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Key words: cardiovascular biomarkers, carotid IMT scores, cognitive function, cognitive decline, executive function

Objective: Multiple cardiovascular risk factors are associated with early cognitive decline. Measures of complex information processing provide one of the earliest signs of cognitive decline and appear related to arterial plaque growth. The purpose of this study was to determine how cardiovascular risk factors and carotid intima-media thickness (IMT) scores are associated with cognitive function and complex information processing scores.

Methods: This study used a retrospective, cross-sectional analysis of 536 men and women attending an executive evaluation program. Measurements were made of body composition, cardiovascular status, fitness and diet, and laboratory measures, including carotid IMT. Each subject was tested with a computerized neurocognitive test battery.

Results: Complex information processing (CIP), also called *executive function*, is independently related to carotid IMT scores ($p < 0.01$), as are other cardiovascular biomarkers, including aerobic capacity fiber, B12, and long-chain n-3 fatty acid intake ($p < 0.01$ for each). However, after controlling for carotid IMT, only IMT showed a significant relationship with CIP scores.

Conclusions: Carotid IMT scores are the strongest independent cardiovascular biomarker for cognitive function, especially complex information processing. Greater intake of fiber, long-chain n-3 fatty acids (N3FAs), and vitamin B12, as well as measures of aerobic fitness, is associated with enhanced cognitive function, yet controlling for IMT scores diminished their association. Because decreasing CIP scores are linearly associated with cognitive decline, future randomized clinical trials that yield improvements in carotid IMT scores should also assess for changes in cognitive function.

INTRODUCTION

Cognitive impairment without dementia is common, clinically important, and strongly related to cardiovascular disease (CVD) risk factors. Approximately 5 million Americans have cognitive decline without dementia, progressing to dementia at a rate of 10%–15% yearly [1]. Because the progression of cognitive decline to dementia is high, and the ability to treat end-stage dementia is very limited, early identification of cognitive impairment is a high priority.

CVD risk factors have been shown to predict cognitive decline [2–5] and progression to dementia [6–8]. Yet there remains controversy over which are the best cardiovascular biomarkers and what is the most sensitive measurement of cognitive function that can identify initial cognitive decline. Clearly, tools that clarify early cognitive decline are essential in the design of future randomized clinical trial regimens that will eventually lead to a decrease in cognitive decline, especially lifestyle information that includes diet and fitness.

Computerized cognitive testing identifies early cognitive decline. In particular, measures of complex information processing, which a computerized test can measure with millisecond accuracy, can be used to identify early cognitive impairment. Computerized neurocognitive test batteries generate scores clarifying the function of several cognitive domains and show promise as a tool to monitor cognitive function.

Many studies have measured cognitive function in elderly subjects (older than 65 or 70) and in patients with diabetes or metabolic syndrome [3,4,9,10]. Carotid IMT scores have also been shown to be associated with cognitive decline in the elderly [11–13] as well as in middle-aged adults [30,31]. Yet this is the first study that we are aware of that aims to assess the

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relationship between cardiovascular risk factors, carotid IMT scores, and cognitive function in healthy middle-aged adults and is able to control for multiple cardiovascular risk factors including aerobic fitness, nutrient intake, and detailed anthropometric and laboratory analyses simultaneously.

MATERIALS AND METHODS

This study was a retrospective, cross-sectional analysis of 536 subjects. It was performed at the Carillon Outpatient Center in St. Petersburg, FL, and was approved by the Institutional Review Board at the Morton Plant Hospital; subjects gave informed consent. For additional information on this database, please see Masley et al. [28].

Subjects

Five hundred thirty-six adult subjects, age 23 to 65 (mean = 48.2), were participants at an executive health clinic, a wellness-oriented program for private patients who are well educated, professionally accomplished, and mostly in good health. The data were collected during subjects' first comprehensive, all-day examination and were analyzed retrospectively. All subjects signed a consent form to allow their unidentified data to be analyzed for research purposes. The evaluation included a comprehensive medical assessment that included detailed laboratory studies, fitness testing, stress electrocardiogram (ECG) testing, carotid intima-media thickness (IMT) measures, nutritional intake analysis, anthropometric measures, and a computerized neurocognitive test battery. Subjects enrolled consecutively from 2006 until 2009.

Biometric Indicators

Anthropometric measures included body composition, body fat, and weight obtained with a Tanita 310 Analyzer (Arlington Heights, IL, USA). Blood pressure was obtained in the right and left arms while the subjects were sitting for at least 5 minutes, with the lower of the 2 blood pressure numbers entered. Body mass index (BMI) was calculated on the basis of weight from the Tanita 310 Analyzer and measured height. Waist circumference measures were taken in the horizontal plane as the smallest circumference above the iliac crest and below the 12th rib with a relaxed abdomen after 2 large expirations.

Fitness measures were performed with a Woodway Cortex Metalyzer and a Reynolds Cardio Collect system during stress ECG testing on a Woodway treadmill using a standard Bruce Protocol [32]. Measures included maximum volume of oxygen burned during peak exercise (VO_2max as ml/kg/min), aiming to push subjects to a respiratory exchange ratio (RER) score between 1.05 and 1.1. Blood pressures were measured at baseline and after 1 minute and 30 seconds during each 3-minute stage. The diastolic blood pressure change from baseline to peak exercise was measured. Total duration achieved on the Bruce Protocol treadmill test was measured in minutes. The peak heart rate at maximum exertion was collected, as was the heart rate 1 minute after stopping the stress ECG test.

Laboratory studies (total cholesterol, low-density lipoprotein, high-density lipoprotein, glucose, mercury, homocysteine, and C-reactive protein) were drawn after a minimum 9-hour fast.

Dietary data were collected from a 3-day dietary record, which included both food and supplement information. The food record was reviewed with a registered dietician and analyzed using Nutribase 7 software (Cybersoft Inc., Phoenix, AZ, USA). Computerized dietary analyses measured macronutrient and micronutrient intake, including long-chain N3FAs. N3FA dietary intake was assessed by combining reported weekly fish intake with fish oil intake in supplemental form. A separate questionnaire inquired after subjects' weekly consumption of seafood in general and large-mouth fish in particular.

Carotid IMT scores were obtained using high-resolution B-mode ultrasonography of the common carotid arteries with a linear-array, 5- to 10-MHz transducer using a SonoSite MicroMaxx ultrasound machine and scores calculated with SonoCalc 3.4. Each subject had 10 or more images collected from the far wall of the right and left distal 1 cm of the common carotid arteries at end diastole according to Bots et al. [33] and Stein et al. [34]. In this study, calculated scores also followed Stein et al.'s recommendation to use the average of 3 views, anterior, lateral, and posterior, of the right and left carotid arteries. Because the mean carotid IMT measurements are reported to provide greater precision and reproducibility with serial measurements than maximum carotid IMT measures, the authors chose the mean carotid IMT result in this study as their carotid IMT score. If plaque was present in the 1-cm distal common carotid artery segments, the IMT score was included in these measurements; however, less than 5% of subjects in this database had measured plaque lesions. A plaque lesion refers to a ≥1.5-mm IMT within the segment measured. A single technician performed the tests and analyzed the scores on all subjects. All subjects were new to the clinical practice. Tests were performed and analyzed without knowledge of other results. Site-specific precision analyses of mean carotid IMT scores were calculated at 3%. The mean score from the 10 or more 1-cm segment images was calculated with SonoCalc software and logged into the database as the mean IMT score.

Cognitive Indicators

The CNS Vital Signs (VS7) is a computerized neurocognitive test battery comprised of seven familiar neuropsychological tests that generate 10 independent scores; the test scores cover 4 factors or cognitive domains; see Table 1.

The first factor is complex information processing (CIP), commonly referred to as *executive function*, which is composed of 3 tests. Symbol Digit Coding, based on the Symbol Digit

Table 1. Tests in the VS7 Battery

Index Score
Memory
Verbal Memory Test
Visual Memory Test
Complex Information Processing
Symbol Digit Coding
Stroop Test
Shifting Attention Test
Effortful Attention
Stroop Errors
Continuous Performance Test
Motor Speed
Finger Tapping Test
Simple Reaction Time

Modalities Test [14]. The Stroop Test [15] has 3 parts that generate simple and complex reaction times. Averaging the 2 complex reaction time scores generates the response time score. The Shifting Attention Test measures the subject's ability to shift from one instruction set to another quickly and accurately [16,17].

The second factor is effortful attention, composed of 2 tests: the number of errors committed during the Stroop Test and a conventional Continuous Performance Test (CPT). The CPT is a measure of vigilance or sustained attention [18].

The third factor is memory, with verbal memory and visual memory components [19]. Fifteen words and 15 shapes are provided initially. After 1 and 30 minutes, the subject needs to select the original 15 words and shapes from a total of 30 words and shapes.

The fourth factor is motor speed, calculated from the Finger Tapping Test and the Simple Reaction Time Test in the Stroop Test. The Choice Reaction Time score is from the CPT.

Scores are standardized by adjusting for age (on the basis of data from 4400 normal subjects age 6 to 96) to a mean of 100 with a standard deviation of 15. Test–retest reliability and concurrent validity of the VS7 battery are comparable to similar conventional neuropsychological tests [20]. The discriminant validity of the VS7 has been established in studies of patients with mild cognitive impairment and early dementia [21]; post-concussion syndrome and severe traumatic brain injury [22]; ADHD [23,24]; depression [25,26]; and schizophrenia and bipolar disorder [27].

Analyses

Scores that did not have a normal distribution were log-transformed or standardized with elimination of outliers who scored more than 6 standard deviations from the mean. Group comparisons were done with multivariate analysis of variance, controlling simultaneously for age, race, gender, education, alcohol intake, self-reported computer familiarity, and finger tapping speed, and by one-way analysis of variance with Bonferroni correction. Finger tapping speed is included as a control variable because slow tapping speed can result in a disproportionate reduction in cognitive score. Regression analysis was by the generalized linear model with continuous, not categorical, variables (all analyses were conducted with SPSS software).

RESULTS

In Table 2 we show the demographic information for the entire group, organized by gender. The subjects were predominantly white (95%) and well educated (>16 years). They ranged in age from 23 to 65 (mean age 48.2) and the majority were males (73%). Self-reported computer familiarity was high (1 = *none*, 2 = *some*, 3 = *frequent*; mean 2.85).

The only significant difference between the genders was age, which is significantly correlated with cognition. None of the other demographic or biometric variables differed significantly or were correlated to cognition.

To illustrate the variety of cardiovascular risk factors measured, the minimal, maximal, mean, and standard deviations are noted in Table 3 for anthropometric and carotid IMT testing, stress treadmill testing, dietary intake, and laboratory values. The range of cognitive test scores is also presented in Table 3.

In Table 4, the biometric variables are compared across the various cognitive domains by analysis of variance. Carotid IMT scores showed the strongest independent relationship with multiple aspects of cognitive function, in particular measures of complex information processing, but not memory or attention, when demographic variables and other cardiovascular risk factors were controlled. None of the anthropometric or typical cardiovascular-related laboratory measures were significantly related to cognitive function. Yet several measures of aerobic fitness were correlated with cognitive function, including VO_2max scores, 1-minute heart rate recovery after exercise, and total minutes performed on a Bruce protocol exercise treadmill test. Several dietary intake markers were also highly associated with various aspects of cognition, in particular greater intake of fiber, long-chain N3FAs, and B12 were associated with higher

Table 2. Demographic characteristics

	N	Minimum	Maximum	Mean	SD
Age	536	23	65	47.97	7.449
Educ	440	8	21	16.78	2.117
Computer familiarity (1–3)	534	1	3	2.85	0.384
	N	Percent			
Male	389	72.6			
Female	147	27.4			
White	510	95.1			
Non-white	26	4.9			

Table 3. Biometric Variables Used to Compare With Cognitive Function

	N	Minimum	Maximum	Mean	SD
BMI	536	16.9	49.4	27.4	4.7
SYSBP	535	54	190	117.7	15.3
DIABP	536	50	120	75.7	10.4
WCcm	525	11.8	141	93.9	14.3
BODYFAT	536	11.3	55.2	28.4	7.6
IMT	399	0.4	1.3	0.7	0.1
VO2max	481	3	58	32	7.6
ETTDIABP	522	−40	36	−0.6	8.7
@1MINHR	513	1	65	23.6	9.7
DURmin	525	4.5	21	12.3	2.6
Excpweek	228	0	14	2.3	2.6
FIBER	518	3	59	18.2	8.7
SATFAT	518	1	66	21.9	10.5
N3FAGM	531	0	67	0.8	2.9
FOLATES	517	3	2279	487.8	325.4
B12	518	0	890	32.5	93
VITDIU	517	0	1002	239.8	238.8
CAFFEINE	518	0	3100	170.9	242.1
ALCOHOL	518	0	274	13.3	19.7
TCHOL	431	107	355	204.6	38.9
LDL	429	41	241	129.6	33.5
TCHDL	430	1.5	615	7.1	38.8
GLUCOSE	530	67	287	98.7	15.6
HG	384	1.8	40.2	7.2	6.5
HCY	499	3.7	37.6	10.9	3.5
HSCRP	418	0.2	30	2.1	2.7
INDEX	536	9.9	122.5	98.0	15.0
MEMORY	536	9.9	137.3	100.0	22.1
PROC SPEED	536	51.2	140.1	99.1	12.5
ATTENTION	536	9.9	112.8	98.0	16.7
MSPEED	536	41.6	141.1	101.1	12.9

MSPEED = motor speed.

cognitive scores, whereas saturated fat, caffeine, and alcohol intake were not related. However, as an indication of the strength of the relationship between carotid IMT score and cognitive function, after controlling for carotid IMT scores as a covariable, none of the aerobic fitness or dietary intake markers continued to show a significant association with cognitive function.

Table 5 and Fig. 1 show that the regression of carotid IMT scores with CIP remains highly significant, even when controlling for motor speed and biometric or demographic variables. None of the other significant correlations retained their significance after controlling for the other pertinent variables.

DISCUSSION

In this study, carotid IMT scores were shown to be the most sensitive cardiovascular biomarker associated with overall cognitive function and with CIP and were independent of demographic and other biometric variables. Because a decline in CIP can be measured relatively easily and is strongly correlated with cognitive decline, this relationship holds promise for future clinical trials.

Initial observations showed a correlation with aerobic fitness measures and nutrient intake (fiber, long-chain N3FAs, B12). However, after controlling for the powerful association between cognition and carotid IMT scores, the nutritional markers lost their statistically significant association. Further studies are warranted to compare diverse cardiovascular risk factors with cognitive function and to ascertain whether the nutritional factors are solely related to their association with carotid IMT scores or whether they have other independent relationships.

The findings in this study are similar those noted by Sander et al. [11] in their Invade Study with elderly subjects, with Wendell et al. [12] in the Baltimore Longitudinal Study of aging [11], and Silvestrini et al. [13] in Italy. All 3 study groups showed a strong association between increasing carotid IMT scores and cognitive decline, although these were longitudinal studies and this study is cross sectional; thus, a detailed comparison should not be made.

There are also two cross-sectional studies in middle-aged adults that support this database's findings that cognitive function is negatively associated with carotid IMT scores [30,31].

In contrast, the findings from this database differ from those noted previously by Johnston et al. [29]. Johnston et al. [29] compared carotid stenosis and carotid IMT scores in 4006 participants with Mini-Mental Status examination and Digit Symbol Substitution testing scores. They noted that carotid artery stenosis was associated with both initial cognitive function and over time with cognitive decline. The carotid IMT scores were initially correlated with cognitive function scores both by Mini-Mental State Exam and Digit Symbol Substitution Test scores, but after controlling for multiple cardiovascular risk factors the associations diminished and lost statistical significance. A possible explanation for the difference in findings is that the Mini-Mental State Exam is a gross measure of cognitive function and the conventionally administered Digit Symbol Substitution is timed with less precision than it is when administered by computer. The more detailed testing protocol used in our database may be more likely to generate accurate results. The more advanced carotid stenosis and cognitive decline findings do suggest the need to identify earlier stages that are amenable to clinical treatment with the potential to decrease both cognitive decline and arterial plaque growth. Whether treatment protocols designed to reduce progression of arterial plaque growth will also reduce cognitive decline will require further study.

This study has several strengths, including a rich and comprehensive clinical database enabling control of a large number of potential confounders; a relatively large sample size of healthy, high-functioning adults; and a comprehensive neurocognitive test battery that can measure reaction times with an accuracy in milliseconds [20].

Limitations include the selection of a single measure of cognitive function and cardiovascular biomarkers to assess the association between CVD risk factors and neurocognition. The use of CNS VS software as the sole measure of cognition without

Table 4. Correlation Coefficients Between Cognitive Measures and Biometric Variables[a]

Correlations	Index	MEM	CIP	EA	MSPEED
Age	0.241**	0.130**	0.403**	0.117**	0.250**
Race	0.001	−0.019	0.023	−0.014	−0.023
Education	0.013	0.008	0.037	0.015	0.016
Gender	0.037	−0.018	0.015	0.024	0.020
BMI	−0.019	−0.026	−0.005	−0.044	0.026
Systolic blood pressure	0.023	0.039	−0.078	0.005	−0.065
Diastolic blood pressure	0.036	0.038	−0.039	0.009	0.013
Waist circumference (cm)	0.013	−0.054	0.019	0.001	0.004
Body fat percentage	−0.058	−0.047	−0.062	−0.049	−0.075
Carotid IMT score	−0.131**	−0.090	−0.200**	−0.056	−0.169**
Stress exercise treadmill testing fitness markers					
VO_2max	0.041	0.003	0.113*	0.030	0.151**
Diastolic blood pressure change	−0.032	0.026	−0.063	−0.031	−0.081
1-Minute heart rate ↓	−0.108*	−0.058	−0.048	−0.094*	−0.053
Duration (minutes)	0.001	−0.010	0.054	−0.014	0.109*
Nutritional intake					
Fiber (g/day)	−0.045	−0.038	−0.120**	0.011	−0.048
Saturated fat (mg/day)	0.039	−0.023	0.032	0.058	0.025
Long-chain N3FA (g/day)	−0.083	−0.046	−0.153**	−0.047	−0.042
Folate (g/day)	−0.059	−0.025	−0.087*	−0.007	−0.051
B12	−0.073	−0.060	−0.118**	−0.006	−0.123**
Vitamin D (international units)	−0.080	−0.065	−0.083	0.006	−0.069
Caffeine	−0.007	0.010	−0.008	−0.003	0.014
Alcohol	0.038	0.014	0.058	0.014	0.003
Fasting laboratory levels					
Total cholesterol	−0.036	−0.088	−0.006	0.018	−0.077
LDL cholesterol	−0.004	−0.066	0.011	0.033	−0.061
Total cholesterol/HDL ratio	0.084	0.085	0.047	0.034	0.038
Glucose	−0.006	−0.014	−0.044	−0.005	−0.053
Mercury	0.032	−0.019	0.000	0.035	−0.041
Homocysteine	0.008	−0.061	−0.014	0.025	−0.037
HS-CRP	−0.024	0.007	−0.014	−0.046	−0.021

MEM = memory, CIP = continuous information processing, EA = attention, BMI = body mass index, IMT = intima-media thickness, N3FA = n-3 fatty acid, LDL = low-density lipoprotein, HDL = high-density lipoprotein, HS-CRP = high-sensitivity C-reactive protein.

[a]Pearson's product-moment correlation. $N = 536$.

$^{**}p < 0.01$. $^{*}p < 0.05$.

other neuropsychological testing is also a weakness. Further, the homogeneity of the participants compromises the degree to which our findings might be generalized to the wider population. On the other hand, if cognitive dysfunction occurs in healthy, highly productive individuals, with ample cognitive reserve, the effect is likely to be amplified in more vulnerable populations. Despite these limitations, it is reasonable to suggest that carotid IMT scores, measures of aerobic capacity, and specific nutrient intake (fiber, N3FAs, B12) are associated with cognitive function.

Table 5. Continuous information processing remains strongly associated with carotid intima-media thickness scores, independent of motor speed and all biometric variables[a]

			95% Wald Confidence Interval		Hypothesis Test	
Parameter	B	ST ERR	Lower	Upper	Wald's Chi-Square	Sig.
IMT	−22.229	5.2821	−32.582	−11.876	17.710	0.000026
IMT (motor speed)	−22.229	5.2821	−32.582	−11.876	17.710	0.000026
IMT (all biometric)	−22.135	5.2826	−32.489	−11.782	17.558	0.000028
IMT (age, race, sex, education, computer familiarity)	−25.533	5.9545	−37.204	−13.863	18.387	0.000018

IMT = intima-media thickness.

[a]Stepwise linear regression, SPSS.

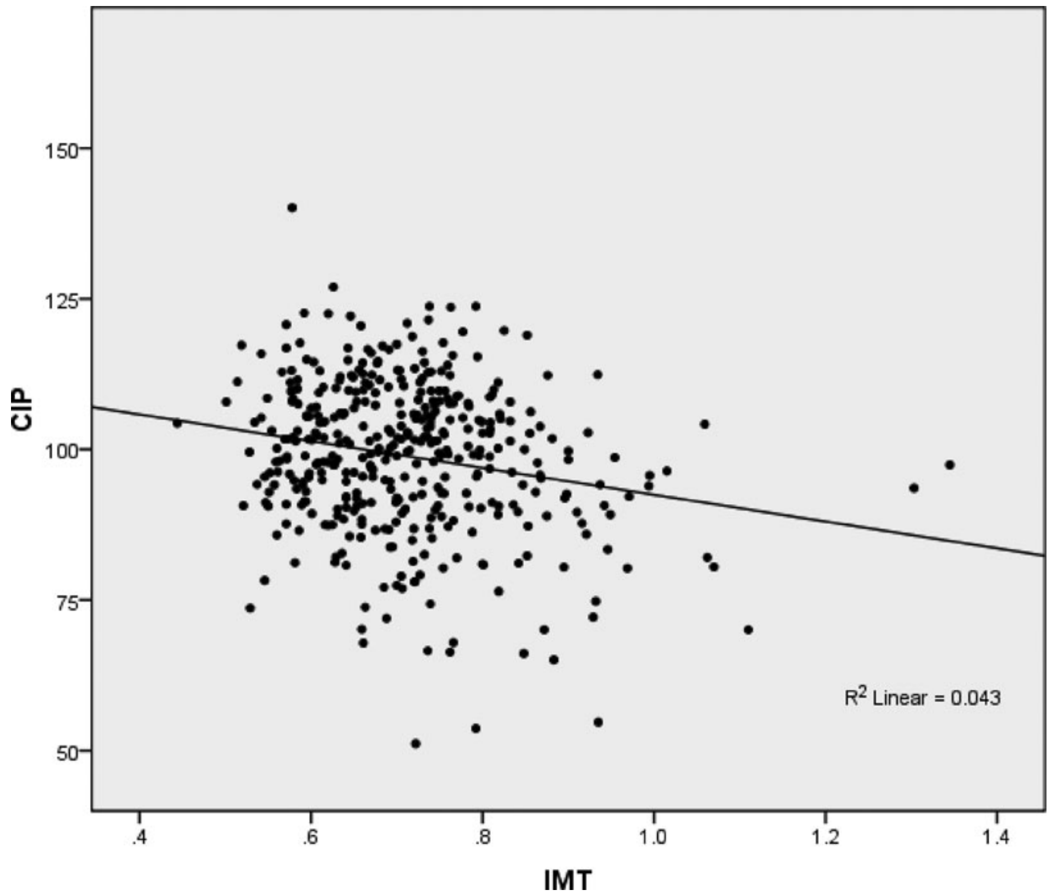

Fig. 1. Regression of carotid IMT scores with CIP. The regression of carotid IMT scores with CIP remains highly significant, even when controlling for motor speed and biometric or demographic variables.

CONCLUSION

Carotid IMT scores are strongly associated with CIP, a direct measure of executive function. Both fitness and nutrition intake are also associated with better cognitive performance; in particular, greater intake of fiber, long-chain N3FAs, and B12 are highly associated with greater CIP, although the statistical relationship between nutritional measurements and fitness was diminished after controlling for carotid IMT scores. However, it is unclear how much of the nutrient and fitness benefit is directly associated with their influence on carotid IMT scores, versus a direct impact on cognitive function, and additional research is required in this area.

Further studies are warranted to clarify whether these findings aid in the earliest possible detection of cognitive decline and lead to slowing progression. This study suggests that researchers designing randomized clinical trials intending to slow arterial plaque progression should also monitor declines in cognitive function while controlling for measures of fitness and nutrient intake because there is the potential to improve cardiovascular and cognitive outcomes with the same intervention.

REFERENCES

1. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, Burke JR, Hurd MD, Potter GG, Rodgers WL, Steffens DC, McArdle JJ, Willis RJ, Wallace RB: Prevalence of cognitive impairment without dementia in the US. Ann Int Med 148:427–434, 2008.
2. Convit A, Wolf OT, Tarshish C, De Leon MJ: Reduced glucose tolerance is associated with poor memory performance and hippocampal atrophy among normal elderly. Proc Natl Acad Sci U S A 100:2019–2022, 2003.
3. Cukierman-Yaffe T, Gerstein HC, Williamson JD, Lazar RM, Lovato L: Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors (ACCORD-MIND trial). Diabetes Care 32:221–227, 2009.
4. Yaffe K, Kanaya A, Lindquist K, Simonsick EM, Harris T, Shorr RI, Tylavsky FA, Newman AB: The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA 292:2237–2242, 2004.
5. Helzner EP, Luchsinger JA, Scarmeas N, Cosentino S, Brickman AM, Glymour MM, Stern Y: Contribution of vascular risk factors to the progression in Alzheimer disease. Arch Neurol 66:343–348, 2009.

6. Craft S: The role of metabolic disorders in Alzheimer disease and vascular dementia. Arch Neurol 66:300–305, 2009.
7. Schwartz E, Wicinski B, Schmeidler J, Haroutunian V, Hof PR: Cardiovascular risk factors affect hippocampal microvasculature in early Alzheimer's disease. Transl Neurosci 1:292–299, 2010.
8. Monsuez JJ, Gesquière-Dando A, Rivera S: Cardiovascular prevention of cognitive decline. Cardiol Res Pract 2011. doi: 10.4061/2011/250970.
9. Jokinen H, Kalska H, Ylikoski R, Madureira S, Verdelho A, van der Flier WM, Scheltens P: Longitudinal cognitive decline in subcortical ischemic vascular disease—the LADIS Study. Cerebrovasc Dis 27:384–391, 2009.
10. Kerola T, Kettunen R, Nieminen T: The complex interplay of cardiovascular system and cognition: how to predict dementia in the elderly? Int J Cardiol 150:123–129, 2011.
11. Sander K, Bickel H, Förstl H, Etgen T, Briesenick C, Poppert H, Sander D: Carotid-intima media thickness is independently associated with cognitive decline. The Invade Study. Int J Geriatr Psychiatry 25:389–394, 2011.
12. Wendell CR, Zonderman AB, Metter EJ, Najjar SS, Waldstein SR: Carotid intimal medial thickness predicts cognitive decline among adults without clinical vascular disease. Stroke 40:3180–3185, 2009.
13. Silvestrini M, Gobbi B, Pasqualetti P, Bartolini M, Baruffaldi R, Lanciotti C, Cerqua R, Altamura C, Provinciali L, Vernieri F: Carotid atherosclerosis and cognitive decline in patients with Alzheimer's disease. Neurobiol Aging 30:1177–1183, 2009.
14. Smith A: "Symbol Digit Modalities Test (SDMT) Manual." Los Angeles, CA: Western Psychological Services, 1982.
15. Stroop J: Studies of interference in serial verbal reactions. J Exp Psychol 18:643–662, 1935.
16. Le TH, Pardo JV, Hu X: 4 T-fMRI study of nonspatial shifting of selective attention: cerebellar and parietal contributions. J Neurophysiol 79:1535–1548, 1998.
17. Nagahama Y, Sadato N, Yamauchi H, Katsumi Y, Hayashi T, Fukuyama H, Kimura J, Shibasaki H, Yonekura Y: Neural activity during attention shifts between object features. Neuroreport 9:2633–2638, 1998.
18. Rosvold HE, Delgado JM: The effect on delayed-alternation test performance of stimulating or destroying electrically structures within the frontal lobes of the monkey's brain. J Comp Physiol Psychol 49:365–337, 1956.
19. Rey A: "L'examen Clinique en Psychologie." Paris, France: Presses Universitaires de France, 1964.
20. Gualtieri C, Johnson L: Reliability and validity of a computerized neurocognitive test battery, CNS vital signs. Arch Clin Neuropsychol 21:623–643, 2006.
21. Gualtieri C, Johnson L: Neurocognitive testing supports a broader concept of mild cognitive impairment. Am J Alzheimers Dis Other Demen 20:359–366, 2005.
22. Gualtieri C, Johnson L: A computerized test battery sensitive to mild and severe brain injury. Medscape J Med 10:90, 2008.
23. Gualtieri C, Johnson L: Efficient allocation of attentional resources in patients with ADHD: maturational changes from age 10 to 29. J Atten Disord 9:534–542, 2006.
24. Gualtieri C, Johnson L: Medications do not necessarily normalize cognition in ADHD patients. J Atten Disord 11:459–469, 2008.
25. Gualtieri C, Johnson L, Benedict K: Neurocognition in depression: patients on and off medication versus healthy comparison subjects. J Neuropsychiatry Clin Neurosci 18:217–225, 2006.
26. Gualtieri C, Johnson L: Age-related cognitive decline in patients with mood disorders. Prog Neuropsychopharmacol Biol Psychiatry 32:962–967, 2008.
27. Gualtieri C, Johnson L: A computerized neurocogntive test battery for studies of schizophrenic and bipolar patients. Schizophr Res 81:122, 2006.
28. Masley SC, Masley LV, Gualtieri C: Effect of mercury levels and seafood intake on cognitive function in middle-aged adults. Integr Med 11:32–40, 2012.
29. Johnston SC, O'Meara ES, Manolio TA, Lefkowitz D, O'Leary DH, Goldstein S, Carlson MC, Fried LP, Longstreth WT Jr.: Cognitive function and carotid artery disease. Ann Intern Med 140:1–34, 2004.
30. Cerhan JR, Folsom AR, Mortimer JA, Shahar E, Knopman DS, McGovern PG, Hays MA, Crum LD, Heiss G: Correlates of cognitive function in middle-aged adults. Gerontology 44:95–105, 1998.
31. Zhong W, Cruickshanks KJ, Huang GH, Klein BEK, Klein R, Nieto FJ, Pankow JS, Schubert CR: Carotid atherosclerosis and cognitive function in midlife: the Beaver Dam Offspring Study. Atherosclerosis 219:330–333, 2011.
32. Hossack KF, Kusumi F, Bruce RA: Approximate normal standards of maximal cardiac output during upright exercise in women. Am J Cardiol 47:1080–1086, 1981.
33. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS: Use of carotid ultrasound to identify subclinical vascular society of echocardiography carotid intima-media thickness task force endorsed by the society of vascular medicine. Journal of the American Society of Echocardiography 21:93–111, 2008.
34. Bots ML, Evans GW, Riley WA, Grobbee DE: Carotid intima-media thickness measurements in intervention studies: Design options, progression rates, and sample size considerations: A point of view. Stroke 34:2985–2994, 2003.

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