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Plasma IGF-I levels and cognitive performance in older women

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Abstract

Background: Emerging biologic and epidemiologic evidence suggests bene ts of insulin-like growth factor-I (IGF-I) in cognitive aging.
Objective: To examine the relation of circulating IGF-I to cognition.
Methods: We measured plasma IGF-I and IGF-binding protein-3 (IGFBP-3) in 590 women aged 60–68 years. An average 10 years later, we administered telephone-based tests of general cognition (Telephone Interview of Cognitive Status [TICS]), verbal memory, category uency, and attention. We estimated multivariable-adjusted mean differences in performance across levels of IGF-I/IGFBP-3 molar ratio.
Results: On the TICS, each standard deviation (S.D.) increase in molar ratio was signi cantly associated with better performance: multivariable-adjusted mean difference = 0.2 units, 95% con dence interval (0.0, 0.4), $p = 0.05$. This effect estimate for each S.D. increase in molar ratio was cognitively equivalent to the mean difference we observed on the TICS between women 1 year apart in age. On a global score combining all tests, there was also a trend of better performance with each S.D. increase in molar ratio ($p = 0.07$).
Conclusions:

One emerging candidate is insulin-like growth factor-I (IGF-I). IGF-I, IGF-II and insulin itself comprise the three growth hormones of the IGF family[24]. Biologic data suggest a relation between IGF-I and brain health. For example, IGF-I both protects against amyloid-induced toxicity in cultured rat neurons and reverses early indicators of degeneration in cells pretreated with harmful amyloid-beta fragments[12]. Consistent with these findings, limited epidemiologic data, largely from very small-scale studies, suggest that higher IGF-I levels may be associated with better cognitive performance[2,28,30,35] and lower risk of cognitive decline[11,23] in older individuals.

Thus, to explore this issue further, we examined the relation between mid-life IGF-I levels and later cognitive perfor-

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mance in a cohort of community-dwelling, older participants of the Nurses' Health Study.

2. Methods

2.1. Nurses• Health Study

The Nurses' Health Study (NHS) is a prospective cohort of 121,700 U.S., female nurses that began in 1976, when the women were aged 30–55 years. Participants complete biennial mailed questionnaires updating information on lifestyle and medical history.

From 1989 to 1990, blood samples were requested from all participants, and one-third agreed to provide them. Nurses were mailed a venipuncture kit, and returned their sample by overnight mail, with a frozen water bottle; the vast majority of samples arrived within 26 h of being drawn. Whole blood samples were centrifuged and aliquotted as plasma, buffy coat, and red blood cells. We previously established that IGF-I and IGFBP-3 levels remain detectable and stable over many years of freezing with these collection and processing methods [18]. Total follow-up for these women, as of 2002 (the most recently completed follow-up period), exceeds 98%. Finally, health and lifestyle characteristics were similar between the whole NHS cohort and those who returned blood samples (e.g., for both groups, mean age was 56 years, mean body mass index was 26 kg/m^2, and mean alcohol intake was 5 g/day; 43% of the entire cohort versus 46% of those who provided blood never smoked), thus there is no obvious source of bias among subjects in the blood cohort.

2.2. Cognitive function assessment

From 1995 to 2001, NHS participants aged 70 years and older, and free of diagnosed stroke, participated in a telephone cognitive assessment. Of those for whom we had telephone numbers, 92% completed the interview (n=19,514). Of these women, 6855 had provided a blood sample. Participation in the cognitive study was similar among those who had and had not given blood, suggesting little possibility for bias in examining associations within those providing samples.

Initially, we used only the Telephone Interview for Cognitive Status (TICS) [14], a telephone version of the Mini-Mental State Examination (MMSE) [15]. We gradually added five other cognitive tests to our battery; thus, the sample size differs somewhat for each test. We administered: immediate and delayed recalls of the East Boston Memory Test (EBMT) [11] to assess verbal memory, as well as a delayed recall of the TICS 10-word list; a test of category fluency, in which women named animals during 1 min; and digita

studies who did not have IGF measures, mean body mass index was 25.4 kg/m^2, 75% had an associate's degree, and 7% had an advanced degree. Thus, despite using a convenience sample for these analyses, there did not appear to be a likelihood of meaningful bias.

Because IGF-I circulates primarily bound to IGFBP-3 [24], we calculated the IGF-I/IGFBP-3 molar ratio, which may re ect the amount of unbound and biologically active IGF-I [27]. IGF-I and IGFBP-3 were assayed by enzyme-linked immunoabsorbent assay in the laboratory of Dr. Michael Pollak, McGill University, Canada, using reagents provided by Diagnostic Systems Laboratory (Webster, Texas). Blinded quality control specimens were used to calculate the intra- and interassay coef cients of variation (CV) ($n = 11$ batches): for IGF-I, these ranges were 3–16% and 5–22%, respectively; for IGFBP-3, the ranges were 4–13% and 8–19%, respectively. We conducted secondary analyses excluding participants from the four batches

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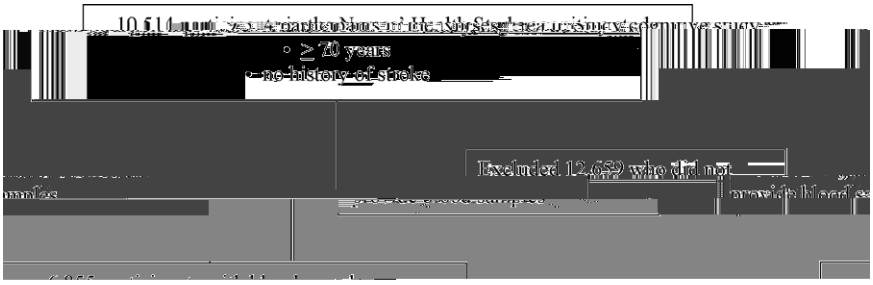

Fig. 1. Determination of population for analysis. At each step, women who were excluded had similar characteristics compared to women who were included.

Table 1
Characteristics of the study population, across quintiles of IGF-I/IGFBP-3 molar ratio

Characteristics at blood draw	Quintile of IGF-I/IGFBP-3 molar ratio				
	1st	2nd	3rd	4th	5th
Median IGF-I (μg/L)	104.6	140.5	155.2	176.1	221.1
Median molar ratio	0.10	0.12	0.14	0.16	0.20
Number of participants	115	120	122	117	116
Mean age (years)	64.2	64.6	64.1	64.4	63.9
Masters/Doctoral degree (%)	10	8	10	9	9
History of hypertension (%)	37	38	39	32	31
Current smoking (%)	17	12	19	22	15
Past smoking (%)	42	37	35	30	41
Alcohol: 0.1–4.9 g/day (%)	24	30	27	32	24
5–14.9 g/day (%)	22	22	17	19	18
15+ g/day (%)	17	9	16	9	9
Antidepressant use history (%)	4	8	7	3	2
Past hormone use (%)	44	33	34	32	33
Median body mass index (kg/m^2)	25.7	25.8	25.5	24.6	24.7
Cognitive performance, average of 10 years after blood draw	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)
TICS	33.5 (3.2)	33.5 (2.5)	33.8 (2.7)	33.7 (2.2)	34.4 (3.1)
Category uency	16.7 (4.7)	17.4 (4.5)	16.9 (4.8)	17.2 (5.3)	17.8 (4.7)
Digit span backwards	6.2 (2.0)	5.9 (2.2)	6.8 (2.4)	6.7 (2.2)	7.2 (2.8)
East Boston Memory Test—immediate recall	9.6 (2.0)	9.3 (1.7)	9.6 (1.7)	9.4 (1.7)	9.7 (1.7)
East Boston Memory Test—delayed recall	8.8 (2.6)	9.1 (1.8)	9.0 (2.1)	8.7 (2.3)	9.1 (2.0)
TICS 10-word list—immediate recall	4.4 (1.6)	4.5 (1.5)	4.6 (1.7)	4.4 (1.5)	5.0 (1.8)
10-word list—delayed recall	2.0 (1.5)	2.0 (1.8)	2.5 (2.0)	2.0 (1.8)	2.7 (2.3)

Table 2
Mean Differences in cognitive function, across levels of IGF-I/IGFBP-3 molar ratio

Cognitive test	Quintile of IGF-I/IGFBP-3 molar ratio					Per S.D.[a] increase in molar ratio
	1st	2nd	3rd	4th	5th	
Global Score[b] (n = 448) age/education-adjusted	−1.4 (−2.7, −0.1)	−1.4 (−2.7, −0.1)	−0.5 (−1.8, 0.7)	−1.3 (−2.6, 0.0)	0.0	0.4 (0.0, 0.8), p = 0.03
Multivariable-adjusted[c] (95% CI)	−1.2 (−2.5, 0.1)	−1.2 (−2.5, 0.1)	−0.6 (−1.8, 0.7)	−1.2 (−2.5, 0.1)	0.0	0.4 (0.0, 0.8), p = 0.07
TICS[b] (n = 590) age/education-adjusted	−0.8 (−1.5, −0.1)	−0.7 (−1.4, 0.0)	−0.4 (−1.1, 0.2)	−0.6 (−1.3, 0.1)	0.0	0.3 (0.0, 0.5), p = 0.03

between blood collection and cognitive testing (n = 34) (data not shown).

4. Discussion

We found that IGF-I, especially the IGF-I/IGFBP-3 ratio, was related to general cognitive function in these older women. Specifically, those in the bottom quintile of IGF-I/IGFBP-3 molar ratio had worse performance on both the TICS and global score than those in the top quintile, with a linear trend of better performance with each S.D. increment in the molar ratio. On the TICS, the mean difference in performance with each S.D. increase in molar ratio was cognitively equivalent to the mean difference we observed on the TICS score between women 1 year apart in age. Findings persisted after adjustment for a wide variety of potential confounders, including health and lifestyle factors.

IGF-I plays a significant part in human brain development and function throughout the life cycle, and accumulating biologic data emphasize its potential role during aging. IGF-I is produced locally in the brain and also passes from the circulation into the brain via the blood–brain barrier [34]; increases in plasma IGF-I directly correspond with increased levels of IGF-I in the cerebrospinal fluid [33]. IGF-I receptors are distributed differentially in the brain, with the highest density of receptors in the medial temporal lobe (i.e., the hippocampus and parahippocampal structures) [41]; this brain region is essential for memory and is particularly associated with cognitive deficits in dementia. IGF-I protects hippocampal rat neurons from toxicity induced amyloid-beta fragments [12]; it has also been shown to increase hippocampal neurogenesis [35]. Together, these findings lend strong support to the idea that IGF-I may compensate for and promote survival of vulnerable neurons in cognition [21].

Although there are limited large-scale epidemiologic data [11,23] on the role of IGF-I in cognitive decline, epidemiologic findings suggest a protective role for IGF-I on cognition [2,28,30,35]. In a study of 186 non-diabetic men and women (aged 55–80 years) in the Rotterdam cohort, Kalmijn et al. [23] found that each S.D. increase in IGF-I/IGFBP-3 molar ratio yielded a 41% reduction in risk for cognitive decline on the MMSE over 2 years. Dik and colleagues [11] observed 1318 men and women (aged 65–88) over 3 years and identified a threshold effect; there was significantly increased risk of decline in information processing speed comparing those in the bottom quintile versus quintiles II–V (1.78, 95% CI 1.19, 2.68), although IGF-I was not related to decline in several other cognitive tests (immediate and delayed verbal recall, fluid intelligence, and MMSE).

It is important to note that circulating IGF-I levels are likely related to multiple disease outcomes in different ways; thus, considering the benefits of “higher” versus “lower” levels of IGF-I in absolute terms is complex. For example, recent community-based prospective studies reported an inverse association between IGF-I levels and risk of ischemic heart disease [22] and congestive heart failure [42]. However, data from our study and other large-scale prospective cohorts have demonstrated that levels of IGF-I and IGF-I/IGFBP-3 molar ratio in the higher end of the normal range may be associated with increased risk of several cancers (breast, prostate, colorectal) [32]. Nonetheless, cancer risk may partly depend on the period of exposure [19]: prospective studies have consistently found no association between IGF-I levels and risk of breast cancer among postmenopausal women, but most investigators have reported elevated risk associated with higher IGF-I levels in premenopausal women [18], especially those under ag31.9(underg 17.91ithoderg 17.91circulating)-30(o

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References

[1] Albert M, Smith LA, Scherr PA, Taylor JO, Evans DA, Funkenstein HH. Use of brief cognitive tests to identify individuals in the community with clinically diagnosed Alzheimer's disease. Intern J Neurosci 1991;57:167–78.

[2] Aleman A, Verhaar HJ, De Haan EH, De Vries WR, Samson MM, Drent ML, et al. Insulin-like growth factor-I and cognitive function in healthy older men. J Clin Endocrinol Metab 1999;84(2): 471–5.

[3] Berwick DM, Murphy JM, Goldman PA, Ware Jr JE, Barsky AJ, Weinstein MC. Performance of a ve-item mental health screening test. Med Care 1991;29:169–76.

[4] Brandt J, Spencer M, Folstein M. The telephone interview for cognitive status. Neuropsych, Neuropsychol, Behav Neurol 1988;1:111–7.

[5] Cardim HJ, Lopes CM, Giannella-Neto D, da Fonseca AM, Pinotti JA. The insulin-like growth factor-I system and hormone replacement therapy. Fertil Steril 2001;75(2):282–7.

[6] Chan JM, Stampfer MJ, Giovannucci E, Gann PH, Ma J, Wilkinson P, et al. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. Science 1998;279(5350):563–6.

[7] Chen P, Ratcliff G, Belle SH, Cauley JA, DeKosky ST, Ganguli M. Patterns of cognitive decline in presymptomatic Alzheimer disease: a prospective community study. Arch Gen Psychiatry 2001;58(9):853–8.

[8] Cherrier MM, Plymate S, Mohan S, Asthana S, Matsumoto AM, Bremner W, et al. Relationship between testosterone supplementation and insulin-like growth factor-I levels and cognition in healthy older men. Psychoneuroendocrinology 2004;29(1):65–82.

[9] DeLellis K, Rinaldi S, Kaaks RJ, Kolonel LN, Henderson B, Le Marchand L. Dietary and lifestyle correlates of plasma insulin-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3): the multiethnic cohort. Cancer Epidemiol Biomarkers Prev 2004;13:1444–51.

[10] den Heijer T, Vermeer SE, van Dijk EJ, Prins ND, Koudstaal PJ, Hofman A, et al. Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. Diabetologia 2003;46(12):1604–10.

[11] Dik MG, Pluijm SM, Jonker C, Deeg DJ, Lomecky MZ, Lips P. Insulin-

[37] Sandhu MS, Heald AH, Gibson JM, Cruickshank JK, Dunger DB, Wareham NJ. Circulating concentrations of insulin-like growth factor-I and development of glucose intolerance: a prospective observational study. Lancet 2002;359:1740–5.

[38] Schernhammer ES, Holly JM, Pollak MN, Hankinson SE. Circulating levels of insulin-like growth factors, their binding proteins, and breast cancer risk. Cancer Epidemiol Biomarkers Prev 2005;14(3):699–704.

[39] Small BJ, Fratiglioni L, Viitanen M, Winblad B, Backman L. The course of cognitive impairment in preclinical Alzheimer disease: three- and 6-year follow-up of a population-based sample. Arch Neurol 2000;57(6):839–44.

[40] Stolk RP, Breteler MM, Ott A, Pols HA, Lamberts SW, Grobbee DE, et al. Insulin and cognitive function in an elderly population: the Rotterdam study. Diabetes Care 1997;20:792–5.

[41] van Dam PS, Aleman A. Insulin-like growth factor-I, cognition and brain aging. Eur J Pharmacol 2004;490:87–95.

[42] Vasan RS, Sullivan LM, D'Agostino RB, Roubenoff R, Harris T, Sawyer DB, et al. Serum insulin-like growth factor I and risk for heart failure in elderly individuals without a previous myocardial infarction: the Framingham Heart Study. Ann Intern Med 2003;139(8):642–8.

[43] Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003;348(13):1215–22.

[44] Wei EK, Ma J, Pollak MN, Rifai N, Fuchs CS, Hankinson SE, et al. A prospective study of C-peptide, insulin-like growth factor-I, insulin-like growth factor binding protein-1, and the risk of colorectal cancer in women. Cancer Epidemiol Biomarkers Prev 2005;14(4):850–5.

[45] Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F. Physical activity, including walking, and cognitive function in older women. JAMA 2004;292(12):1454–61.

[46] Wilson RS, Schneider JA, Barnes LL, Beckett LA, Aggarwal NT, Cochran EJ, et al. The apolipoprotein E epsilon 4 allele and decline in different cognitive systems during a 6-year period. Arch Neurol 2002;59(7):1154–60.