HHS Public Access

Author manuscript

Neurobiol Aging. Author manuscript; available in PMC 2019 June 01.

Published in final edited form as:

Neurobiol Aging. 2018 June ; 66: 68–74. doi:10.1016/j.neurobiolaging.2017.11.017.

The association between peripheral total IGF-1, IGFBP-3, and their molar ratio levels and functional and cognitive outcomes in the Mayo Clinic Study of Aging

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Abstract

Levels of insulin-like growth factor (IGF)-1, IGF binding protein (IGFBP)-3, and their ratio in the blood may be useful for monitoring those at risk of cognitive and functional decline. However, the association between IGF measures and functional and cognitive outcomes has been mixed, and the associations may vary by sex. The present study investigated the cross-sectional, sex-specific associations between serum measures total IGF-1, IGFBP-3, and the IGF-1/IGFBP-3 ratio, gait speed, and cognition in 1,320 cognitively unimpaired participants aged 50-95 enrolled in the Mayo Clinic Study of Aging. We utilized multivariable linear regression models to determine the association between IGF measures and gait speed or cognitive test performance by sex. IGF measures were not associated with cognitive or functional performance among men. Among women, higher levels of log total IGF-1 and IGFBP-3 were associated with better performance in attention, visuospatial, and global cognitive domains, independent of gait speed. These findings suggest that among women IGF measures are associated with cognition, and these associations are independent of function.

Keywords

IGF-1; Function; Cognition; Aging

1. Introduction

As the population ages, functional (e.g., frailty, sarcopenia) and cognitive impairment are becoming increasingly prevalent. Cognitive and functional impairment are related, such that disrupted gait, a robust measure of function, has been associated with cognitive decline

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(Mielke et al., 2013, Savica et al., 2017) and dementia-related pathology (Wennberg et al., 2017). Moreover, the combination of cognitive impairment and slow gait has been associated with an increased risk of dementia beyond the risk associated with either of those conditions alone (Waite et al., 2005). Understanding the mechanisms driving functional and cognitive decline, and the relationship between the two, could be important for identifying those at greatest risk of dementia and frailty.

Insulin-like growth factor 1 (IGF-1), which decreases with age, has anti-inflammatory effects, and promotes neuronal plasticity and skeletal muscle formation (Wrigley et al., 2017). Recent evidence has suggested that IGF-1 may be related to both cognitive and functional performance; however, the direction and strength of these associations has been mixed. While some studies have shown that lower levels of circulating IGF-1 are associated with poorer cognition (Dik et al., 2003, Kalmijn et al., 2000, Sanders et al., 2014), other studies have found that lower IGF-1 levels are associated with better cognition (Perice et al., 2016, Tumati et al., 2016), or that there was no association (Licht et al., 2014). Studies have also shown that lower levels of IGF-1 are associated with slow gait speed (Doi et al., 2015) and incident disability (as certified by Long Term Care Insurance) (Doi et al., 2016), but, again, other studies have found trends for an opposite (Meng et al., 2015) or null (Perice et al., 2016) association.

In the periphery, approximately 99% of circulating IGF-1 is bound to IGF binding proteins (IGFBPs), with more than 80% bound to IGFBP-3. The remaining 1% of circulating IGF-1 remains free, in a biologically available form (Favelyukis et al., 2001, Rajaram et al., 1997). Unbound IGF-1 can cross the blood brain barrier (Anlar et al., 1999, Coculescu, 1999). Higher levels of IGF-1 are associated with better outcomes (e.g., proliferation, function, cognition), and within the brain, IGF-1 is associated with neuron proliferation and differentiation, and myelination (Anlar et al., 1999, Coculescu, 1999). The ratio of IGF-1 to IGFBP-3 is considered a proxy for bioavailable IGF-1 (Rajaram et al., 1997). Few studies have investigated the association between levels of IGFBP-3 and the IGF-1/IGFBP-3 ratio with cognitive and functional outcomes. In community-based samples, lower IGFBP-3 levels were associated with poorer cognition (Landi et al., 2007, Sanders et al., 2014), but not with measures of function (i.e., grip strength, gait speed) (Sanders et al., 2014)

We investigated the cross-sectional associations between levels of total IGF-1, IGFBP-3, and the ratio of IGF-1/IGFBP-3 and gait speed and cognitive test performance among cognitively unimpaired (CU) adults aged 50 to 95 years enrolled in the Mayo Clinic Study of Aging (MCSA). We hypothesized that higher total IGF-1 and IGFBP-3 levels and the IGF-1/IGFBP-3 ratio would be associated with faster gait speed and better cognitive test performance. Because past research (Doi et al., 2016, Meng et al., 2015, Perice et al., 2016) has shown that sex modifies the association between IGF measures and cognitive and functional outcomes, we investigated these associations separately for men and women.

2. Methods

2.1. Participants

The MCSA is a prospective population-based study aimed at characterizing the incidence and prevalence of mild cognitive impairment (MCI) in Olmsted County, Minnesota (Roberts et al., 2008). In 2004, Olmsted County residents between the ages of 70 and 89 were identified for recruitment using an age- and sex-stratified random sampling design to ensure that men and women were equally represented in each 10-year age strata. The study was extended to include those aged 50 and older in 2012. The present study included 1,320 CU participants aged 50 years and older, who had total IGF-1 and IGFBP-3 levels, gait assessment, and cognitive testing at the same visit. Participants with a history of stroke, alcoholism, Parkinson's disease, subdural hematoma, and/or normal pressure hydrocephalus were excluded from the present analyses because these conditions are strongly associated with gait disruption.

The study protocols were approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. All participants provided written informed consent.

2.2. Participant assessment

MCSA visits included a physician examination, an interview by a study coordinator, and neuropsychological testing by a psychometrist (Roberts et al., 2008). The physician examination included a medical history review, complete neurological examination, and administration of the Short Test of Mental Status (Kokmen et al., 1991). The study coordinator interview included demographic information, medical history, and questions about memory to both the participant and an informant using the Clinical Dementia Rating (CDR) scale (Morris, 1993).

GAITRite® instrumentation (CIR systems Inc., Havertown, PA) was used to assess gait speed (Hollman et al., 2011). GAITRite® is an electronic walkway 5.6 m in length and 0.9 m wide. Participants were instructed to walk at their normal pace without gait aids on the walkway, initiating and terminating their walk 1 m before and after the walkway. We created a sample-specific gait speed z-score to make outcomes more comparable.

The neuropsychological battery was administered by a psychometrist and included nine tests covering four domains: 1) memory (Auditory Verbal Learning Test Delayed Recall Trial (Rey, 1964); Wechsler Memory Scale-Revised Logical Memory II & Visual Reproduction II) (Wechsler, 1987); 2) language (Boston Naming Test (Kaplan et al., 1983) and Category Fluency (Strauss et al., 2006); 3) attention (Trail Making Test B (Reitan, 1958) and WAIS-R Digit Symbol subtest (Wechsler, 1981); and 4) visuospatial (WAIS-R Picture Completion and Block Design subtests) (Wechsler, 1981). We calculated sample-specific z-scores for all cognitive tests, and created domain scores by averaging the z-scores within each domain. We created a global cognitive score using the z-transformation of the average of the four domains.

We additionally classified participants as having low gait speed if they had a gait speed z-score in the lowest tertile and low cognitive performance if they had a global z-score in the

lowest tertile. We then created an ordinal variable, and participants were coded as '0' if they had neither low gait speed nor cognitive performance; '1' if they met criteria for low gait speed but not cognitive performance; '2' if they met criteria for low cognitive performance but not low gait speed; and '3' if they met criteria for both low cognitive performance and gait speed.

2.3. Diagnostic determination of CU status

For each participant, cognitive performance in each domain was compared with the age-adjusted scores of CU individuals previously obtained using Mayo's Older American Normative Studies (Ivnik et al., 1996, Ivnik et al., 1992a, 1992b). This approach relies on prior normative work and extensive experience with the measurement of cognitive abilities in an independent sample of subjects from the same population. Participants with scores approximately 1 SD or more below the age-specific mean in the general population were considered for a diagnosis of possible MCI. A final decision to diagnose MCI was based on a consensus agreement between the study coordinator, examining physician, and neuropsychologist who evaluated the participant, after taking into account education, prior occupation, visual or hearing deficits, and reviewing all other participant clinical information (Petersen, 2004). Individuals who performed in the normal range and did not meet criteria for MCI or dementia, which was diagnosed using DSM-IV criteria (American Psychiatric Association, 1994), were deemed CU.

2.4. Primary exposure: laboratory analyses of IGF-1 and IGFBP-3

Participants' blood was collected at the in-clinic exam, centrifuged, aliquoted, and stored at −80 °C. Serum total IGF-1 and IGFBP-3 levels were measured at the Mayo Clinic Immunochemical Core Laboratory. Total IGF-1 was a solid-phase, chemiluminescent immunometric assay on the Siemens Immulite 2000 automated immunoassay system (Siemens Healthcare Diagnostics, Deerfield, IL 60015). Intra-assay coefficients of variation (CV's) were 3.5% and 4.2% at 70 and 236 ng/mL, respectively. Inter-assay CV's were 4.9%, 3.5% and 5.0%, at 37, 68 and 225 ng/mL respectively. IGFBP-3 was a solid-phase, chemiluminescent immunometric assay on the Siemens Immulite 2000 automated immunoassay system (Siemens Healthcare Diagnostics, Deerfield, IL 60015). Intra-assay CV's were 4.2% and 2.5% at 1.0 and 4.4 ug/mL respectively. Inter-assay CV's were 4.0% and 3.9% at 1.0 and 4.3 ug/mL, respectively. We calculated the molar ratio of total IGF-1 to IGFBP-3 for each participant as a proxy of free (bioavailable) IGF-1.

2.5. Assessment of covariates

Demographic variables (e.g., age, education) were collected by self-report during the in-clinic exam. Participants' height (cm) and weight (kg) were measured during the in-clinic exam, and used to calculate body mass index (BMI) (kg/m^2). Medical conditions and the Charlson comorbidity index (CCI) (Charlson et al., 1987) were determined for each participant by medical record abstraction using the medical records-linkage system of the Rochester Epidemiology Project (Rocca et al., 2012, St Sauver et al., 2012). Depressive symptoms were assessed using the Beck Depression Inventory (BDI) (Beck et al., 1988); participants with a score of ≥13 were considered to have depression. Participants' blood sample collected in-clinic was also used to determine APOE ε4 genotype.

2.6. Statistical analyses

IGF-1, IGFBP-3, and IGF-1/IGFBP-3 were positively skewed, so they were log-transformed to normalize the distribution. We used Wilcoxon rank sum and Fisher's exact tests to examine participant characteristics by sex. We created tertiles (T1 [lowest], T2, and T3 [highest]) of total IGF-1, IGFBP-3, and IGF-1/IGFBP-3. Linear regression models were then used to determine the association between tertiles of total IGF-1, IGFBP-3, or IGF-1/IGFBP-3 (independent variables) and either gait speed or cognitive z-scores (dependent variables). Multinomial logistic regression models were used to determine the association between continuous levels of log total IGF-1, IGFBP-3, and IGF-1/IGFBP-3 (independent variables) and low gait speed and/or cognitive test performance (dependent variables). Models were adjusted for age, education, BMI, and CCI score. All analyses were stratified by sex and completed using Stata Version 13.0 (StataCorp, College Station, TX).

3. Results

Men, as compared to women, were older, had completed more years of education, had higher BMI, and had more medical comorbidities (Table 1). Additionally, men had faster gait speed, poorer performance on tests of memory, attention, language, and global cognition, and higher levels of total IGF-1 and IGF-1/IGFBP-3. Conversely, women had poorer visuospatial performance and higher levels of IGFBP-3.

3.1. Linear regression analyses

There was no association between any IGF measures and gait speed in men (Table 2). Among women, there was a trend in multivariable models for the highest tertiles of total IGF-1 (B = 0.17, 95% CI [−0.001, 0.34]) and IGFBP-3 (B = 0.15, 95% CI [−0.02, 0.32]) to be associated with faster gait speed, but these associations were not significant at the $p < 0.05$ level. Further, we did not observe any association between IGF measures and cognitive test z-scores among men. Among women, higher levels (T2 and T3) of total IGF-1 were associated with better attention, visuospatial, and global z-scores, though the coefficients were higher for T2 as compared to T3. T2 IGFBP-3 was associated with better attention z-score and higher levels (both T2 and T3) of IGFBP-3 were associated with better visuospatial and global z-scores. These findings suggest an inverse U-shaped association between IGF measures and cognition in women, such that those in T2 performed better on cognitive tests, as compared to T1 or T3.

3.2. Multinomial regression analyses

Given the trend for the association between IGF and gait speed and the significant association for IGF and cognition among women, we next investigated whether continuous IGF measures were associated with risk of low gait speed and/or cognition (defined as the lowest tertile). Among men, there were no associations between any IGF measure and low gait speed or cognitive test performance (Table 3). Among women, higher IGFBP-3 levels were associated with a lower relative risk ratio of low global cognitive performance (relative risk ratio (RRR) = 0.23, 95% CI [0.08, 0.67]) and with both low gait speed and low global cognitive performance combined (RRR = 0.24, 95% CI [0.09, 0.69]).

3.3. Sensitivity analyses

In sensitivity analyses we additionally adjusted for global z-score in models that specified gait speed as the outcome and gait speed in models that specified cognitive z-scores as the outcome. We did not find any evidence that cognitive test performance mediated the association between serum total IGF-1, IGFBP-3, and IGF-1/IGFBP-3 and gait speed, or vice versa. We further adjusted for diabetes treatment (insulin, oral medication), depression, and APOE ε4 genotype, but found these did not alter the results. We examined whether age (50-69 versus ≥70 years old) or APOE ε4 genotype modified the association between IGF-1 or IGFBP-3 levels and gait speed or cognition by adding interaction terms to the models, but found no evidence of effect modification by age or APOE ε4 genotype.

4. Discussion

In this population-based study of 1,320 middle-aged to older participants, higher total IGF-1 and IGFBP-3 levels were cross-sectionally associated with better cognitive test performance among women. Moreover, our findings suggest an inverse U-shaped association between IGF measures and cognition in women, such that those in T2 tended to have better cognitive performance, as compared to those in T1 or T3. Adjusting for gait speed did not affect these associations, suggesting that IGF measures are independently associated with cognition. This finding was further supported using multinomial regression analyses, because, among women, higher IGFBP-3 levels were associated with a lower relative risk ratio of both poor cognition alone and poor cognition and low gait speed combined. The finding that higher IGFBP-3 was associated with reduced risk of low gait speed and cognition combined was likely driven by the association between IGFBP-3 and cognition.

The generative properties of IGF-1 suggest that higher levels would be associated with better cognitive and functional outcomes (Wrigley et al., 2017). IGF-1 is widely expressed in the brain, and in areas related to cognition, including the hypothalamus, cortex, hippocampus, and cerebellum. IGF-1 expression in the brain is associated with axon outgrowth, dendritic maturation, and synaptogenesis, and peripheral IGF-1 increases cellular proliferation in the hippocampus (Aberg et al., 2006). Additionally, it is hypothesized that IGF-1 and IGFBP-3 are increased after hypoxic-ischemic injury in effort to reduce injury after insult (Aberg et al., 2006). IGF-1 has also been shown to be specifically related to Alzheimer's pathology. It decreases tau phosphorylation (Hong and Lee, 1997) and increases amyloid-beta clearance (Carro et al., 2002).

Indeed, past studies have found an association between higher IGF-1 levels and better cognition and function. A recent study among older adults (mean age = 72) found lower serum IGF-1 levels were associated with incident disability, independent of cognitive test performance (Doi et al., 2016). However, in another study, lower IGF-1 levels were significantly associated with MCI diagnosis, but not with slow gait after accounting for confounding variables (Doi et al., 2015). Our findings that total IGF-1 and IGFBP-3 were positively associated with cognitive test performance, but not gait speed, among women in part support these past findings. Together these findings suggest that IGF measures may be more strongly associated with cognition as compared to slow gait. However, we did not

examine the associations with more impaired outcomes, such as disability, so it is still possible that IGF measures are associated with more severe functional phenotypes.

Our results are in contrast to studies that have shown that higher levels of IGF-1 are associated with poorer cognitive and functional outcomes. In the oldest old (≥90 years), lower IGF-1 levels and the ratio IGF-1/IGFBP-3 were associated with living longer and with better functionality (Milman et al., 2014, van der Spoel et al., 2015). Additionally, in a study of adults aged 95 years and older, women, but not men, with lower levels of IGF-1 had lower odds of cognitive impairment (Perice et al., 2016).

These discrepant findings may be potentially explained by differing samples. The oldest old (≥90 years) (Milman et al., 2014, Perice et al., 2016, van der Spoel et al., 2015) may be "super agers" and more robust, thus exhibiting different relationships between peripheral markers and functional and cognitive outcomes compared to individuals who experience normal aging. In the present study, our sample size of individuals aged 90 and older was not large enough (N = 20) to explore this hypothesis with sufficient power.

IGFBP-3 shows proliferative and anti-proliferative effects, both through and independently of IGF-1, and its role in function and cognition has yet to be fully elucidated (Baxter, 2000, Hollowood et al., 2000). In community-dwelling older adults aged 80 and older, lower IGFBP-3 levels were associated with cognitive impairment (Landi et al., 2007). Similarly, in a longitudinal study of older adults (mean age = 76), decreasing IGFBP-3 was associated with a decrease in global cognition, but not with changes in grip strength or gait speed (Sanders et al., 2014). These findings are consistent with the results from the present study. In sum, the available evidence suggests that lower or decreasing IGFBP-3 levels are associated with worse or decreasing cognition. Future research should further investigate these associations and work to determine whether IGFBP-3 is associated with cognitive outcomes independent of IGF-1, through IGF-1-related mechanisms, or both.

Our finding that the association between IGF measures and cognition was stronger in women as compared to men is consistent with past evidence (Doi et al., 2016, Meng et al., 2015, Perice et al., 2016). Women had higher IGFBP-3 levels than men and they performed better in all cognitive domains, except visuospatial. These differences may contribute to these sex-specific associations. However, there is also evidence that the interaction between estrogen and IGF-1 is neuroprotective and promotes skeletal muscle (Garcia-Segura et al., 2010, Tarantino et al., 2013). This may explain why higher levels of IGF-1 and IGFBP-3 in women, but not men, are more strongly associated with better outcomes. However, it should be noted that the majority of women in this sample were post-menopausal, therefore the effects of estrogen may be less robust or proximal. The pattern for observed sex differences should be furthered explored utilizing both basic science and epidemiological methods, to better understand how sex may act as a modifier in the association between IGF measures and cognition and function.

This study has multiple strengths, including the large population-based sample, extensive phenotyping, and multiple measures of cognition. However, the study also has limitations to be considered. We measured total IGF-1 and IGFBP-3 and used the ratio of the two to create

a proxy measure of bioavailable IGF-1. Although this ratio has been widely accepted as a proxy (Rajaram et al., 1997), it still is not as accurate as a direct measure of free IGF-1. Additionally, our findings may not be directly generalizable to other populations. In particular, Olmsted County residents are largely of northern European ancestry and IGF-1 and IGFBP-3 levels have been shown to vary by race/ethnicity (Berrigan et al., 2009); thus, the study need to be replicated in other ethnicities. Finally, this study is cross-sectional, so directionality cannot be inferred. Future longitudinal studies are needed to further investigate the association between total IGF-1, IGFBP-3, and IGF-1/IGFBP-3 and cognitive and functional outcomes.

5. Conclusions

These findings show that total IGF-1 and IGFBP-3 are associated with measures of cognition, and that these associations are stronger among women and independent of gait speed. Overall, though, evidence of direction of these associations and how they may be modified by sex and/or age is conflicting. Future longitudinal research is needed to fully elucidate these relationships. If validated, peripheral markers, such as IGF-1 and IGFBP-3, may prove to be useful in understanding mechanisms of functional and cognitive decline and impairment, and could potentially be harnessed to evaluate patients in clinical settings.

Acknowledgments

This work was supported by the National Institutes of Health/National Institute on Aging grants U01 AG006786, R01 AG011378, R01 AG041851, P50 AG44170, RF1 AG55151, and R01 AG049704; the Robert H. and Clarice Smith and Abigail van Buren Alzheimer's Disease Research Program, and was made possible by the Rochester Epidemiology Project (R01 AG034676).

Disclosure statement

Dr. Wennberg, Mr. Hagen, and Dr. Hollman have no disclosures to report. Drs. Machulda receives research support from the National Institutes of Health (U01 AG006786). Dr. Roberts receives research support from the National Institutes of Health (U01 AG006786) and an unrestricted research grant from F. Hoffman-La Roche. Dr. Knopman served as Deputy Editor for *Neurology*®; serves on a Data Safety Monitoring Board for Lundbeck Pharmaceuticals and for the DIAN study; is an investigator in clinical trials sponsored by TauRx Pharmaceuticals, Lilly Pharmaceuticals and the Alzheimer's Disease Cooperative Study; and receives research support from the NIH (R01 AG011378, P50 AG016574, U01 AG006786, AG029550, AG032306, and U01 HL096917). Dr. Petersen serves on scientific advisory boards for Roche, Inc., Merck, Inc., Biogen, Inc., and Genentech, Inc.; receives royalties from the publication of *Mild Cognitive Impairment* (Oxford University Press, 2003); and receives research support from the National Institutes of Health (P50 AG016574, U01 AG006786, U01 AG024904, and R01 AG011378). Dr. Mielke served as a consultant to Eli Lilly and Lysosomal Therapeutics, Inc., and receives research support from the National Institutes of Health (R01 AG49704, P50 AG44170, U01 AG06786, RF1 AG55151), Department of Defense (W81XWH-15-1), and unrestricted research grants from Biogen, Roche, and Lundbeck.

References

Aberg ND, Brywe KG, Isgaard J. Aspects of growth hormone and insulin-like growth factor-I related to neuroprotection, regeneration, and functional plasticity in the adult brain. TheScientificWorldJournal. 2006; 6:53–80.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Washington, DC: 1994.

Anlar B, Sullivan KA, Feldman EL. Insulin-like growth factor-I and central nervous system development. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme. 1999; 31(2–3):120–5. [PubMed: 10226791]

Baxter RC. Insulin-like growth factor (IGF)-binding proteins: interactions with IGFs and intrinsic bioactivities. American journal of physiology Endocrinology and metabolism. 2000; 278(6):E967–76. [PubMed: 10826997]

Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988; 56(6):893–7. [PubMed: 3204199]

Berrigan D, Potischman N, Dodd KW, Hursting SD, Lavigne J, Barrett JC, et al. Race/ethnic variation in serum levels of IGF-I and IGFBP-3 in US adults. Growth hormone & IGF research: official journal of the Growth Hormone Research Society and the International IGF Research Society. 2009; 19(2):146–55.

Carro E, Trejo JL, Gomez-Isla T, LeRoith D, Torres-Aleman I. Serum insulin-like growth factor I regulates brain amyloid-beta levels. Nature medicine. 2002; 8(12):1390–7.

Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5):373–83. [PubMed: 3558716]

Coculescu M. Blood-brain barrier for human growth hormone and insulin-like growth factor-I. Journal of pediatric endocrinology & metabolism: JPEM. 1999; 12(2):113–24. [PubMed: 10392357]

Dik MG, Pluijm SM, Jonker C, Deeg DJ, Lomecky MZ, Lips P. Insulin-like growth factor I (IGF-I) and cognitive decline in older persons. Neurobiol Aging. 2003; 24(4):573–81. [PubMed: 12714114]

Doi T, Shimada H, Makizako H, Tsutsumimoto K, Hotta R, Nakakubo S, et al. Association of insulin-like growth factor-1 with mild cognitive impairment and slow gait speed. Neurobiol Aging. 2015; 36(2):942–7. [PubMed: 25467636]

Doi T, Shimada H, Makizako H, Tsutsumimoto K, Hotta R, Nakakubo S, et al. Insulin-Like Growth Factor-1 Related to Disability Among Older Adults. J Gerontol A Biol Sci Med Sci. 2016; 71(6): 797–802. [PubMed: 26424830]

Favelyukis S, Till JH, Hubbard SR, Miller WT. Structure and autoregulation of the insulin-like growth factor 1 receptor kinase. Nature structural biology. 2001; 8(12):1058–63. [PubMed: 11694888]

Garcia-Segura LM, Arevalo MA, Azcoitia I. Interactions of estradiol and insulin-like growth factor-I signalling in the nervous system: new advances. Prog Brain Res. 2010; 181:251–72. [PubMed: 20478442]

Hollman JH, McDade EM, Petersen RC. Normative spatiotemporal gait parameters in older adults. Gait Posture. 2011; 34(1):111–8. [PubMed: 21531139]

Hollowood AD, Lai T, Perks CM, Newcomb PV, Alderson D, Holly JM. IGFBP-3 prolongs the p53 response and enhances apoptosis following UV irradiation. International journal of cancer. 2000; 88(3):336–41. [PubMed: 11054660]

Hong M, Lee VM. Insulin and insulin-like growth factor-1 regulate tau phosphorylation in cultured human neurons. The Journal of biological chemistry. 1997; 272(31):19547–53. [PubMed: 9235959]

Ivnik RJ, Malec JF, Smith GE, Tangalos EG, Petersen RC. Neuropsychological tests' norms above age 55: COWAT, BNT, MAE token, WRAT-R reading, AMNART, STROOP, TMT, and JLO. The Clinical Neuropsychologist. 1996; 10(3):262–78.

Ivnik RJ, Malec JF, Smith GE, Tangalos EG, Petersen RC, Kokmen E, et al. Mayo's older americans normative studies: Updated AVLT norms for ages 56 to 97. Clinical Neuropsychologist. 1992a; 6(sup001):83–104.

Ivnik RJ, Malec JF, Smith GE, Tangalos EG, Petersen RC, Kokmen E, et al. Mayo's older americans normative studies: WAIS-R norms for ages 56 to 97. Clinical Neuropsychologist. 1992b; 6(sup001):1–30.

Kalmijn S, Janssen JA, Pols HA, Lamberts SW, Breteler MM. A prospective study on circulating insulin-like growth factor I (IGF-I), IGF-binding proteins, and cognitive function in the elderly. The Journal of clinical endocrinology and metabolism. 2000; 85(12):4551–5. [PubMed: 11134107]

Kaplan, E., Goodglass, H., Weintraub, S. Boston Naming Test. Philadelphia: Lee & Febiger; 1983.

Kokmen E, Smith GE, Petersen RC, Tangalos E, Ivnik RC. The short test of mental status. Correlations with standardized psychometric testing. Archives of neurology. 1991; 48(7):725–8. [PubMed: 1859300]

Landi F, Capoluongo E, Russo A, Onder G, Cesari M, Lulli P, et al. Free insulin-like growth factor-I and cognitive function in older persons living in community. Growth hormone & IGF research: official journal of the Growth Hormone Research Society and the International IGF Research Society. 2007; 17(1):58–66.

Licht CM, van Turenhout LC, Deijen JB, Koppes LL, van Mechelen W, Twisk JW, et al. The Association between IGF-1 Polymorphisms, IGF-1 Serum Levels, and Cognitive Functions in Healthy Adults: The Amsterdam Growth and Health Longitudinal Study. International journal of endocrinology. 2014; 2014:181327. [PubMed: 25114679]

Meng Y, Wu H, Yang Y, Du H, Xia Y, Guo X, et al. Relationship of anabolic and catabolic biomarkers with muscle strength and physical performance in older adults: a population-based cross-sectional study. BMC musculoskeletal disorders. 2015; 16:202. [PubMed: 26286594]

Mielke MM, Roberts RO, Savica R, Cha R, Drubach DI, Christianson T, et al. Assessing the temporal relationship between cognition and gait: slow gait predicts cognitive decline in the Mayo Clinic Study of Aging. J Gerontol A Biol Sci Med Sci. 2013; 68(8):929–37. [PubMed: 23250002]

Milman S, Atzmon G, Huffman DM, Wan J, Crandall JP, Cohen P, et al. Low insulin-like growth factor-1 level predicts survival in humans with exceptional longevity. Aging cell. 2014; 13(4):769–71. [PubMed: 24618355]

Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993; 43:2412–4.

Perice L, Barzilai N, Verghese J, Weiss EF, Holtzer R, Cohen P, et al. Lower circulating insulin-like growth factor-I is associated with better cognition in females with exceptional longevity without compromise to muscle mass and function. Aging. 2016; 8(10):2414–24. [PubMed: 27744417]

Petersen RC. Mild cognitive impairment as a diagnostic entity. Journal of internal medicine. 2004; 256(3):183–94. [PubMed: 15324362]

Rajaram S, Baylink DJ, Mohan S. Insulin-like growth factor-binding proteins in serum and other biological fluids: regulation and functions. Endocrine reviews. 1997; 18(6):801–31. [PubMed: 9408744]

Reitan RM. Validity of the trail making test as an indicator of organic brain damage. Perceptual and Motor Skills. 1958; 8:271–6.

Rey A. L'examen psychologique dans les cas d'encephalopathie traumatique. Archives de Psychologie. 1964; 28:286–340.

Roberts RO, Geda YE, Knopman DS, Cha RH, Pankratz VS, Boeve BF, et al. The Mayo Clinic Study of Aging: design and sampling, participation, baseline measures and sample characteristics. Neuroepidemiology. 2008; 30(1):58–69. [PubMed: 18259084]

Rocca WA, Yawn BP, St Sauver JL, Grossardt BR, Melton LJ 3rd. History of the Rochester Epidemiology Project: half a century of medical records linkage in a US population. Mayo Clin Proc. 2012; 87(12):1202–13. [PubMed: 23199802]

Sanders JL, Ding V, Arnold AM, Kaplan RC, Cappola AR, Kizer JR, et al. Do changes in circulating biomarkers track with each other and with functional changes in older adults? J Gerontol A Biol Sci Med Sci. 2014; 69(2):174–81. [PubMed: 23811185]

Savica R, Wennberg AM, Hagen C, Edwards K, Roberts RO, Hollman JH, et al. Comparison of Gait Parameters for Predicting Cognitive Decline: The Mayo Clinic Study of Aging. J Alzheimers Dis. 2017; 55(2):559–67. [PubMed: 27662317]

St Sauver JL, Grossardt BR, Yawn BP, Melton LJ 3rd, Pankratz JJ, Brue SM, et al. Data resource profile: the Rochester Epidemiology Project (REP) medical records-linkage system. International journal of epidemiology. 2012; 41(6):1614–24. [PubMed: 23159830]

Strauss, E., Sherman, EM., Spreen, O. A compendium of neuropsychological tests: Administration, norms, and commentary. 3rd. New York: Oxford University Press; 2006.

Tarantino U, Baldi J, Celi M, Rao C, Liuni FM, Iundusi R, et al. Osteoporosis and sarcopenia: the connections. Aging clinical and experimental research. 2013; 25(Suppl 1):S93–5. [PubMed: 24046056]

Tumati S, Burger H, Martens S, van der Schouw YT, Aleman A. Association between Cognition and Serum Insulin-Like Growth Factor-1 in Middle-Aged & Older Men: An 8 Year Follow-Up Study. PLoS One. 2016; 11(4):e0154450. [PubMed: 27115487]

van der Spoel E, Rozing MP, Houwing-Duistermaat JJ, Slagboom PE, Beekman M, de Craen AJ, et al. Association analysis of insulin-like growth factor-1 axis parameters with survival and functional status in nonagenarians of the Leiden Longevity Study. Aging. 2015; 7(11):956–63. [PubMed: 26568155]

Waite LM, Grayson DA, Piguet O, Creasey H, Bennett HP, Broe GA. Gait slowing as a predictor of incident dementia: 6-year longitudinal data from the Sydney Older Persons Study. J Neurol Sci. 2005; 229–230:89–93.

Wechsler, D. Wechsler Adult Intelligence Scale - Revised Manual. New York: The Psychological Corporation; 1981.

Wechsler, D. Wechsler Memory Scale - Revised Manual. San Antonio, TX: Psychological Corporation; 1987.

Wennberg AM, Savica R, Mielke MM. Association between Various Brain Pathologies and Gait Disturbance. Dement Geriatr Cogn Disord. 2017; 43(3–4):128–43. [PubMed: 28152532]

Wrigley S, Arafa D, Tropea D. Insulin-Like Growth Factor 1: At the Crossroads of Brain Development and Aging. Frontiers in cellular neuroscience. 2017; 11:14. [PubMed: 28203146]

Table 1

Participant characteristics at baseline by sex, median (IQR) or N (%)

	All (N=1,320)	Men (N=701)	Women (N=619)	*p*
Age	71.7 (63.5, 78.0)	72.3 (64.2, 78.9)	71.3 (63.0, 77.4)	**0.027**
Education	14 (12, 16)	16 (12, 17)	14 (12, 16)	**<0.001**
Body mass index (kg/m^2)	27.8 (25.1, 31.3)	28.3 (25.5, 31.0)	27.4 (24.3, 31.8)	**0.014**
Charlson comorbidity index score	5 (3, 7)	5 (3, 8)	5 (3, 7)	**<0.001**
Hypertension	784 (60)	445 (64)	339 (56)	**0.002**
CABG	67 (5)	56 (8)	11 (2)	**<0.001**
Myocardial infarction	162 (12)	125 (18)	37 (6)	**<0.001**
Cancer	256 (23)	152 (26)	104 (21)	0.073
Gait speed (m/s)	1.0 (0.95, 1.3)	1.0 (1.0, 1.3)	1.0 (0.95, 1.3)	**<0.001**
Z Memory	0.98 (0.21, 1.66)	0.76 (0.05, 1.42)	1.22 (0.50, 1.93)	**<0.001**
Z Attention	0.97 (0.33, 1.52)	0.78 (0.15, 1.32)	1.12 (0.56, 1.69)	**<0.001**
Z Language	0.72 (0.12, 1.28)	0.58 (0.04, 1.16)	0.83 (0.27, 1.42)	**<0.001**
Z Visuospatial	0.83 (0.22, 1.43)	0.98 (0.35, 1.60)	0.67 (0.05, 1.27)	**<0.001**
Z Global	1.07 (0.43, 1.67)	0.96 (0.34, 1.55)	1.22 (0.56, 1.80)	**<0.001**
Low gait and cognitive performance *				**<0.001**
Unimpaired	643 (50)	332 (49)	311 (51)	
Low gait speed	213 (17)	86 (12)	127 (21)	
Low cognitive performance	210 (16)	142 (21)	68 (11)	
Low gait speed & cognitive performance	214 (17)	115 (17)	99 (16)	
Total IGF-1 (ng/ml)	118.0 (92.0, 149.0)	125.0 (99.0, 156.0)	111.0 (85.0, 141.0)	**<0.001**
IGFBP-3 (μg/ml)	3.5 (2.9, 4.1)	3.3 (2.7, 3.8)	3.8 (3.2, 4.4)	**<0.001**
IGF-1/IGFBP-3	0.14 (0.12, 0.17)	0.16 (0.13, 0.19)	0.12 (0.10, 0.15)	**<0.001**

* Defined as the lowest tertile of gait speed and z-score global cognitive score.

Table 2

Cross-sectional association between IGF-1, IGFBP-3, IGF-1/IGFBP-3 and gait speed and cognition among cognitively unimpaired MCSA participants aged 50-95 by sex

		Total IGF-1			**IGFBP-3**			**IGF-1/IGFBP-3**	
	N	**B (95% CI)**	***p***	**N**	**B (95% CI)**	***p***	**N**	**B (95% CI)**	***p***
Men									
Z Gait speed	699			701			699		
Tertile 1		Reference			Reference			Reference	
Tertile 2		0.09 (−0.06, 0.24)	0.219		0.06 (−0.09, 0.20)	0.461		0.15 (−0.03, 0.33)	0.094
Tertile 3		0.04 (−0.11, 0.19)	0.597		0.11 (−0.06, 0.27)	0.196		0.04 (−0.13, 0.21)	0.627
Z Memory	699			701			699		
Tertile 1		Reference			Reference			Reference	
Tertile 2		0.15 (−0.01, 0.30)	0.068		−0.03 (−0.19, 0.13)	0.700		0.05 (−0.14, 0.24)	0.620
Tertile 3		0.05 (−0.11, 0.20)	0.568		−0.09 (−0.27, 0.08)	0.278		0.11 (−0.07, 0.29)	0.244
Z Attention	682			684			682		
Tertile 1		Reference			Reference			Reference	
Tertile 2		−0.006 (−0.13, 0.12)	0.931		−0.08 (−0.20, 0.05)	0.247		0.002 (−0.15, 0.16)	0.978
Tertile 3		−0.02 (−0.15, 0.11)	0.747		−0.02 (−0.16, 0.12)	0.736		0.004 (−0.14, 0.15)	0.957
Z Language	689			691			689		
Tertile 1		Reference			Reference			Reference	
Tertile 2		0.10 (−0.04, 0.23)	0.150		−0.07 (−0.20, 0.07)	0.343		0.07 (−0.10, 0.23)	0.411
Tertile 3		0.01 (−0.12, 0.15)	0.842		−0.06 (−0.21, 0.09)	0.409		0.07 (−0.09, 0.23)	0.372
Z Visuospatial	679			681			679		
Tertile 1		Reference			Reference			Reference	
Tertile 2		−0.02 (−0.17, 0.13)	0.792		−0.04 (−0.19, 0.11)	0.593		0.04 (−0.14, 0.23)	0.640
Tertile 3		0.05 (−0.10, 0.20)	0.528		0.11 (−0.06, 0.27)	0.207		−0.02 (−0.19, 0.16)	0.841
Z Global	673			675			673		
Tertile 1		Reference			Reference			Reference	
Tertile 2		0.06 (−0.07, 0.19)	0.346		−0.08 (−0.20, 0.05)	0.240		0.05 (−0.11, 0.20)	0.541
Tertile 3		0.03 (−0.10, 0.16)	0.683		−0.04 (−0.18, 0.10)	0.608		0.05 (−0.10, 0.20)	0.495
Women		Total IGF-1			IGFBP-3			IGF-1/IGFBP-3	
	N	B (95% CI)	p	N	B (95% CI)	p	N	B (95% CI)	p

	Total IGF-1			IGFBP-3			IGF-1/IGFBP-3		
	N	**B (95% CI)**	***p***	**N**	**B (95% CI)**	***p***	**N**	**B (95% CI)**	***p***
Z Gait speed	616			618			616		
Tertile 1		Reference			Reference			Reference	
Tertile 2		0.12 (−0.04, 0.29)	0.151		0.14 (−0.03, 0.31)	0.104		−0.004 (−0.16, 0.15)	0.959
Tertile 3		0.17 (−0.001, 0.34)	0.051		0.15 (−0.02, 0.32)	0.084		0.08 (−0.12, 0.28)	0.413
Z Memory	616			618			616		
Tertile 1		Reference			Reference			Reference	
Tertile 2		0.11 (−0.07, 0.29)	0.234		0.11 (−0.07, 0.30)	0.216		−0.06 (−0.22, 0.11)	0.489
Tertile 3		0.06 (−0.12, 0.25)	0.504		0.12 (−0.07, 0.31)	0.218		−0.11 (−0.33, 0.10)	0.308
Z Attention	611			613			611		
Tertile 1		Reference			Reference			Reference	
Tertile 2		0.27 (0.13, 0.41)	**<0.001**		0.16 (0.02, 0.30)	**0.028**		0.11 (−0.02, 0.24)	0.097
Tertile 3		0.15 (0.005, 0.30)	**0.042**		0.08 (−0.06, 0.23)	0.263		−0.03 (−0.20, 0.14)	0.736
Z Language	612			614			612		
Tertile 1		Reference			Reference			Reference	
Tertile 2		0.11 (−0.04, 0.26)	0.164		0.04 (−0.11, 0.19)	0.626		−0.06 (−0.20, 0.08)	0.393
Tertile 3		0.08 (−0.07, 0.23)	0.302		0.15 (−0.004, 0.31)	0.056		−0.08 (−0.26, 0.09)	0.356
Z Visuospatial	607			609			607		
Tertile 1		Reference			Reference			Reference	
Tertile 2		0.30 (0.13, 0.47)	**<0.001**		0.21 (0.05, 0.38)	**0.013**		0.07 (−0.09, 0.22)	0.400
Tertile 3		0.25 (0.08, 0.43)	**0.004**		0.18 (0.003, 0.35)	**0.046**		0.09 (−0.11, 0.29)	0.371
Z Global	602			604					
Tertile 1		Reference			Reference			Reference	
Tertile 2		0.23 (0.09, 0.38)	**0.002**		0.16 (0.009, 0.30)	**0.037**		0.01 (−0.12, 0.14)	0.865
Tertile 3		0.16 (0.007, 0.31)	**0.041**		0.16 (0.01, 0.31)	**0.034**		−0.05 (−0.22, 0.13)	0.594

Models adjusted for age, education, body mass index, and the Charlson comorbidity index score.

Neurobiol Aging. Author manuscript; available in PMC 2019 June 01.

Table 3

Cross-sectional association between log total IGF-1, IGFBP-3, and IGF-1/IGFBP-3 levels and relative risk of low gait speed and/or cognitive test performance among cognitively unimpaired MCSA participants aged 50-95 by sex

Men									
		Log Total IGF-1			**Log IGFBP-3**			**Log IGF-1/IGFBP-3**	
	N	**RRR (95% CI)**	***p***	**N**	**RRR (95% CI)**	***p***	**N**	**RRR (95% CI)**	***p***
Unimpaired	673	Reference		675	Reference		673	Reference	
Low gait speed		0.55 (0.27, 1.13)	0.105		0.45 (0.18, 1.12)	0.087		0.82 (0.28, 2.38)	0.716
Low global cognition		0.63 (0.33, 1.19)	0.153		0.53 (0.23, 1.20)	0.129		0.88 (0.35, 2.24)	0.791
Low gait speed & global cognition		0.74 (0.35, 1.57)	0.429		0.49 (0.18, 1.30)	0.151		1.39 (0.45, 4.30)	0.563
Women		Log Total IGF-1			Log IGFBP-3			Log IGF-1/IGFBP-3	
	N	RRR (95% CI)	p	N	RRR (95% CI)	p	N	RRR (95% CI)	p
Unimpaired	602	Reference		604	Reference		602	Reference	
Low gait speed		0.78 (0.44, 1.38)	0.393		0.47 (0.19, 1.13)	0.091		1.10 (0.49, 2.47)	0.814
Low global cognition		0.67 (0.33, 1.37)	0.275		0.23 (0.08, 0.67)	**0.008**		1.53 (0.53, 4.38)	0.428
Low gait speed & global cognition		0.62 (0.30, 1.26)	0.185		0.24 (0.09, 0.69)	**0.008**		1.33 (0.47, 3.77)	0.587

Low gait speed defined as the lowest tertile.

Low cognitive test performance defined the lowest tertile.

Models adjusted for age, education, body mass index, and the Charlson comorbidity index.

Key: RRR, Relative risk ratio.