Plasma IGF-I levels and cognitive performance in older women

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Abstract

Background: Emerging biologic and epidemiologic evidence suggests benefits 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 fluency, 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 significantly associated with better performance: multivariable-adjusted mean difference = 0.2 units, 95% confidence 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 ($p = 0.07$). IGF-I levels were not associated with performance in verbal memory.
Conclusions: Higher IGF-I levels may be associated with better general cognition.

Keywords: Insulin-like growth factors; Cognition; Aging

1. Background

A growing body of literature focuses on the role of metabolic factors in cognitive aging. For example, recent work has suggested that elevated insulin secretion has direct negative consequences on cognitive function of older persons [26], after accounting for vascular complications of diabetes [10], and even in the absence of diabetes [29,40]. Such findings have generated interest in identifying related metabolic factors that may impact on cognition.

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) [4], 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) [1] 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 digit span-backwards, in which women repeated backwards increasingly long series of digits, to evaluate attention and working memory. All cognitive tests were administered by telephone under comparable environmental conditions (e.g., all participants were asked to be in a quiet place at home, away from noise or distractions) by specially trained nurses who were unaware of the study hypothesis.

The two primary outcomes of this study were general cognition and also verbal memory, as studies have established that verbal memory is a strong predictor of Alzheimer's disease (AD) development [7,14,39]. For assessing general cognition, we considered the TICS, and a global score that we calculated by summing the z-scores for each of the six cognitive tests. We computed a verbal memory score by summing the z-scores from the immediate and delayed recalls of the EBMT and the 10-word list. The global and verbal memory scores were only calculated for women who completed all component tests. Such composite scores are regularly used in cognitive research [43,46] because they integrate information from a variety of sources and provide a more stable representation of cognition than a single test.

2.3. Reliability and validity of telephone assessments

Since the cognitive function study required numerous interviewers to conduct assessments, we addressed instrument reliability in two ways. To evaluate test–retest reliability, we compared TICS scores among a sub-sample of nurses at two time-points 31 days apart; the Pearson correlation was 0.70 and statistically significant ($p < 0.0001$). We formally assessed inter-interviewer reliability as well: all interviewers were recorded while conducting the cognitive battery, and test scores were then assessed by multiple interviewers; we found correlations of $r \geq 0.95$ for score assignments across interviewers for each test in the battery.

To establish the validity of telephone-based testing compared to the more common and expensive approach of in-person testing, we assessed 61 nuns from the Rush Religious Order Study (a population of high-functioning, highly educated subjects—similar to our health professionals). We compared the global composite score from our telephone-administered interview to the global score from an in-person interview consisting of 21 tests, and we found a correlation of 0.81 comparing overall performance on our brief telephone interview to overall performance measured from an in-person interview.

2.4. Ascertainment of IGF-I measures

Of the 6855 participants in the cognitive study who provided blood samples, 1137 had measures of IGF-I and IGF-binding protein-3 (IGFBP-3), which were previously assayed in nested case-control studies of myocardial infarction, colon polyps, and breast, colon and ovarian cancers. Characteristics of women in the cognitive study who had IGF measures available were quite similar to those with no IGF measures available. For example, mean age at cognitive assessment was 74 years in both groups. Similarly, among the women with IGF measures, mean body mass index was 25.7 kg/m^2, 74% had an associate's degree, and 8% had an advanced graduate degree; while, among the women in the cognitive and blood

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 reflect 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 coefficients 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 with an IGF-I or IGFBP-3 interassay CV > 15%, and results were unchanged. Details of the assay methods have been published previously [36].

2.5. Validity of using a single blood sample to represent long-term levels

Because we used results from a single blood collection, it was important to establish that these samples accurately represent long-term levels. First, there is no evidence of seasonal [17] or diurnal [16] variation in IGF-I; thus, timing of collection is of little concern. In addition, the correlation coefficients for IGF-I and IGFBP-3 measures obtained twice over 5 years ranged from 0.70 to 0.75 in a sample of 49 men from the Physicians' Health Study—a similar cohort of male health professionals [31]. Finally, the best evidence that a single sample is a valid representation of long-term levels is its ability to predict disease risk over many years [6,38]; for example, over 10 years of follow-up, NHS participants with higher baseline plasma levels of IGF-I/IGFBP-3 molar ratio had a substantially increased risk of colorectal cancer (multivariable-adjusted relative risk = 2.82; 95% confidence interval [CI] = 1.35–5.88, comparing top to bottom quartiles; p-trend = 0.01) [44].

2.6. Population for analysis

Of the 1137 women with IGF-I and IGFBP-3 measurements, we excluded 547 women with (1) diagnosed diabetes ($n = 91$), (2) current postmenopausal hormone use ($n = 262$) as of the blood collection, and (3) all cases in the nested case-control studies of cancer ($n = 144$) or MI ($n = 50$). Current hormone users were excluded because active postmenopausal hormone use greatly suppresses circulating IGF-I levels [5,13]. We also excluded diabetics since IGF-I may reduce risk of diabetes [37], and diabetes elevates risk of cognitive impairment and dementia. Thus, analyses presented here are based on 590 participants (Fig. 1).

2.7. Statistical analysis

We examined quintiles of IGF-I, as well as the IGF-I/IGFBP-3 molar ratio. There was some evidence of batch-to-batch variation and the quality control samples followed the same pattern—suggesting laboratory drift rather than differences in the populations being assayed; therefore, we created batch-specific quintiles to account for this. We also constructed batch-specific z-scores to examine IGF-I and the molar ratio as continuous variables; the unit of analysis was a batch-specific one S.D. increment (average S.D. of molar ratio = 0.04; average S.D. of IGF-I = 54.5 μg/L).

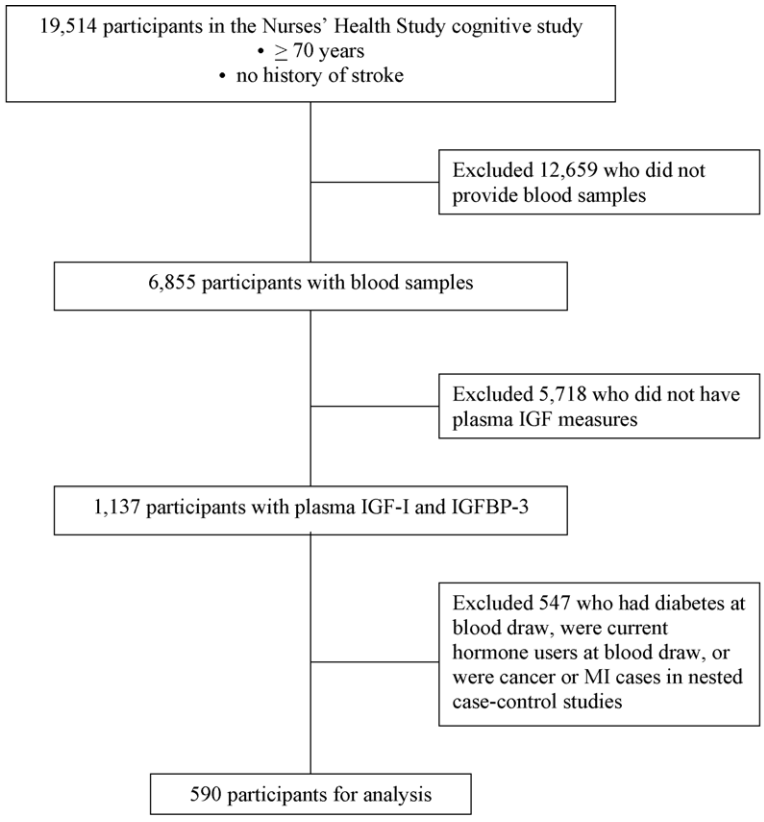
In regression models, we adjusted for a variety of covariates that may influence IGF-I and cognition [9]. We included the following potential confounding variables: age, highest attained education, history of hypertension, cigarette smoking, regular use of antidepressants, body mass index, and alcohol intake. Information on potential confounding variables was determined as of the time of blood collection. In addition, models focusing on IGF-I as the primary exposure were further adjusted for IGFBP-3.

Several secondary models were also constructed. In one alternative model, we also adjusted for physical activity (measured as metabolic equivalents per week), as this has been associated with IGF-I [20] and cognitive function [45] in the NHS cohort. To further explore confounding by depression, we also constructed a model in which we controlled for symptoms of depression using continuous scores from a validated 5-item mental health index [3]. To consider the possible influence of baseline IGF-I levels on covariate status over the 10 years of follow-up, we conducted an analysis in which information on potential confounders was updated through the time of the cognitive interview. Finally, to evaluate the potential influence of subclinical diabetes at blood draw, we further excluded all women who developed type 2 diabetes between blood draw and cognitive assessment.

3. Results

There was a large distribution of IGF-I levels among our participants (Table 1); median molar ratio in the top quintile was twice that in the bottom quintile. Characteristics of subjects were generally similar across molar ratio quintiles. Although IGF-I levels decrease with age [17], due to the narrow age range of our population (60–68 years at blood draw), mean age was also similar across quintiles of molar ratio. In addition, compared to women in the top quintile of molar ratio, women in the bottom quintile had worse mean performance on all cognitive tests.

We found significant differences in general cognition for those with higher vs. lower levels of the IGF-I/IGFBP-3 molar ratio (Table 2). After adjustment for age and education, on the TICS, women in the bottom quintile scored −0.8 points (95% CI −1.5, −0.1) lower than those in the top quintile. There was a trend of better performance on the TICS with each S.D.



* At each step, women who were excluded had similar characteristics compared to women who were included.

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 fluency	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), $p=0.02$
Multivariable-adjusted[c] (95% CI)	−0.7 (−1.4, 0.0)	−0.6 (−1.3, 0.1)	−0.4 (−1.1, 0.3)	−0.7 (−1.4, 0.0)	0.0	0.2 (0.0, 0.4), $p=0.05$
Verbal memory[b] ($n=448$) age/education-adjusted	−0.5 (−1.3, 0.3)	−0.6 (−1.4, 0.2)	−0.2 (−1.0, 0.6)	−0.8 (−1.6, 0.0)	0.0	0.2 (−0.1, 0.4), $p=0.2$
Multivariable-adjusted[c] (95% CI)	−0.4 (−1.2, 0.4)	−0.5 (−1.3, 0.3)	−0.1 (−0.9, 0.7)	−0.7 (−1.5, 0.1)	0.0	0.1 (−0.1, 0.4), $p=0.4$

[a] S.D. = standard deviation; average S.D. for IGF-I/IGFBP-3 molar ratio = 0.04.

[b] Verbal memory score combines results of immediate and delayed recalls of both the East Boston Memory Test and 10-word list; TICS = Telephone Interview for Cognitive Status; global score combines results of TICS, category fluency test, digit span backwards, and immediate and delayed recalls of East Boston Memory Test and 10-word list.

[c] Adjusted for age (years), education (associate's degree, bachelor's degree, master's/doctoral degree), high blood pressure (yes, no), cigarette smoking (never, current, past), alcohol use (quartiles), body mass index (quartiles), and use of antidepressants (yes, no).

increment in the molar ratio (0.3 points [95% CI 0.0,0.5]; p-trend = 0.02). This mean difference of 0.3 points on the TICS with each S.D. increment in the molar ratio was similar to the mean difference in TICS score that we find between women 1 year apart in age; thus, each increase in molar ratio appeared cognitively equivalent to staying younger by 1 year. Consistent with findings for the TICS, the mean difference on the global score, comparing the bottom to top quintile, was −1.4 units (95% CI −2.7, −0.1), and there was a significant trend of better performance with increasing molar ratio (p-trend = 0.03). Estimates were generally similar following multivariable adjustment. On verbal memory, there were no significant mean differences across levels of IGF-I/IGFBP-3 molar ratio.

In the age- and education-adjusted models examining IGF-I (with statistical control for IGFBP-3), we found consistent results (Table 3). There was apparent better performance on the TICS with each S.D. increment in total IGF-I (0.3 points per S.D. increase, 95% CI 0.0, 0.6; $p=0.02$). On the global score, higher IGF-I was also associated with better performance: 0.6 units per S.D. increase, 95% CI 0.1, 1.1; $p=0.03$. Multivariable adjustment had little impact on these estimates. As with the findings for the IGF-I/IGFBP-3 molar ratio, there was no association between total IGF-I and verbal memory performance.

In a secondary analysis with additional adjustment for physical activity, results were identical; for example, on the global score, each S.D. increment was associated with an increase of 0.4 units (95% CI 0.0, 0.8; $p=0.06$). A separate analysis that included continuous depression scores from the mental health index also revealed similar findings. In a model that adjusted for covariates updated through the time of the cognitive interview, findings were again unchanged. When we evaluated whether eventual development of diabetes might partly explain our findings, results remained similar after excluding women newly diagnosed with diabetes

Table 3
Mean differences in cognitive function, across levels of IGF-I

Cognitive test	Quintile of IGF-I					Per S.D.[a] increase in IGF-I
	1st	2nd	3rd	4th	5th	
Global score[b] ($n=448$) age/education-adjusted[c]	−1.6 (−3.2, −0.1)	−1.3 (−2.7, 0.1)	−0.8 (−2.1, 0.5)	−1.0 (−2.3, 0.3)	0.0	0.6 (0.1, 1.1), $p=0.03$
Multivariable-adjusted[d] (95% CI)	−1.4 (−2.9, 0.2)	−1.1 (−2.6, 0.3)	−0.8 (−2.2, 0.6)	−1.0 (−2.3, 0.3)	0.0	0.5 (−0.1, 1.0), $p=0.08$
TICS[b] ($n=590$) age/education-adjusted[c]	−0.7 (−1.6, 0.1)	−0.7 (−1.4, 0.1)	−0.3 (−1.0, 0.5)	−0.5 (−1.2, 0.2)	0.0	0.3 (0.0, 0.6), $p=0.02$
Multivariable-adjusted[d] (95% CI)	−0.7 (−1.6, 0.1)	−0.5 (−1.3, 0.3)	−0.2 (−0.9, 0.5)	−0.4 (−1.1, 0.3)	0.0	0.3 (0.0, 0.6), $p=0.05$
Verbal memory[b] ($n=448$) age/education-adjusted[c]	−0.5 (−1.5, 0.5)	−0.5 (−1.4, 0.4)	−0.3 (−1.1, 0.6)	−0.5 (−1.4, 0.3)	0.0	0.2 (−0.1, 0.5), $p=0.2$
Multivariable-adjusted[d] (95% CI)	−0.4 (−1.4, 0.7)	−0.4 (−1.3, 0.5)	−0.3 (−1.1, 0.6)	−0.6 (−1.4, 0.3)	0.0	0.2 (−0.2, 0.5), $p=0.3$

[a] S.D. = standard deviation; average S.D. for IGF-I = 54.5 μg/L.

[b] Verbal memory score combines results of immediate and delayed recalls of both the East Boston Memory Test and 10-word list; TICS = Telephone Interview for Cognitive Status; global score combines results of TICS, category fluency test, digit span backwards, and immediate and delayed recalls of East Boston Memory Test and 10-word list.

[c] Adjusted for age (years), education (associate's degree, bachelor's degree, master's/doctoral degree), and IGFBP-3 (continuous).

[d] Adjusted for age, education, high blood pressure (yes, no), cigarette smoking (never, current, past), alcohol use (quartiles), body mass index (quartiles), use of antidepressants (yes, no), and IGFBP-3 (continuous).

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 [25]. 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 age 50 [38]. Although our study related mid-life exposure—generally for women in their early 60s—to late-life cognitive function, and the Rotterdam study focused on older subjects, more data are clearly needed with respect to the role of exposure period and duration of IGF-I levels in impacting cognitive function as well.

Limitations of our study should be considered. As in any observational study, confounding remains an important concern. We collected detailed data on potential confounding factors over many years, and, as noted above, adjusted for a wide array of covariates. Importantly, multivariable adjustment had relatively little impact on effect estimates, rendering it less likely that residual or uncontrolled confounding could completely explain the significantly worse cognitive performance we observed among those with the lowest IGF-I levels. In addition, the relative homogeneity of the cohort reduces the potential influence of some unmeasured confounders (e.g., access to healthcare or health knowledge). Random misclassification of cognitive performance is also possible. However, we have established high validity and reliability of our telephone instrument for measuring cognition.

Generalizability is another concern for our study. There is no clear reason to believe that biologic relations in these nurses differ from other women of this age group. However, the population-based norms for IGF-I levels are significantly higher in older men than older women, and hormonal environments may influence the effects of IGF-I differently in men compared to women [17]. Thus, it is possible that these findings may not apply to men. Nonetheless, a recent randomized controlled trial of testosterone supplementation in elderly male subjects showed that circulating IGF-I levels did not change in response to increased serum testosterone levels, and the relation of IGF-I to cognitive performance among men was independent of testosterone [8]. In addition, previous cohort studies that specifically examined effect modification by gender [11,23] did not observe differences in relations of IGF-I to cognition—thus, meager, existing data indicate that associations between IGF-I and cognitive function may be consistent in men and women.

Overall, increasing evidence suggests that IGF-I may have an important impact on late-life cognition. Much additional work is required to understand this association, as well as to fully elucidate the mechanisms by which IGF-I may influence cognitive function.

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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 five-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-like growth factor I (IGF-I) and cognitive decline in older persons. Neurobiol Aging 2003;24:573–81.

[12] Doré S, Kar S, Quirion R. Insulin-like growth factor I protects and rescues hippocampal neurons against β-amyloid- and human amylin-induced toxicity. Proc Natl Acad Sci USA 1997;94:4772–7.

[13] Duschek EJJ, de Valk-de Roo GW, Gooren LJ, Netelenbos C. Effects of conjugated equine estrogen vs. raloxifene on serum insulin-like growth factor-I and insulin-like growth factor binding protein-3: a 2-year, double-blind, placebo-controlled study. Fertil Steril 2004;82(2):384–90.

[14] Elias MF, Beiser A, Wolf PA, Au R, White RF, D'Agostino RB. The preclinical phase of Alzheimer disease: a 22-year prospective study of the Framingham Cohort. Arch Neurol 2000;57(6):808–13.

[15] Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.

[16] Froesch ER, Schmid C, Schwander J, Zapf J. Actions of insulin-like growth factors. Annu Rev Physiol 1985;47:443–67.

[17] Goodman-Gruen D, Barrett-Connor E. Epidemiology of insulin-like growth factor-I in elderly men and women: the Rancho Bernardo study. Am J Epidemiol 1997;145(11):970–6.

[18] Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, et al. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 1998;351(9113): 1393–6.

[19] Hankinson SE, Schernhammer ES. Insulin-like growth factor and breast cancer risk: evidence from observational studies. Breast Dis 2003;17:27–40.

[20] Holmes MD, Pollak MN, Hankinson SE. Lifestyle correlates of plasma insulin-like growth factor I and insulin-like growth factor binding protein 3 concentrations. Cancer Epidemiol Biomarkers Prev 2002;11(9):862–7.

[21] Jafferali S, Dumont Y, Sotty F, Robitaille Y, Quirion R, Kar S. Insulin-like growth factor-I and its receptor in the frontal cortex, hippocampus, and cerebellum of normal human and Alzheimer disease brains. Synapse 2000;38(4):450–9.

[22] Juul A, Scheike T, Davidsen M, Gyllenborg J, Jørgensen T. Low serum insulin-like growth factor I is associated with increased risk of ischemic heart disease: a population-based case–control study. Circulation 2002;106(8):939–44.

[23] 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. J Clin Endocrinol Metab 2000;85(12):4551–5.

[24] LeRoith D. Seminars in medicine of the Beth Israel Deaconess Medical Center: insulin-like growth factors. N Engl J Med 1997;336(9):633–40.

[25] Lichtenwalner RJ, Forbes ME, Bennett SA, Lynch CD, Sonntag WE, Riddle DR. Intracerebroventricular infusion of insulin-like growth factor-I ameliorates the age-related decline in hippocampal neurogenesis. Neuroscience 2001;107(4):603–13.

[26] Luchsinger J, Tang M-X, Shea S, Mayeux R. Hyperinsulinemia and risk of Alzheimer disease. Neurology 2004;63(7):1187–92.

[27] Ma J, Giovannucci E, Pollak M, Chan JM, Gaziano JM, Willett W, et al. Milk intake, circulating levels of insulin-like growth factor-I, and risk of colorectal cancer in men. J Natl Cancer Inst 2001;93(17): 1330–6.

[28] Morley JE, Kaiser F, Raum WJ, Perry 3rd HM, Flood JF, Jensen J, et al. Potentially predictive and manipulable blood serum correlates of aging in the healthy human male: progressive decreases in bioavailable testosterone, dehydroepiandrosterone sulfate, and the ratio of insulin-like growth factor 1 to growth hormone. Proc Natl Acad Sci USA 1997;94:7537–42.

[29] Okereke O, Hankinson SE, Hu FB, Grodstein F. Plasma c-peptide and cognitive function among older women without diabetes. Arch Intern Med 2005;165:1651–6.

[30] Papadakis MA, Grady D, Tierney MJ, Black D, Wells L, Grunfeld C. Insulin-like growth factor 1 and functional status in healthy older men. J Am Geriatr Soc 1995;43:1350–5.

[31] Pollak M, Ma J. Unpublished results in Chan JM, Stampfer MJ, Ma J, et al. Insulin-like growth factor-I (IGF-I) and IGF binding protein-3 as predictors of advanced-stage prostate cancer. J Natl Cancer Inst 2002;94:1099–106.

[32] Pollak MN, Schernhammer ES, Hankinson SE. Insulin-like growth factors and neoplasia. Nat Rev Cancer 2004;4(7):505–18.

[33] Pulford BE, Ishii DN. Uptake of circulating insulin-like growth factors (IGFs) into cerebrospinal fluid appears to be independent of the IGF receptors as well as IGF-binding proteins. Endocrinology 2001;142(1):213–20.

[34] Reinhardt RR, Bondy CA. Insulin-like growth factors cross the blood–brain barrier. Endocrinology 1994;135(5):1753–61.

[35] Rollero A, Murialdo G, Fonzi S, Garrone S, Gianelli MV, Gazzerro E, et al. Relationship between cognitive function, growth hormone and insulin-like growth factor I plasma levels in aged subjects. Neuropsychobiology 1998;38:73–9.

[36] Ruan W, Newman C, Kleinberg D. Intact and amino-terminally shortened forms of insulin-like growth factor I induce mammary gland differentiation and development. Proc Natl Acad Sci USA 1992;89:10872–6.

[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.