructed to orally fill in the blanks with the digit that correspond to each symbol. The test score is the total number of correct sequential matching of digits to symbols in a 90 second interval. Another perceptual speed test, *Figure Identification*, Psif, from Dureman and Sälde (1959) was also used to assess perceptual speed. Participants are asked to match, as quickly

as possible, a target figure with one identical figure placed in line among four others. The maximum score is 60 and the time limit is 4 min.

Crystallized abilities. These abilities can be described as the general knowledge acquired through education and other cultural experiences over the entire life span (Horn, 1991; Horn & Noll, 1997). In the OCTO Twin Study, two tests from the Swedish version of the Wechsler Adult Intelligence Scale (Jonsson & Molander, 1964; Wechsler & De Lemos, 1981) were used: the Swedish version of the Information Task and the Synonyms Test. The Information Task includes questions of general knowledge, which requires participants to provide answers to questions assessing acquired semantic knowledge of facts. The Synonyms Test is a verbal meaning test where the respondent has to find a synonym that matches a target word among five alternatives. Higher scores represent higher levels of knowledge.

Other Data

Sociodemographic data Sociodemographic information included the participant's sex, age at study entry, and years of education.

Body Mass Index. Body mass index (BMI) was derived as kg/m^2 using height and weight measures collected by nurses.

Physical activity. Individuals were asked "Are you presently doing, or have you previously done anything special to train your body or keep your body fit?". The possible responses were "no" (0), "yes, to some extent" (1), or "yes, to a great extent" (2) and responses coded on a scale from 0 to 2. Using these responses, we derived a binary indicator collapsing positive responses into a single category coded as 1 and negative responses into another category coded as 0.

Analytical Approach

Cognitive dispersion scores were derived using an adaptation of the method described by Holzer et al. (Holtzer et al., 2019; Holtzer et al., 2008). We only included data from individuals who were dementia free at study entry. The method applies a z-transformation to the raw scores of each test using parameters from the distribution of the entire sample, and then, the application of the formula:

$$Dispersion = \sqrt{\frac{\sum_{k=1}^{k=K} (T_{ik} - S_i)^2}{K - 1}}$$

where T_{ik} is the k^{th} z-transformed test for participant i , K is the number of tests, and S_i is participant i 's mean of the transformed scores.

Average cognitive performance scores were derived by taking the mean of scores in the different cognitive tests.

To estimate grip strength trajectories, following evidence about sex differences in grip strength, we fitted a series of independent linear mixed effects models to grip strength measures from men and women structured as a function of time in study. Initially, the intercept and slope parameters of the models were adjusted for cognitive dispersion, mean cognitive performance, age at study entry and BMI (centered at their mean values). That is, cognitive dispersion for men was centered at 0.49 and for women at 0.53; mean cognitive function was centered at 0.11 and 0.08 respectively for men and

women whereas BMI was centered at 24.4 and 24.9 for men and women respectively too. Physical activity was coded as 1 if the individuals trained their body and 0 if the individual did not train their body. We also included terms indicating whether individuals smoked or had smoked before entering the study (yes=1, no=0), had had a history of stroke (yes=1, no=0). Then, interaction terms between mean cognitive performance and dispersion were added to the models.

All models were estimated using Mplus, accounting for the correlations between twins using the Clustering option available in the package. Models were estimated using maximum likelihood estimation, and missing data are assumed to be missing at random.

RESULTS

Descriptive Statistics. The initial sample included 702 participants, of which there were 98 individuals who had been diagnosed with dementia at study entry. Of the 604 individuals who were free from dementia at baseline, there were 19 individuals (12 women, 7 men) who had missing data in all cognitive tests included in the derivation of the dispersion index. Their grip strength baseline measures did not differ from the baseline grip strength measures of those who had valid cognitive scores (t -test(621)=0.48, $p < 0.05$) and were therefore, excluded from the analysis, and 12 individuals did not have data on education. Hence, the final analytical samples included 204 men and 373 women who were free from dementia at study entry. Women were older than men (83.58 (0.17) vs 82.87 (SD=0.18), t -test, p -value=0.007) and had fewer years of education (7.02 (0.10) vs 7.50 (0.20), t -test, p -value=0.01). Yet, there were no statistically significant differences between men and women in body mass index (24.42 (0.20) vs 24.96 (0.25), t -test, $p=0.10$), mean cognitive performance (0.11(0.02) vs 0.08 (0.04) t -test, p -value=0.53) and cognitive dispersion (0.49(0.02) vs 0.53(0.03), t -test, p -value=0.08). See Figure 2 for box plots of mean cognitive performance and cognitive dispersion in the sample of men and women in the study and Table 2 the descriptive characteristics of the results of each of the cognitive tests in men and women. In addition, there were differences between men and women in smoking habits (72% of men compared to 77% of women, $\chi^2=140.13$, p -value=0.001), engagement in physical activity (68.0% of men trained their body compared to 55.5% of women, $\chi^2=10.18$, p -value=0.006) but not in stroke prevalence before joining the study ($\chi^2=2.39$, p -value=0.30). Further demographic details are shown in Table 1.

Grip strength trajectories. We present results from the longitudinal models fitted to the sample of men and women separately below. Box plots of grip strength measures at each study wave are presented in Figure 1.

Men's grip strength trajectories. For a reference man (aged 83 years old at study entry, with an average body mass index, and no history of stroke before entering the study, who trains his body and has average cognitive dispersion and mean levels of cognition), grip strength at study entry was estimated at 111.57 (SD=0.53) kgs, with an annual rate of decline of 2.00 (SD=0.33) kg, although this estimate did not reach conventional significance levels (see Table 3 for results).

Results suggest that the association of cognitive dispersion scores with baseline grip strength and its annual rate of decline varies with the level of mean cognitive function. We found that for the same level of average cognitive function, men with more dispersed scores showed weaker grip and they declined at a slower rate than men with less dispersed cognitive scores. See Figure 3 for a graphical representation of grip strength trajectories for prototypical individuals.

Except for older baseline age that had a negative association with grip strength at study entry, no other factor emerged as associated with grip trajectories.

Women's grip strength trajectories. For a reference woman, grip strength at study entry was estimated at 7.72 (SD=0.32) kgs with a rate of decline of -0.36 (SD=0.02) kgs/year. Contrary to results in the sample of men, neither cognitive dispersion nor mean cognitive performance emerged as associated with baseline grip strength level or its rate of decline. Older baseline age (-0.12 (SD=0.05)) was associated with weaker grip strength whereas higher body mass index and physical activity were associated with stronger grip (0.08 (SD=0.03) and 0.70 (SD=0.28) respectively). Finally, women who had a history of stroke declined at a faster rate than unaffected women (-0.16 (SD=0.08)).

DISCUSSION

In our investigation exploring whether dispersion in cognitive function is associated with grip strength trajectories in a sample of the oldest old, we found that the association varied between men and women. Whilst in men, we found an association that varied by level of mean cognitive function, no association was found between cognitive dispersion or cognitive mean function in the sample of women. Hence, our hypotheses that cognitive dispersion would be negatively associated with grip strength level and positively associated with rate of change (i.e. decline) in men *and* women was only partially confirmed by our findings.

The question of whether cognitive function is associated with physical function, and in particular with grip strength, an indicator of biological vitality, has been studied extensively following the postulation of the common cause hypothesis (Baltes & Lindenberger, 1997), whereby it has been suggested that cognition and grip strength share similar variability of change that is influenced by a common neurological cause (Bjork et al., 2016). The relationship between cognitive dispersion and grip strength can be similarly explained, but perhaps cognitive dispersion, relative to mean level cognitive function, captures more insidious brain aging changes (Bangen et al., 2019). To date, most investigations have focused on associations between mean levels of specific cognitive domains and grip strength in cross sectional and longitudinal studies. Although previous studies have linked cognitive dispersion with deteriorating trajectories of functional indicators (Bangen et al., 2019; Fellows & Schmitter-Edgecombe, 2015), to the best of our knowledge, our study is the first that specifically examined the association of cognitive dispersion with grip strength.

Reports of the associations between cognitive dispersion and poorer white matter integrity (Halliday et al., 2018) and with some but not all cerebrospinal fluid biomarkers of Alzheimer's disease (Duchek et al., 2009; Gleason et al., 2018; T. Watermeyer et al., 2020) has led researchers to postulate dispersion as an early marker of pathological brain changes. Yet, as these investigations were conducted in samples of younger adults, the question about onset and timing of the association of dispersion with different markers of deterioration remains to be further investigated. Previous work with the Octo-Twin cohort found that rates of decline in cognitive function were closely related to rate of decline in grip strength before death (Björk et al., 2016) supporting the terminal decline hypothesis, in which proximity to death is accompanied by sharper cognitive decline (Muniz-Terrera et al., 2011). Our study with the same cohort differs from this report in that we focused on grip strength changes outside the context of proximate death and we were interested in cognitive dispersion, not level of cognitive performance, as a marker for grip decline, and thus, age-related change. Relative to level of cognitive performance, increased dispersion may reflect more subtle disintegration and/or re-

organization of neural processes and activities in ageing individuals before the onset of overt cognitive symptoms are detectable through traditional methods (see Holzer et al, 2019). Therefore, incorporation of this measure alongside average level of cognitive performance, might offer earlier adjunct information regarding an individual's neurocognitive integrity and future decline in vitality, as measured by grip strength.

Indeed, in a previous report where we studied the association of dispersion with dementia risk in a sample of OCTO-Twin participants, we found that individuals with greater cognitive dispersion scores have an increased risk of dementia, above and beyond controlling for level of cognitive performance (Tamlyn Watermeyer et al., 2020). This previous investigation, taken together with our new analysis of grip strength trajectories, partly supports the common cause hypothesis although some questions remain unanswered.

We only found an association between cognitive dispersion and grip strength trajectories in the sample of men but not women, despite no significant differences in dispersion or mean cognitive functioning between men and women. Although women were slightly older than men, their mean and dispersion cognitive scores were not significantly different. Instead, within the female sample, body mass index and being physically active correlated with grip strength at baseline, while only a previous incident of stroke related to rate of change in grip strength. Such gender differences add to the small but growing literature showing gender-specific predictors of physical status in mid-to-later life (Fragala et al., 2012; Mohd Hairi et al., 2010) and the oldest-old (Parker et al., 1996) and supports the call for integration of sex and gender in health promotion and intervention research (Mauvais-Jarvis et al., 2020; Tannenbaum et al.). Further, although the examination of incident dementia in the sample of men and women showed that there were fewer men than women (48 vs 79) who received a diagnosis of dementia during the study follow up, their age at diagnosis was only borderline significantly different (m:86.04 (0.49) vs f:87.29 (0.21), t-test, p-value=0.005) and there were significant differences in the time past between diagnosis and study entry (m:3.61 (0.34) vs f:3.76(0.29), t-test, p-value=0.74). Hence, it is unlikely that the differences in our results are explained by proximity to dementia diagnosis. We therefore encourage further investigations to fully understand these results.

Our research has some limitations. To begin with, we assumed missing data are missing at random, an assumption that may not be fulfilled. Because of the relatively small number of individuals in the subsample of men and women, we only included a core set of variables in our analysis. For example, we did not account for comorbidities such as diabetes or many healthy lifestyle variables, only controlling for a simple measure of physical activity. This study was initiated already in 1991, when research about the role of lifestyle on the preservation of function was still in early stages and therefore, the physical activity question asked is not optimal judging by current standards. Similarly, the construction of our dispersion metric is restricted by the tests available from the neuropsychological battery. The domains covered by the 15 tests used in this study do not have sufficient overlap to derive within-domain dispersion scores. Instead, our dispersion composite captures multiple domains of cognitive functioning and thus for any individual participant could reflect, for example, high inconsistent performance within a single cognitive domain or milder variability across multiple domains. This might minimize the clinical significance of our findings. Nonetheless, using the same construction approach, previous work has demonstrated that variability across tests were sensitive to dementia diagnosis, above and beyond average cognitive performance, suggesting our metric may possess incremental validity in predicting cognitive decline (Holtzer et al., 2008; Watermeyer et al., 2020). Furthermore, performance variability across tests correlates poorly with global cognitive indices (Watermeyer et al, 2020), suggesting that such scores might reflect

distinct aspects of brain health and/or cognitive aging. Future work is required to determine the best construction method to optimize sensitivity and specificity for physical decline, neuropathology, and cognitive decline to support dispersion metric's clinical relevance.

Notwithstanding these limitations, our study's strengths lie in its longitudinal design and relatively well characterized oldest-old cohort. Furthermore, this is the first investigation of the association of cognitive dispersion with grip strength, a marker of biological vitality or aging. This work opens several lines of future research: we strongly encourage replication of our methods in other samples of older adults and further examination of whether the timing of associations between cognitive dispersion and grip strength differ by sex.

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REFERENCES

- Anstey, K. J., Luszcz, M. A., & Sanchez, L. (2001). A Reevaluation of the Common Factor Theory of Shared Variance Among Age, Sensory Function, and Cognitive Function in Older Adults. *The Journals of Gerontology: Series B*, *56*(1), P3-P11.
<https://doi.org/10.1093/geronb/56.1.P3>
- Anstey, K. J., Mack, H. A., Christensen, H., Li, S. C., Rejlade-Meslin, C., Maller, J., Kumar, R., Dear, K., Easteal, S., & Sachdev, P. (2007). Corpus callosum size, reaction time speed and variability in mild cognitive disorders and in a normative sample. *Neuropsychologia*, *45*(8), 1911-1920.
<https://doi.org/10.1016/j.neuropsychologia.2006.11.020>
- Ashdown-Franks, G., Stubbs, B., Koyanagi, A., Schuch, F., Firth, J., Veronese, N., & Vancampfort, D. (2019). Handgrip strength and depression among 34,129 adults aged 50 years and older in six low- and middle-income countries. *Journal of Affective Disorders*, *243*, 448-454. <https://doi.org/10.1016/j.jad.2018.09.036>
- Baltes, P. B., & Lindenberger, U. (1997). Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging? *Psychology and Aging*, *12*(1), 12-21.
<https://doi.org/10.1037//0882-7974.12.1.12>
- Bangen, K. J., Weigand, A. J., Thomas, K. R., Delano-Wood, L., Clark, L. R., Eppig, J., Werhane, M. L., Edmonds, E. C., & Bondi, M. W. (2019). Cognitive dispersion is a sensitive marker for early neurodegenerative changes and functional decline in nondemented older adults. *Neuropsychology*, *33*(5), 599-608.
<https://doi.org/10.1037/neu0000532>
- Björk, M. P., Johansson, B., & Hassing, L. B. (2016). I forgot when I lost my grip - Strong associations between cognition and grip strength in level of performance and change

across time in relation to impending death. *Neurobiology and Aging*, 38, 68-72.

<https://doi.org/10.1016/j.neurobiolaging.2015.11.010>

Bohannon, R. W. (2008). Hand-grip dynamometry predicts future outcomes in aging adults.

Journal of Geriatric Physical Therapy, 31(1), 3-10.

<https://doi.org/10.1519/00139143-200831010-00002>

Carson, R. G. (2020). What accounts for the association between grip strength and mental functioning in aging people? *Maturitas*, 138, 80-81.

<https://doi.org/10.1016/j.maturitas.2020.01.010>

Celis-Morales, C. A., Welsh, P., Lyall, D. M., Steell, L., Petermann, F., Anderson, J., Iliodromiti, S., Sillars, A., Graham, N., Mackay, D. F., Pell, J. P., Gill, J. M. R., Sattar, N., & Gray, S. R. (2018). Associations of grip strength with cardiovascular, respiratory, and cancer outcomes and all cause mortality: prospective cohort study of half a million UK Biobank participants. *BMJ*, 361, k1651.

<https://doi.org/10.1136/bmj.k1651>

Cherbuin, N., Sachdev, P., & Anstey, K. J. (2010). Neuropsychological predictors of transition from healthy cognitive aging to mild cognitive impairment: The PATH through life study. *The American Journal of Geriatric Psychiatry*, 18(8), 723-733.

<https://doi.org/10.1097/jgp.0b013e3181cdecf1>

Cooper, R., Hardy, R., Aihie Sayer, A., Ben-Shlomo, Y., Birnie, K., Cooper, C., Craig, L., Deary, I. J., Demakakos, P., Gallacher, J., McNeill, G., Martin, R. M., Starr, J. M.,

Stephens, A., & Kuh, D. (2011). Age and gender differences in physical capability levels from mid-life onwards: the harmonisation and meta-analysis of data from eight UK cohort studies. *PLoS One*, 6(11), e27899.

<https://doi.org/10.1371/journal.pone.0027899>

- Costa, A. S., Dogan, I., Schulz, J. B., & Reetz, K. (2019). Going beyond the mean: Intraindividual variability of cognitive performance in prodromal and early neurodegenerative disorders. *Clinical Neuropsychologist*, *33*(2), 369-389. <https://doi.org/10.1080/13854046.2018.1533587>
- Denk, K., Lennon, S., Gordon, S., & Jaarsma, R. L. (2018). The association between decreased hand grip strength and hip fracture in older people: A systematic review. *Experimental Gerontology*, *111*, 1-9. <https://doi.org/10.1016/j.exger.2018.06.022>
- Duchek, J. M., Balota, D. A., Tse, C. S., Holtzman, D. M., Fagan, A. M., & Goate, A. M. (2009). The utility of intraindividual variability in selective attention tasks as an early marker for Alzheimer's disease. *Neuropsychology*, *23*(6), 746-758. <https://doi.org/10.1037/a0016583>
- Fellows, R. P., & Schmitter-Edgecombe, M. (2015). Between-domain cognitive dispersion and functional abilities in older adults. *Journal of Clinical and Experimental Neuropsychology*, *37*(10), 1013-1023. <https://doi.org/10.1080/13803395.2015.1050360>
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189-198. [https://doi.org/10.1016/0022-3956\(75\)90026-6](https://doi.org/10.1016/0022-3956(75)90026-6)
- Fragala, M. S., Clark, M. H., Walsh, S. J., Kleppinger, A., Judge, J. O., Kuchel, G. A., & Kenny, A. M. (2012). Gender differences in anthropometric predictors of physical performance in older adults. *Gender Medicine*, *9*(6), 445-456. <https://doi.org/10.1016/j.genm.2012.10.004>
- Frederiksen, H., Hjelmberg, J., Mortensen, J., McGue, M., Vaupel, J. W., & Christensen, K. (2006). Age trajectories of grip strength: cross-sectional and longitudinal data among

8,342 Danes aged 46 to 102. *Annals of Epidemiology* 16(7), 554-562.

<https://doi.org/10.1016/j.annepidem.2005.10.006>

- Gleason, C. E., Norton, D., Anderson, E. D., Wahoske, M., Washington, D. T., Umucu, E., Kosciak, R. L., Dowling, N. M., Johnson, S. C., Carlsson, C. M., Asthana, S., & Initiative, A. s. D. N. (2018). Cognitive variability predicts incident Alzheimer's disease and mild cognitive impairment comparable to a cerebrospinal fluid biomarker. *Journal of Alzheimer's Diseases*, 61(1), 79-89. <https://doi.org/10.3233/JAD-170498>
- Halliday, D. W. R., Stawski, R. S., Cerino, E. S., DeCarlo, C. A., Grewal, K., & MacDonald, S. W. S. (2018). Intraindividual variability across neuropsychological tests: Dispersion and disengaged lifestyle increase risk for Alzheimer's disease. *Journal of Intelligence* 6(1). <https://doi.org/10.3390/jintelligence6010012>
- Holtzer, R., Jacobs, S., & Demetriou, E. (2019). Intraindividual variability in verbal fluency performance is moderated by and predictive of mild cognitive impairments. *Neuropsychology*. <https://doi.org/10.1037/neu0000576>
- Holtzer, R., Verghese, J., Wang, C., Hall, C. B., & Lipton, R. B. (2008). Within-person across-neuropsychological test variability and incident dementia. *JAMA*, 300(7), 823-830. <https://doi.org/10.1001/jama.300.7.823>
- Jackson, J. D., Balota, D. A., Duchek, J. M., & Head, D. (2012). White matter integrity and reaction time intraindividual variability in healthy aging and early-stage Alzheimer disease. *Neuropsychologia*, 50(3), 357-366. <https://doi.org/10.1016/j.neuropsychologia.2011.11.024>
- Kim, K. H., Park, S. K., Lee, D. R., & Lee, J. (2019). The relationship between handgrip strength and cognitive function in elderly Koreans over 8 years: A prospective population-based study using Korean Longitudinal Study of Ageing. *Korean Journal of Family Medicine*, 40(1), 9-15. <https://doi.org/10.4082/kjfm.17.0074>

Kobayashi-Cuya, K. E., Sakurai, R., Suzuki, H., Ogawa, S., Takebayashi, T., & Fujiwara, Y. (2018). Observational evidence of the association between handgrip strength, hand dexterity, and cognitive performance in community-dwelling older adults: A systematic review. *Journal of Epidemiology*, 28(9), 373-381. <https://doi.org/10.2188/jea.JE20170041>

Koscik, R. L., Berman, S. E., Clark, L. R., Mueller, K. D., Okonkwo, O. C., Gleason, C. E., Hermann, B. P., Sager, M. A., & Johnson, S. C. (2016). Intraindividual cognitive variability in middle age predicts cognitive impairment 8-10 years later: Results from the Wisconsin Registry for Alzheimer's Prevention. *Journal of the International Neuropsychological Society*, 22(10), 1016-1025. <https://doi.org/10.1017/s135561771600093x>

Mauvais-Jarvis, F., Bairey Merz, N., Barnes, P. J., Brinton, R. D., Carrero, J. J., DeMeo, D. L., De Vries, G. J., Epperson, C. N., Govindan, R., Klein, S. L., Lonardo, A., Maki, P. M., McCullough, L. D., Regitz-Zagrosek, V., Regensteiner, J. G., Rubin, J. B., Sandberg, K., & Suzuki, A. (2020). Sex and gender: modifiers of health, disease, and medicine. *Lancet*, 396(10250), 565-582. [https://doi.org/10.1016/s0140-6736\(20\)31561-0](https://doi.org/10.1016/s0140-6736(20)31561-0)

Mohd Hairi, F., Mackenbach, J. P., Andersen-Ranberg, K., & Avendano, M. (2010). Does socio-economic status predict grip strength in older Europeans? Results from the SHARE study in non-institutionalised men and women aged 50+. *Journal of Epidemiology Community Health*, 64(9), 829-837. <https://doi.org/10.1136/jech.2009.088476>

Muniz-Terrera, G., Matthews, F. E., Stephan, B., Brayne, C., & Group, C. C. C. (2011). Are terminal decline and its potential indicators detectable in population studies of the

oldest old? *International Journal of Geriatric Psychiatry*, 26(6), 584-592.

<https://doi.org/10.1002/gps.2566>

Paggi, M. E., Jopp, D., & Hertzog, C. (2016). The importance of leisure activities in the relationship between physical health and well-being in a life span sample.

Gerontology, 62(4), 450-458. <https://doi.org/10.1159/000444415>

Parker, M. G., Thorslund, M., Lundberg, O., & Kareholt, I. (1996). Predictors of physical function among the oldest old: a comparison of three outcome variables in a 24-year follow-up. *Journal of Aging and Health*, 8(3), 444-460.

<https://doi.org/10.1177/089826439600800307>

Prince, M., Bryce, R., Albanese, E., Wimo, A., Ribeiro, W., & Ferri, C. P. (2013). The global prevalence of dementia: A systematic review and metaanalysis. *Alzheimer's & Dementia*, 9(1), 63-75.e62.

<https://doi.org/10.1016/j.jalz.2012.11.007>

Rantanen, T., Era, P., & Heikkinen, E. (1997). Physical activity and the changes in maximal isometric strength in men and women from the age of 75 to 80 years. *Journal of the American Geriatrics Society*, 45(12), 1439-1445.

<https://doi.org/10.1111/j.1532-5415.1997.tb03193.x>

Roalf, D. R., Quarmley, M., Mechanic-Hamilton, D., Wolk, D. A., Arnold, S. E., & Moberg, P. J. (2016). Within-individual variability: An index for subtle change in neurocognition in mild cognitive impairment. *Journal of Alzheimer's Disease*, 54(1),

[325-335. https://doi.org/10.3233/jad-160259](https://doi.org/10.3233/jad-160259)

Salthouse, T. A., Hambrick, D. Z., & McGuthry, K. E. (1998). Shared age-related influences on cognitive and noncognitive variables. *Psychology and Aging*, 13(3), 486-500.

<https://doi.org/10.1037//0882-7974.13.3.486>

Samy, A. L., Kamaruzzaman, S. B., Krishnaswamy, S., & Low, W. Y. (2020). Predictors of Quality of life among older people with mild cognitive impairment attending urban

primary care clinics. *Clinical Gerontologist*, 43(4), 441-454.

<https://doi.org/10.1080/07317115.2019.1608611>

- Stawski, R. S., MacDonald, S. W. S., Brewster, P. W. H., Munoz, E., Cerino, E. S., & Halliday, D. W. R. (2019). A comprehensive comparison of quantifications of intraindividual variability in response times: A measurement burst approach. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences*, 74(3), 397-408. <https://doi.org/10.1093/geronb/gbx115>
- Tales, A., Leonards, U., Bompas, A., Snowden, R. J., Philips, M., Porter, G., Haworth, J., Wilcock, G., & Bayer, A. (2012). Intra-individual reaction time variability in amnesic mild cognitive impairment: A precursor to dementia? *Journal of Alzheimer's Disease*, 32(2), 457-466. <https://doi.org/10.3233/jad-2012-120505>
- Tannenbaum, C., Greaves, L. & Graham, I.D (2016). Why sex and gender matter in implementation research. *BMC Medical Research Methodology*, 16, 145. <https://doi.org/10.1186/s12874-016-0247-7>
- Vianna, L. C., Oliveira, R. B., & Araújo, C. G. (2007). Age-related decline in handgrip strength differs according to gender. *The Journal of Strength and Conditioning Research*, 21(4), 1310-1314. <https://doi.org/10.1519/r-23156.1>
- Viscogliosi, G., Di Bernardo, M. G., Ettore, E., & Chiriack, I. M. (2017). Handgrip strength predicts longitudinal changes in clock drawing test performance. An observational study in a sample of older non-demented adults. *The Journal of Nutrition, Health and Aging*, 21(5), 593-596. <https://doi.org/10.1007/s12603-016-0816-9>
- Watermeyer, T., Goerden, J., Johansson, B., & Muniz-Terrera, G. (2020). Cognitive dispersion and ApoEε4 genotype predict dementia diagnosis in 8 years follow-up of the oldest-old. *Age and Ageing*. <https://doi.org/10.1093/ageing/afaa232>

Watermeyer, T., Marroig, A., Ritchie, C. W., Ritchie, K., Blennow, K., & Muniz-Terrera, G. (2020). Cognitive Dispersion is not Associated with Cerebrospinal Fluid Biomarkers of Alzheimer's Disease: Results from the European Prevention of Alzheimer's Dementia (EPAD) v500.0 Cohort. *Journal of Alzheimer's Disease*. <https://doi.org/10.3233/jad-200514>

Yang, N. P., Hsu, N. W., Lin, C. H., Chen, H. C., Tsao, H. M., Lo, S. S., & Chou, P. (2018). Relationship between muscle strength and fall episodes among the elderly: the Yilan study, Taiwan. *BMC Geriatrics*, 18(1), 90. <https://doi.org/10.1186/s12877-018-0779-2>

Zammit, A. R., Piccinin, A. M., Duggan, E. C., Koval, A., Clouston, S., Robitaille, A., Brown, C. L., Handschuh, P., Wu, C., Jarry, V., Finkel, D., Graham, R. B., Muniz-Terrera, G., Praetorius Björk, M., Bennett, D., Deeg, D. J., Johansson, B., Katz, M. J., Kaye, J., Lipton, R. B., Martin, M., Pederson, N. L., Spiro, A., Zimprich, D., & Hofer, S. M. (2021). A coordinated multi-study analysis of the longitudinal association between handgrip strength and cognitive function in older adults. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences*, 76(2), 229-241. <https://doi.org/10.1093/geronb/gbz072>

Zammit, A. R., Robitaille, A., Piccinin, A. M., Muniz-Terrera, G., & Hofer, S. M. (2019). Associations between aging-related changes in grip strength and cognitive function in older adults: A systematic review. *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences*, 74(4), 519-527. <https://doi.org/10.1093/gerona/gly046>

Table 1. Descriptive characteristics of the sample

	Men (N=204)	Women (N=373)
	Mean (SD)	Mean (SD)
	or n (%)	or n (%)
Baseline Age	82.87 (2.67)	83.58 (3.20)
Education	7.50 (2.90)	7.02 (1.92)
Grip		
Strength		
Baseline	11.06 (2.99)	8.11 (2.30)
First follow up	9.99 (2.74)	7.43 (2.34)
Second follow up	9.21 (3.28)	6.52 (2.40)
Third follow up	8.80 (2.92)	6.09 (2.36)
Fourth follow up	8.19 (3.21)	5.67(2.22)
Body Mass Index	24.96 (3.37)	24.42 (3.84)
Mean cognitive function	0.08 (0.54)	0.11 (0.52)
Dispersion	0.53 (0.33)	0.49 (0.26)
Trains their body		
Y	139 (68.1%)	207 (55.5%)
N	65 (31.9%)	162 (43.7%)
NA	0 (0.0%)	4 (1.0%)
Smoker		
Y	147 (72.1%)	288 (77.2%)
N	57 (27.9%)	81 (21.7%)
NA	0 (0.0%)	4 (1.1%)
Stroke history		
Y	23 (11.3%)	29 (7.8%)
N	179 (87.7%)	342 (92.0%)
NA	2 (1.0%)	2 (0.5%)

Note. NA = Not applicable.

Table 2. Mean and standard deviation of each of the Cognitive Tests included in the derivation of the Dispersion scores in men and women

Cognitive Test	Mean (SD)	
	Men	Women
Block Design	11.36 (7.49)	11.70(6.89)
Clock	13.84 (2.79)	13.85(8.15)
Digit Span Backwards	3.27(1.49)	3.40(1.47)
Digit Span Forwards	5.62(1.26)	5.39(1.17)
Digit Symbol	24.31(10.85)	
Figure	15.57(4.23)	15.45(4.04)
Information	31.77(9.16)	26.05(11.52)
Recall	5.81(2.42)	6.69(2.39)
Correspondence	7.21(2.44)	8.15(2.21)
Recognition	9.89(0.47)	9.61(1.33)
Naming	9.89(0.47)	10 (0.1)
Prose Recall	9.13(4.30)	9.90(3.69)
Synonyms	16.64(6.59)	16.92(5.58)

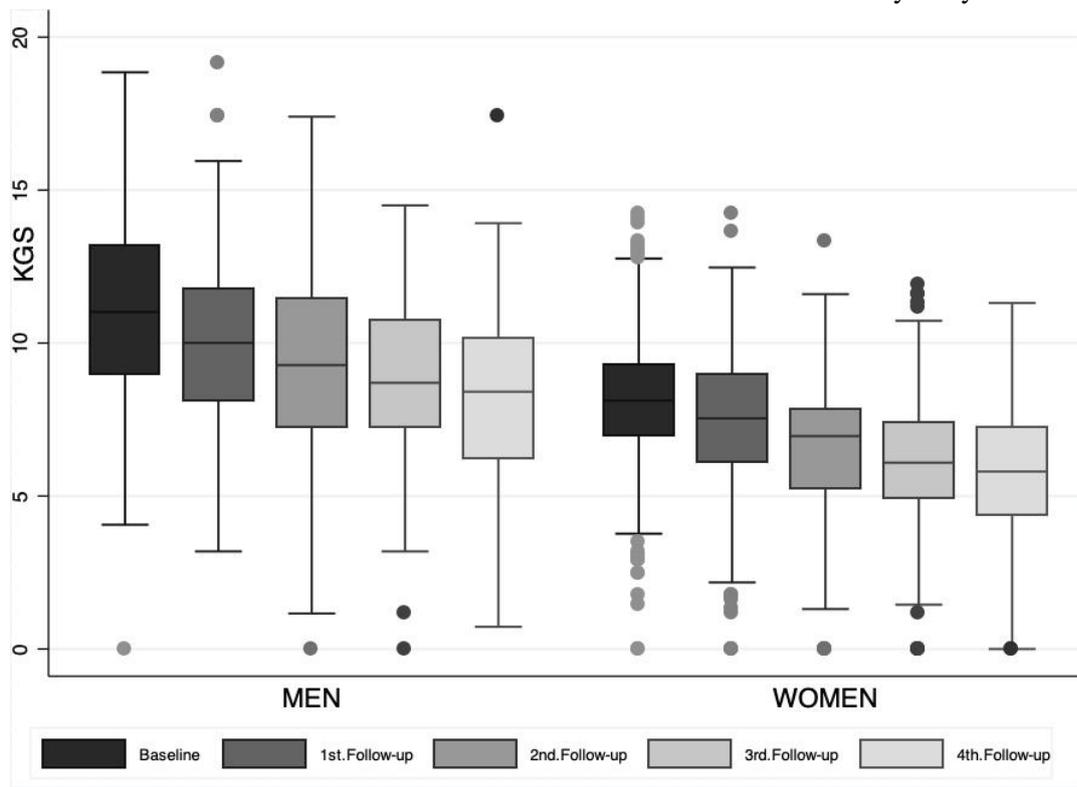
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Table 3. Results from the linear mixed effects model fitted to grip strength measures in a sample of participants in the OCTO-Twin study who remained free of dementia during the study follow up.

	Men		Women	
Fixed effects	Beta (SE) [95% CI]	p-value	Beta (SE) [95% CI]	p-value
<i>Grip strength level</i>	11.57(0.53) [10.68,12.44]	<0.001	7.72(0.32) [7.09,8.34]	0.000
Dispersion	-2.00(0.73) [-3.46,-0.53]	0.007	0.11(0.51) [-0.20,-0.04]	0.83
Mean Cognitive function	2.18(0.79) [0.71,3.64]	0.006	0.93(0.51) [-0.05,1.92]	0.07
Baseline age	-0.19(0.07) [-0.31,-0.06]	0.01	-0.12(0.05) [-0.20,-0.04]	0.003
Body Mass Index	0.01(0.05) [-0.11,0.11]	0.99	0.08(0.03) [0.04,0.13]	0.002
Physically active	0.68(0.42) [-0.07,1.44]	0.10	0.70 (0.28) [0.25,1.14]	0.002
Stroke	-0.59(0.63) [-1.71,0.53]	0.35	-0.21(0.42) [-1.02,0.58]	0.61
Dispersion *Mean Cognitive performance	-3.16(1.17) [-5.09,-1.20]	0.007	-0.30(0.86) [-1.75,1.14]	0.72
<i>Grip strength Rate of change</i>	-0.45(0.11) [-0.63,-0.26]	0.00	-0.36(0.02) [-0.47,-0.23]	0.00
Dispersion	0.06(0.15) [-0.24,0.36]	0.67	0.02(0.09) [-0.15,0.21]	0.81
Mean Cognitive function	-0.49(0.15) [-0.87,-0.02]	0.002	-0.002(0.12) [-0.24,0.24]	0.99
Baseline age	-0.007(0.02) [-0.03,0.01]	0.68	0.008(0.005) [-0.01,0.01]	0.12
Body Mass Index	0.02(0.01) [-0.03,0.03]	0.90	-0.008(0.005) [-0.02,0.15]	0.12
Physically active	-0.06(0.08) [-0.20,0.07]	0.45	-0.06(0.04) [-0.13,0.02]	0.15
Stroke	-0.01(0.14) [-0.32,0.29]	0.94	-0.15(0.08) [-0.37,0.06]	0.04
Dispersion *Mean Cognitive performance	1.00(0.23) [0.41,1.57]	0.00	0.17(0.16) [-0.25,0.60]	0.29

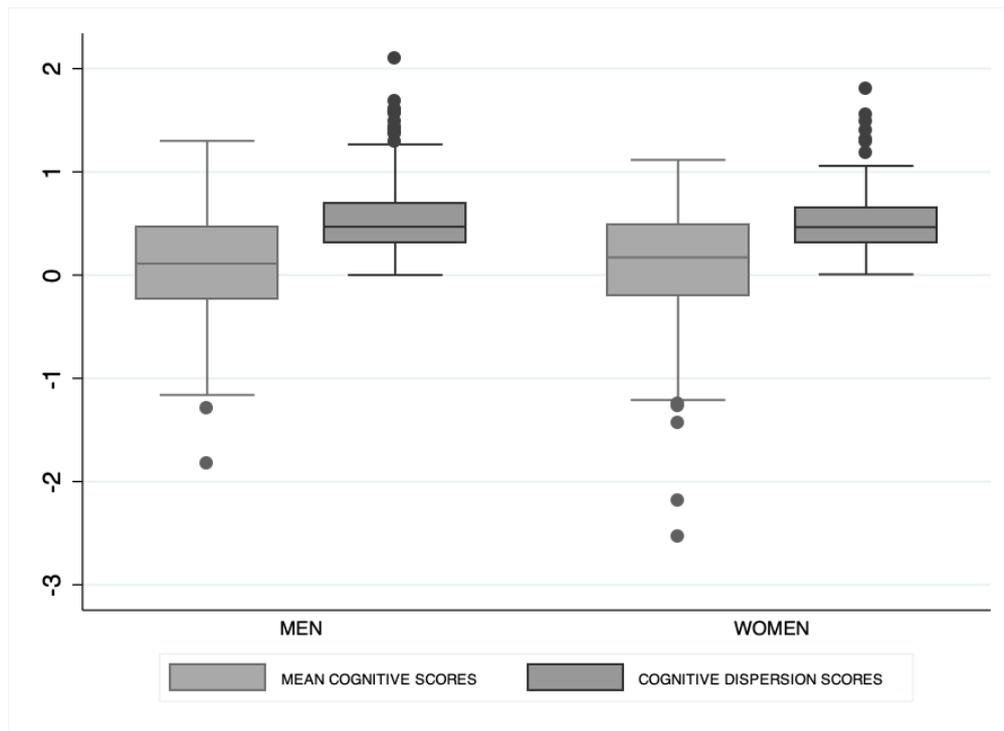
Notes. Random effects: intercept: 2.13, rate of change 0.15, error 1.21, corr (intercept, slope) =-0.49

Figure 1. Box plots of grip strength measurements at baseline and at each of the study follow up data collection waves for men and women who were free from dementia at study entry.



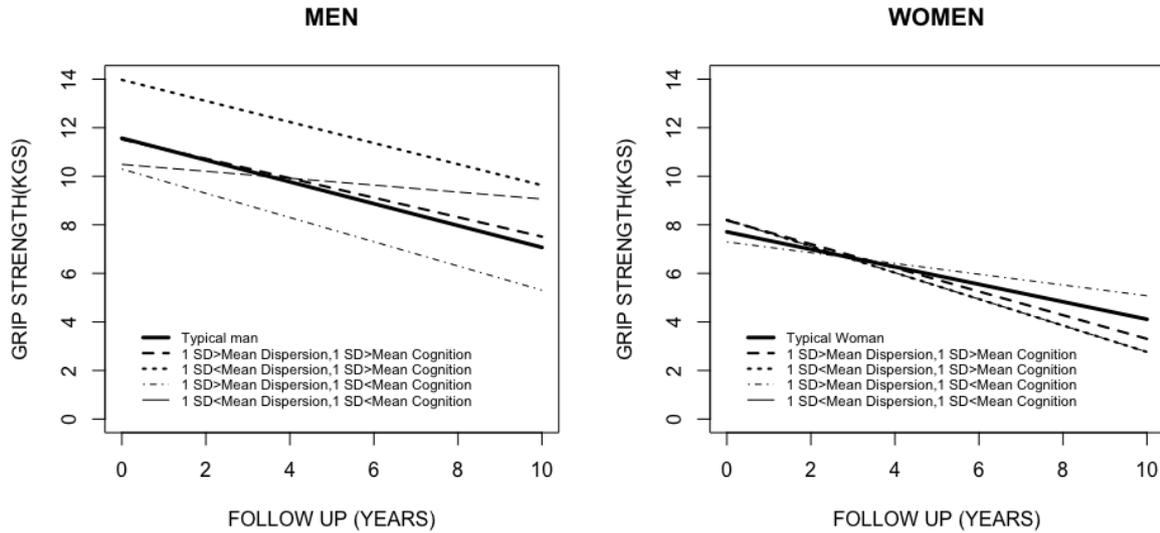
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Figure 2. Box plots of mean cognitive scores and dispersion scores of men and women who were free from dementia at baseline



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Figure 3. Estimated trajectories of a typical man and woman and for individuals with various levels of mean and dispersion scores



Notes. Sample sizes for groups were as follows: 1 SD>mean dispersion, 1SD>mean cognition: n=30; 1SD<mean dispersion, 1SD> mean cognition: n=26; 1SD>mean dispersion, 1SD<mean dispersion: n=113; 1SD<mean dispersion, 1 SD<mean cog: n=35

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