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ORIGINAL ARTICLE

Postoperative cognitive dysfunction after noncardiac surgery: effects of metabolic syndrome

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Abstract

Purpose Vascular risk factors, including metabolic syndrome, are known to contribute to the development of cognitive dysfunction. We tested the hypothesis that patients with metabolic syndrome are more likely to develop cognitive dysfunction after noncardiac surgery.

Methods Age- and education-balanced patients ($n = 60$) undergoing elective noncardiac surgery with and without metabolic syndrome and 30 nonsurgical controls were enrolled. Recent verbal and nonverbal memory and executive functions were assessed using a psychometric test battery before and 1 month after noncardiac surgery or at a 1-month interval in nonsurgical controls.

Results Neurocognitive scores under baseline conditions were similar in surgical patients with versus without metabolic syndrome in all examined cognitive modalities (recent nonverbal and verbal memory, executive functions). Pronounced reductions in tests of verbal memory (delayed story recall, immediate and delayed word list recall) and executive function (backward digit span) were observed in patients with versus without metabolic syndrome after surgery. Overall cognitive performance after surgery was also significantly ($P = 0.03$) more impaired in patients with versus without metabolic syndrome. The prevalence rate of postoperative cognitive dysfunction (POCD) differed in the studied groups (13/30 and 8/30 in patients with versus without metabolic syndrome; $P < 0.02$).

Conclusions The results indicate that cognitive functions were more profoundly impaired in patients with metabolic syndrome undergoing noncardiac surgery compared with their healthier counterparts.

Keywords Metabolic syndrome · Postoperative cognitive dysfunction

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Introduction

Abdominal obesity, hypertriglyceridemia, low serum concentrations of high-density lipoprotein, hypertension, and hyperglycemia are characteristic features of metabolic syndrome [1, 2]. The presence of metabolic syndrome increases the risk of diabetes mellitus and cardiovascular disease [3, 4]. Vascular risk factors, including metabolic syndrome, also are known to contribute to the development of cognitive dysfunction [5]. Obesity [6], paired fasting blood glucose concentration [7], dyslipidemia [8], and hypertension also appear to independently contribute to neuropsychological abnormalities. Patients with metabolic syndrome had lower Mini Mental State Examination scores (screening device for dementia) and demonstrated greater decreases in recent memory after a 3-year interval [9]. The presence of metabolic syndrome risk factors predicted the development of vascular dementia after a 25-year follow-up [10]. Metabolic syndrome has also been linked to Alzheimer's disease [11] and accelerates aging-induced frontal-subcortical syndrome [12]. We recently demonstrated that metabolic syndrome is associated with short-term cognitive decline after cardiac surgery [13]. Postoperative cognitive dysfunction most often occurs after cardiac surgery, but this complication is also observed in a substantial minority of older patients (25% at 1 week, 10% at 3 months after surgery) after noncardiac surgery [14]. The potential consequences of metabolic syndrome on postoperative cognitive function after noncardiac surgery have not been examined. Given that metabolic syndrome patients are more vulnerable to cognitive decline, we hypothesized that these patients sustain more profound postoperative cognitive dysfunction after noncardiac surgery compared with those who do not have this constellation of clinical abnormalities.

Methods

The protocol was approved by the Institutional Review Board of the Zablocki Veterans Administration Medical Center, Milwaukee, WI, USA. All subjects provided written informed consent.

Participants

Sixty age- and education-balanced noncardiac surgical patients were enrolled (30 patients with and without metabolic syndrome in two separate groups) from the Zablocki Veterans Medical Center. Diagnostic criteria for metabolic syndrome for this study included patients presenting at least with three of the four following criteria: abdominal obesity (body mass index >30), insulin resistance (plasma glucose greater than 100 mg/ml or use of medication for hyperglycemia), dyslipidemia (triglycerides greater than 150 mg/dl, HDL cholesterol less than 40 mg/dl, or use of medication for dyslipidemia), and hypertension (systolic pressure greater than 130 mmHg and diastolic pressure greater than 85 mmHg, or use of medication for hypertension). Inclusion criteria included age ≥55 years, written informed consent, and elective noncardiac surgery. Surgical patients underwent ear–nose–throat, urological, gastrointestinal, orthopedic, and plastic surgical procedures under general anesthesia. Thirty additional patients who were not undergoing surgery were recruited from hospital clinics. Fifteen of these nonsurgical patients met the diagnostic criteria for metabolic syndrome. Inclusion of a nonsurgical group was important to account for practice effects of repeated cognitive testing [15]. Exclusion criteria included a history of a cerebrovascular accident, previously documented cognitive deficits, or vascular dementia (Hachinski score [16] >4). Patients with hepatic impairment (aspartate aminotransferase or alanine aminotransferase more than twice the upper normal limit) and chronic renal insufficiency (creatinine >2 mg/dl) were also excluded.

Protocol

Neurological status and neurocognitive functions were assessed within 1 week of surgery. Patients received fentanyl (1–2 μg/kg) and midazolam (1–2 mg) for premedication. Fentanyl (3–5 μg/kg) and sodium thiopental (3–6 mg/kg) were used for anesthetic induction. Anesthesia was maintained with sevoflurane (0.8–2.2%) in an air–oxygen mixture. Neuromuscular blockade was produced with rocuronium (1.0 mg/kg), and was reversed with neostigmine (40–80 μg/kg) and glycopyrrolate (8–16 μg/kg) after completion of the procedure. Neurological status and neurocognitive functions were reassessed 1 month after surgery (1 month after the first test in the nonsurgical groups). For each patient, the same clinician administered both the first and second neurocognitive tests and performed the neurological examinations to achieve optimal testing consistency.

Psychometric testing for cognitive functions

The test battery from several psychological tests was composed of standard clinical measures that were appropriate for use with subjects in the age group studied, making minimal sensory or motor demands. The tests covered three cognitive modalities: verbal recent memory, nonverbal recent memory, and executive functions. Total test administration time was <1 h. Two alternate forms were used to reduce practice effects between sessions. The order of presentation was counterbalanced with half the subjects receiving one form in the first session and the other half receiving the other form. Story Memory and Word List Memory subtests from the Repeatable Battery for the Assessment of Neuropsychological Status [17] were used to test verbal recent memory. Story Memory measures the ability to learn and recall a narrative story in two trials (maximum score, 20) and delayed free recall (maximum score, 10). Word List Memory assesses the ability to learn and remember a list of ten unrelated words across four sequential learning trials (maximum score, 40), and delayed free recall (maximum score, 10). The Brief Visual Memory Test Revised [18] was used to test nonverbal recent memory. A card with six simple geometric designs was shown for 10 s on three sequential trials to test nonverbal recent memory. When the card was removed, the examinee drew the designs in the locations remembered (two points per design; maximum score, 36). A free recall trial was administered 20 min later (maximum score, 12). Backward Digit Span [19], Semantic Fluency [17], i.e., name all the fruits and vegetables (form A) or all the animals in the zoo (form B) that you can think of in 1 min, and Phonemic Fluency [20], i.e., name all the words that you can think of that start with the letter 'S' (form A) and letter 'P' (form B) in 1 min, were used to test executive functions. The test scores are the numbers of correct responses produced in the allotted time. The clinicians who tested the neurocognitive functions were blinded to group participation.

Depression testing

Depression was assessed with the Geriatric Depression Scale 15-item version [21]. The obtained score was the number of symptoms endorsed. Scores range from 0 to 15 with higher scores indicating greater depression.

Sample size determination

We used our pilot data to determine sample size [13]. In our pilot study, with a sample size of 28 patients per group, we successfully demonstrated that patients with metabolic syndrome exhibited more profound short-term cognitive deficits after cardiac surgery than did their healthier counterparts. Therefore, we included 30 subjects per group in the current investigation.

Statistical analysis

Chi-square and Student's *t* tests were used for proportions and continuous variables, respectively, to test for between-group differences in demographic and medical data. Neurocognitive scores were analyzed by repeated measures of analysis of variance followed by Bonferroni correction for multiple comparisons. Moller's *Z* scores were also used to assess cognitive change from baseline to 1 month after surgery [14]. The *Z* score for the change in each neuropsychological assessment was calculated by using the following formula: Z score = [(Change Score) − (Mean Change Score$_{control}$)]/(SD Change Score$_{control}$). A suitable normative population was used to correct for practice effects and variability between sessions (control) [15]. We calculated average *Z* scores for all cognitive indices. Overall cognitive performance between groups, based on

Table 1 Demographics and medical data

Factor	Surgical		Nonsurgical	
	Metabolic (−), $n = 30$	Metabolic (+), $n = 30$	$n = 30$	*P*
Age (years)	65 ± 7	64 ± 6	63 ± 7	0.54
Education (year)	13 ± 2	13 ± 2	12 ± 2	0.90
Body mass index	27 ± 6	35 ± 6	31 ± 6	0.00003
History of smoking (%)	20 (67)	17 (57)	11 (37)	0.06
Sleep disorder (%)	16 (53)	17 (57)	16 (53)	0.92
Hypertension (%)	17 (57)	28 (93)	20 (67)	0.005
Hypercholesterolemia (%)	6 (20)	27 (90)	18 (60)	0.000001
Arrhythmia (%)	4 (13)	5 (17)	3 (10)	0.75
Myocardial infarction (%)	1 (3)	3 (10)	4 (13)	0.38
Peripheral vascular disease (%)	2 (7)	3 (10)	1 (3)	0.58
Type 2 diabetes mellitus (%)	4 (13)	22 (73)	12 (40)	0.00002
Congestive heart failure (%)	4 (13)	3 (10)	2 (7)	0.69
History of depression (%)	6 (20)	8 (27)	10 (33)	0.50
History of anxiety (%)	5 (17)	1 (3)	5 (17)	0.19
Chronic obstructive pulmonary disease (COPD)	1 (3)	3 (10)	2 (7)	0.58
Preoperative medications				
Antihypertensive drugs (%)	19 (63)	26 (87)	21 (70)	0.10
Lipid-lowering drugs (%)	9 (30)	22 (73)	17 (57)	0.003
Oral hypoglycemic (%)	2 (7)	10 (33)	8 (27)	0.04
Insulin (%)	1 (3)	9 (30)	6 (20)	0.02
Neurological abnormality, baseline (%)	3 (10)	5 (17)	4 (13)	0.75
Neurological abnormality, 1 week (%)	3 (10)	5 (17)	4 (13)	0.75

Data are expressed as number (%) or mean ± SD; *P* values are derived from analysis of variance for continuous variables and chi-square for dichotomous variables after the comparison of all three groups average Z scores, was compared using the Wilcoxon rank-sum test. Patients were defined as having postoperative cognitive dysfunction (POCD) when two Z scores in individual tests or the average Z score were less than -1.96. The null hypothesis was rejected when $P < 0.05$. All errors were reported as standard deviations. Statistical calculations were performed using NCSS 2001 (NCSS, Kaysville, UT, USA) and STATA/IC 10.0 (StataCorp LP, College Station, TX, USA) software.

Results

Patients with metabolic syndrome were significantly ($P < 0.05$) more likely to have elevated body mass index, hypertension, hypercholesterolemia, and type 2 diabetes mellitus compared with those who did not have the syndrome (Table 1). Patients with metabolic syndrome also were more frequently receiving preoperative lipid-lowering agents, oral hypoglycemic drugs, and insulin (Table 1). No other significant differences in demographic or medical data were observed. Surgery and postoperative data were similar between groups (Table 2). Neurocognitive scores under the baseline conditions and after a 1-month interval were similar in nonsurgical controls with versus without metabolic syndrome (Table 3). Neurocognitive scores under the baseline conditions were similar in surgical patients with versus without metabolic syndrome in all three cognitive modalities (nonverbal and verbal recent memory, and executive functions) (Table 4). Significant reductions in tests of verbal memory (delayed story recall, immediate and delayed word list recall) and one test of executive function (backward digit span) were observed in patients with versus without metabolic syndrome after surgery (Table 4). No differences in geriatric depression scale ratings were observed between groups. The Hachinski score was less than 4 in all subjects. Overall cognitive performance after surgery was significantly ($P = 0.03$) more profoundly impaired in patients with versus without metabolic syndrome. The difference in surgical types did not affect POCD ($P = 0.25$). The prevalence rate of POCD was different in the studied groups (13/30 and 8/30 in patients with versus without metabolic syndrome; $P < 0.02$).

Discussion

The current results indicate that patients with metabolic syndrome are more likely to develop cognitive impairment 1 month after noncardiac surgery than those without the disorder. These results confirm and extend our previous findings that patients with metabolic syndrome exhibit more profound short-term cognitive deficits, especially those involving verbal recent memory, after cardiac surgery than do their healthier counterparts [13]. Patients to the present investigation were enrolled based on the inclusion criteria: one criterion was that patients had to be at least 55 years of age. During the study interview (after informed consent) patients were asked about their years of education. After statistical analysis it was determined that patient groups in the study were balanced in age and education (see Table 1). The similarities of these criteria are very important when we compare the groups' cognitive functions.

During the past decade, there has been various attempts to standardize the definition of the metabolic syndrome as a diagnostic category, with various criteria proposed by the following institutions: the World Health Organization (1998), the European Group for Study of Insulin Resistance (1999), the National Cholesterol Education program's Adult Treatment Panel III (2001), the American Association of Clinical Endocrinologists (2003), and the Chinese Diabetes Federation proposal (2005) [1, 22–25]. All these agree on the core components of the syndrome: obesity, insulin resistance, dyslipidemia, and hypertension; however, they provide different clinical criteria. In the present

Table 2 Surgery and postoperative data

Surgery	Metabolic (−), $n = 30$	Metabolic (+), $n = 30$	P
Ear, nose, and throat surgery (%)	6 (20)	4 (13)	
Urological surgery (%)	3 (10)	1 (3)	
Gastrointestinal surgery (%)	6 (20)	8 (27)	
Orthopedic surgery (%)	11 (37)	13 (43)	
Plastic surgery (%)	4 (13)	4 (13)	
ASA physical status class II or III	13/17	5/25	
Sevoflurane dose (%)	1.4 ± 0.5	1.6 ± 0.8	0.92
Anesthesia duration (min)	158 ± 74	188 ± 87	0.15
Hospital stay (days)	5 ± 8	6 ± 10	0.61
Postoperative complications (%)	3 (10)	7 (23)	0.30

Data are expressed as number (%), frequency, or mean ± SD

P values are derived from t tests for continuous variables and Fisher's exact test for dichotomous variables

ASA American Society of Anesthesiologists

Table 3 Neurocognitive scores of nonsurgical controls

Variables	Metabolic (−), $n = 15$		Metabolic (+), $n = 15$		pB	p1W
	Baseline	1 week	Baseline	1 week		
Nonverbal memory						
Figure reconstruction	20 ± 6	22 ± 4	21 ± 7	21 ± 8	0.28	0.39
Delayed figure reproduction	8 ± 2	8 ± 2	7 ± 3	8 ± 3	0.8	0.44
Verbal memory						
Immediate story recall	18 ± 3	19 ± 3	17 ± 3	18 ± 3	0.21	0.94
Delayed story recall	9 ± 2	10 ± 2	8 ± 3	9 ± 2	0.2	0.91
Immediate word list recall	24 ± 3	26 ± 4	21 ± 5	24 ± 5	0.22	0.44
Delayed word list recall	5 ± 2	5 ± 3	4 ± 2	5 ± 2	0.56	0.27
Executive functions						
Backward digit span	9 ± 2	10 ± 2	7 ± 2	8 ± 2	0.57	0.67
Semantic fluency	15 ± 4	16 ± 4	15 ± 4	14 ± 3	0.52	0.37
Phonemic fluency	12 ± 4	12 ± 4	12 ± 4	11 ± 3	0.87	0.34
Stroop	41 ± 12	47 ± 16	37 ± 13	37 ± 16	0.3	0.08
GDS-15	6 ± 5	6 ± 5	5 ± 5	4 ± 4	0.39	0.22

Data are expressed as mean ± SD

pB P value for between-group comparisons under baseline conditions (Student's *t* test); *p1W* between-group significance after 1 week (repeated-measures analysis of variance)

Table 4 Neurocognitive scores of surgical patients

Variables	Metabolic (−), $n = 30$			Metabolic (+), $n = 30$			pB	p1W	*Z* score difference
	Baseline	1 week	Z scores	Baseline	1 week	Z scores			
Nonverbal memory									
Figure reconstruction	24 ± 6	21 ± 7	−1.2	24 ± 7	18 ± 9	−1.9	0.88	0.02	−0.7
Delayed figure reproduction	9 ± 2	7 ± 3	−1.4	9 ± 3	6 ± 3	−1.4	0.61	0.9	0.0
Verbal memory									
Immediate story recall	20 ± 2	18 ± 3	−1.4	19 ± 4	16 ± 4	−1.8	0.54	0.2	−0.4
Delayed story recall	10 ± 2	9 ± 2	−1.3	10 ± 2	8 ± 3	−1.9	0.89	0.003*	−0.6
Immediate word list recall	27 ± 5	25 ± 5	−1.1	26 ± 5	21 ± 5	−1.9	0.54	0.00008*	−0.8
Delayed word list recall	7 ± 2	5 ± 2	−1.4	7 ± 2	4 ± 2	−2.0	0.53	0.004*	−0.6
Executive functions									
Backward digit span	10 ± 2	9 ± 2	−1.2	10 ± 2	7 ± 2	−1.9	0.54	0.002*	−0.7
Semantic fluency	16 ± 5	14 ± 4	−0.8	15 ± 3	13 ± 4	−0.7	0.49	0.71	0.1
Phonemic fluency	14 ± 5	13 ± 5	−0.3	11 ± 4	10 ± 4	−0.2	0.03	0.94	−0.1
Stroop	48 ± 10	42 ± 9	−1.0	46 ± 12	40 ± 13	−1.1	0.61	0.47	−0.1
GDS-15	3 ± 3	3 ± 3	−0.1	4 ± 3	3 ± 3	0.3	0.67	0.90	0.2

Data are expressed as mean ± SD

pB P value for between-group significance under baseline conditions (Student's *t* test); *p1W* between-group significance after 1 week (repeated-measures analysis of variance)

*Significant at $P < 0.005$ with Bonferroni correction

investigation we only included people from the American veteran population; therefore, our findings may not translate entirely to populations in other countries including Japan.

The psychometric test battery used in the current and previous [13] investigations was designed to measure performance in recent verbal and nonverbal memory and executive functions because cognitive impairments may develop in these domains after surgery [26, 27]. Postoperative impairment was detected in all examined cognitive modalities, but the most pronounced deterioration occurred in recent verbal memory (delayed story recall, immediate and delayed word list recall) and in one test of executive function (backward digit span) in metabolic syndrome patients. Dysfunction in recent memory may result from impairments in the hippocampi, entorhinal cortices, thalami, and basal forebrain [28]. Executive function deficits may occur because of reduced activity in prefrontal cortices (including the dorsolateral white matter tracts) in middle-aged and elderly individuals [29]. We presume that abnormal activity in these regions may have been responsible for the cognitive dysfunction observed in metabolic syndrome patients, but we did not conduct cerebral activity imaging studies (e.g., functional magnetic resonance imaging) in the current investigation to confirm this hypothesis. Nevertheless, the neuropsychological deficits that we observed in metabolic syndrome patients predict compromised postoperative rehabilitation [30] and have important consequences on activities of daily living.

Differences in the degree of postoperative cognitive impairment observed among individuals may reflect site-specific variability in cognitive reserve [31]. Indeed, this lack of cognitive reserve may be a plausible explanation for the greater occurrence and increased severity of postoperative cognitive dysfunction in patients with versus without metabolic syndrome. Our data suggest that patients with metabolic syndrome, in contrast to healthier individuals, were unable to adequately compensate for the modest cognitive deficits that are commonly associated with noncardiac surgery. These differences may have been further accentuated because our investigation was conducted in older patients (age ≥55 years), who are already known to be at substantially greater risk for postoperative cognitive deficits [32–34] because of reduced brain weight and volume, loss of cellular bodies and myelinated fibers in several brain regions responsible for cognition, decreased synaptic density, and attenuated DNA-repair capability [35–38].

The precise mechanism(s) responsible for postoperative cognitive dysfunction in patients with metabolic syndrome are most likely multifactorial in origin. Many of the diagnostic characteristics that define metabolic syndrome are individually related to cognitive impairment, as hypertension, obesity, elevated serum triglyceride concentrations, and hyperglycemia [39–42] are all known risk factors for postoperative cognitive dysfunction. When combined with effects from anesthetic and analgesic drugs, sleep deprivation, the stress of major surgery, and hospital environmental effects on cognition, these metabolic syndrome determinants may produce additive or synergistic depression of cognitive ability. The presence of other comorbid preexisting diseases also contributes to the development of postoperative cognitive dysfunction, but no differences in other risk factors were observed between groups. Whether general anesthesia contributed to the development of postoperative cognitive dysfunction in the patients with versus without metabolic syndrome is unclear, but anesthesia was standardized between groups to minimize this potential confounding factor. The results must also be qualified because women were not included in the current investigation; the VA patient population consists almost entirely of men. We did not evaluate whether differences in postoperative cognitive dysfunction between patients with or without metabolic syndrome persisted over longer periods of time. However, it is important to emphasize that patients with cognitive dysfunction at hospital discharge are more likely to die during the first 3 months after surgery [28]. Additional study is required to assess the general impact of metabolic syndrome on long-term cognitive functions and quality of life after noncardiac surgery. Last, the current results should also be quantified because baseline cognitive differences were not apparent between study groups. It is certainly possible that our older veterans without metabolic syndrome may have exhibited baseline subclinical cognitive deficits that were not yet detectable with a neuropsychological battery. Under these circumstances, baseline differences in cognitive function between patients with versus without metabolic syndrome may have been obscured.

In summary, the current results demonstrate that patients with metabolic syndrome have more pronounced cognitive deficits, particularly those involving recent verbal memory and executive function, at 1 month after noncardiac surgery than do their healthier counterparts. These data confirm and extend our previous results indicating that metabolic syndrome is a major risk factor for postoperative cognitive dysfunction in patients undergoing cardiac surgery using cardiopulmonary bypass [13]. Additional studies are required to determine the duration or permanence of these cognitive changes and their potential impact on rehabilitation and quality of life in this vulnerable patient population.

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Conflict of interest The authors have no conflicts of interest pursuant to this work.

References

1. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285:2486–97.
2. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung,

and Blood Institute Scientific Statement. Circulation. 2005;112: 2735–52.

3. Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, Isles C, Macfarlane PW, Packard CJ, Cobbe SM, Shepherd J. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. Circulation. 2003;108: 414–9.
4. Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. Am J Epidemiol. 2002;156:1070–7.
5. Elias MF, Sullivan LM, D'Agostino RB, Elias PK, Beiser A, Au R, Seshadri S, DeCarli C, Wolf PA. Framingham stroke risk profile and lowered cognitive performance. Stroke. 2004;35:404–9.
6. Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kareholt I, Winblad B, Helkala EL, Tuomilehto J, Soininen H, Nissinen A. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol. 2005;62:1556–60.
7. Abbatecola AM, Paolisso G, Lamponi M, Bandinelli S, Lauretani F, Launer L, Ferrucci L. Insulin resistance and executive dysfunction in older persons. J Am Geriatr Soc. 2004;52:1713–8.
8. Reitz C, Luchsinger J, Tang MX, Manly J, Mayeux R. Impact of plasma lipids and time on memory performance in healthy elderly without dementia. Neurology. 2005;64:1378–83.
9. Yaffe K, Haan M, Blackwell T, Cherkasova E, Whitmer RA, West N. Metabolic syndrome and cognitive decline in elderly Latinos: findings from the Sacramento Area Latino Study of Aging study. J Am Geriatr Soc. 2007;55:758–62.
10. Kalmijn S, Foley D, White L, Burchfiel CM, Curb JD, Petrovitch H, Ross GW, Havlik RJ, Launer LJ. Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men. The Honolulu-Asia aging study. Arterioscler Thromb Vasc Biol. 2000;20:2255–60.
11. Vanhanen M, Koivisto K, Moilanen L, Helkala EL, Hanninen T, Soininen H, Kervinen K, Kesaniemi YA, Laakso M, Kuusisto J. Association of metabolic syndrome with Alzheimer disease: a population-based study. Neurology. 2006;67:843–7.
12. Roriz-Cruz M, Rosset I, Wada T, Sakagami T, Ishine M, De Sa Roriz-Filho J, Cruz TR, Hosseinkhani M, Rodrigues RP, Sudoh S, Arai H, Wakatsuki Y, Souza AC, Nakagawa M, Kita T, Matsubayashi K. Cognitive impairment and frontal-subcortical geriatric syndrome are associated with metabolic syndrome in a stroke-free population. Neurobiol Aging. 2007;28:1723–36.
13. Hudetz JA, Patterson KM, Iqbal Z, Gandhi SD, Pagel PS. Metabolic syndrome exacerbates short-term postoperative cognitive dysfunction in patients undergoing cardiac surgery: results of a pilot study. J Cardiothorac Vasc Anesth. 2011;25(2):282–7. doi: 10.1053/j.jvca.2010.06.008.
14. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, Langeron O, Johnson T, Lauven PM, Kristensen PA, Biedler A, van Beem H, Fraidakis O, Silverstein JH, Beneken JE, Gravenstein JS. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet. 1998;351:857–61.
15. Rasmussen LS, Larsen K, Houx P, Skovgaard LT, Hanning CD, Moller JT. The assessment of postoperative cognitive function. Acta Anaesthesiol Scand. 2001;45:275–89.
16. Hachinski V, Munoz D. Vascular factors in cognitive impairment—where are we now? Ann N Y Acad Sci. 2000;903:1–5.
17. Randolph C (1998) Repeatable battery for the assessment of neurological status. Psychological Corporation, San Antonio
18. Benedict RH, Schretlen D, Groninger L, Dobraski M, Shpritz B. Revision of the brief visuospatial memory test: studies of normal performance, reliability, and validity. Psychol Assess. 1996;8: 145–53.
19. Wechsler DA (1997) Wechsler adult intelligence scale. 3rd edn. The Psychological Corporation, San Antonio
20. Benton AL, Hamsher K (1989) Multilingual aphasia examination. AJA Associates, Iowa City
21. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982;17: 37–49.
22. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998;15:539–53.
23. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabet Med. 1999;16:442–3.
24. Einhorn D, Reaven GM, Cobin RH, Ford E, Ganda OP, Handelsman Y, Hellman R, Jellinger PS, Kendall D, Krauss RM, Neufeld ND, Petak SM, Rodbard HW, Seibel JA, Smith DA, Wilson PW. American College of Endocrinology position statement on the insulin resistance syndrome. Endocr Pract. 2003;9: 237–52.
25. Holt RI. International Diabetes Federation re-defines the metabolic syndrome. Diabetes Obes Metab. 2005;7:618–20.
26. Dijkstra JB, Houx PJ, Jolles J. Cognition after major surgery in the elderly: test performance and complaints. Br J Anaesth. 1999;82:867–74.
27. Johnson T, Monk T, Rasmussen LS, Abildstrom H, Houx P, Korttila K, Kuipers HM, Hanning CD, Siersma VD, Kristensen D, Canet J, Ibanaz MT, Moller JT. Postoperative cognitive dysfunction in middle-aged patients. Anesthesiology. 2002;96:1351–7.
28. Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, Gravenstein JS. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology. 2008;108: 18–30.
29. Gunning-Dixon FM, Raz N. Neuroanatomical correlates of selected executive functions in middle-aged and older adults: a prospective MRI study. Neuropsychologia. 2003;41:1929–41.
30. Ihara H, Berrios GE, London M. Group and case study of the dysexecutive syndrome in alcoholism without amnesia. J Neurol Neurosurg Psychiatry. 2000;68:731–7.
31. Maze M, Cibelli M, Grocott HP. Taking the lead in research into postoperative cognitive dysfunction. Anesthesiology. 2008;108: 1–2.
32. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, Mark DB, Reves JG, Blumenthal JA. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med. 2001;344:395–402.
33. Newman MF, Croughwell ND, Blumenthal JA, Lowry E, White WD, Spillane W, Davis RD Jr, Glower DD, Smith LR, Mahanna EP, Reves JG. Predictors of cognitive decline after cardiac operation. Ann Thorac Surg. 1995;59:1326–30.
34. Selnes OA, Goldsborough MA, Borowicz LM, McKhann GM. Neurobehavioural sequelae of cardiopulmonary bypass. Lancet. 1999;353:1601–6.
35. Schwartz M, Creasey H, Grady CL, DeLeo JM, Frederickson HA, Cutler NR, Rapoport SI. Computed tomographic analysis of brain morphometrics in 30 healthy men, aged 21 to 81 years. Ann Neurol. 1985;17:146–57.
36. Morrison JH, Hof PR. Life and death of neurons in the aging brain. Science. 1997;278:412–9.
37. Pakkenberg B, Gundersen HJ. Neocortical neuron number in humans: effect of sex and age. J Comp Neurol. 1997;384:312–20.
38. Simic G, Kostovic I, Winblad B, Bogdanovic N. Volume and number of neurons of the human hippocampal formation in

normal aging and Alzheimer's disease. J Comp Neurol. 1997; 379:482–94.
39. Elias MF, Wolf PA, D'Agostino RB, Cobb J, White LR. Untreated blood pressure level is inversely related to cognitive functioning: the Framingham Study. Am J Epidemiol. 1993;138: 353–64.
40. Farr SA, Yamada KA, Butterfield DA, Abdul HM, Xu L, Miller NE, Banks WA, Morley JE. Obesity and hypertriglyceridemia produce cognitive impairment. Endocrinology. 2008;149: 2628–36.
41. West NA, Haan MN. Body adiposity in late life and risk of dementia or cognitive impairment in a longitudinal community-based study. J Gerontol A Biol Sci Med Sci. 2009;64:103–9.
42. Hudetz JA, Warltier DC. Cognitive function in older diabetic subjects with a history of alcohol abuse. Psychol Rep. 2007;101: 1125–32.