2011

Metabolic syndrome, cognitive performance and dementia: A review

Georgina E. Crichton
University of South Australia

Merrill F. Elias
University of Maine, mfelias@maine.edu

Jonathan Buckley
University of South Australia

Karen Murphy
University of South Australia

Janet Bryan
University of South Australia

See next page for additional authors

Journal of Alzheimer's Disease 28 (2011) 1–11
DOI 10.3233/JAD-2011-111022
IOS Press

Review

Metabolic Syndrome, Cognitive Performance, and Dementia

Georgina E. Crichton[a,*], Merrill F. Elias[b], Jonathan Buckley[a], Karen J. Murphy[a] and Janet Bryan[a,c] and Vincenza Frisardi[d]
[a]*Nutritional Physiology Research Centre, University of South Australia, Adelaide, Australia*
[b]*Department of Psychology and Graduate School of Biomedical Sciences, University of Maine, Orono, Maine, USA*
[c]*School of Psychology, University of South Australia, Adelaide, Australia*
[d]*Department of Geriatrics, Center for Aging Brain, Memory Unit, University of Bari, Bari, Italy*

Accepted 10 July 2010

Abstract. Obesity, hypertension, dyslipidemia, and insulin resistance have been associated with an increased risk of cognitive impairment or dementia. Together, these risk factors cluster as metabolic syndrome (MetS). The first aim of this systematic review was to identify and critically review studies assessing associations between MetS and cognition, with consideration given both to early cognitive changes and the severe endpoint of dementia. The second aim was to identify and discuss limitations in the literature and subsequent difficulties in drawing conclusions from research to date. Nine studies that assessed cognitive performance and ten studies that estimated incidence of dementia in relation to MetS were identified and appraised. Limitations in the literature include the lack of standardized nomenclature for cognitive variables, the use of multiple MetS definitions, and the difficulty in differentiating the adverse effects of multiple risk factors on cognition.

Keywords: Alzheimer's disease, cognition, dementia, metabolic syndrome

INTRODUCTION

Cognitive decline and dementia are significant health issues given the aging of the world population [1]. An emerging literature indicates that metabolic syndrome (MetS) is a risk factor for lower cognitive function and dementia. In the present paper we review substantive findings in this literature with a focus on important methodological issues surrounding this research. Importantly, we include research on cognitive deficit in non-demented individuals in our review. We take this approach because poorer performance in cognitively normal individuals is one of the most important risk factors for dementia [2, 3] and Alzheimer's disease (AD) [4].

Several previous reviews have dealt with associations among specific components of MetS and cognitive functioning. It is clear that individual cardiovascular events and risk factors are associated with lowered cognition and dementia [5]; and a growing research literature suggests that multiple vascular risk factors may have an additive adverse effect on cognition, resulting in increased risk for dementia [6–9]. MetS is of concern partly because it represents a clustering of risk factors for morbidity and mortality [10, 11] and partly because these risk factors may interact in a synergistic manner to influence cognition in a negative manner.

MetS has been defined as a clustering of the following risk factors: Central obesity, elevated blood

*Correspondence to: Georgina E. Crichton, Nutritional Physiology Research Centre, University of South Australia, GPO Box 2471, Adelaide, South Australia 5001, Australia. Tel.: +61 8 83021452; Fax: +61 8 83022178; E-mail: whige003@mymail.unisa.edu.au.

ISSN 1387-2877/11/$27.50

pressure, dyslipidemia (elevated triglycerides and lowered high-density lipoprotein cholesterol), and insulin resistance [12]. The clustering of these specific cardiovascular disease (CVD) risk factors is associated with an increased risk of developing CVD and diabetes [12] as compared with the risk associated with each individual risk factor acting alone. MetS is associated with an increased risk of stroke [13], and in addition, abdominal obesity and MetS are strongly associated with elevated concentrations of atherogenic lipoproteins, and therefore increase the risk of coronary heart disease [14]. While there is no single known cause for MetS, a number of non-modifiable factors including age, genetics, ethnicity, and gender, influence its prevalence [15]. Importantly, lifestyle factors, such as diet, are a primary contributor to both the development and subsequent course of MetS [16].

GOALS OF THE REVIEW

One recent review examined nine prospective population-based studies which addressed MetS and one or more of its individual risk factors for cognitive disorders [17]. These authors concluded that MetS is highly likely to be associated with cognitive impairment and vascular dementia (VaD), but not to AD. Following from this review and other papers in this special issue of the *Journal of Alzheimer's Disease*, the major objective of the present review is to address two methodological challenges in this area of research: 1) determining which specific cognitive abilities are adversely affected by MetS; and 2) separating the role of the multiple influence of risk factors specific to MetS from the impact of multiple risk factors in general on cognition. Given the early stage of this research we include both cross-sectional and prospective studies, including longitudinal analyses.

LITERATURE SELECTION

A search was undertaken on electronic databases for studies that examined cognitive functioning associated with MetS, or estimated prevalence or incidence of probable dementia associated with MetS. The search was limited to studies that reported on MetS as a global indicator of vascular risk, and excluded studies that examined only one or more of the individual components of the syndrome. MetS had to be diagnosed based on having any three of five risk factors (elevated waist circumference, elevated triglycerides, reduced high-density lipoprotein cholesterol, elevated blood pressure, elevated fasting glucose) according to Alberti et al. [12]. Cognitive function studies had to provide measures for at least one aspect of cognition obtained from neuropsychological testing. Publications which used self-reported cognitive function were excluded. Dementia risk studies had to provide an estimate of probable dementia, including AD, VaD, or mild cognitive impairment (MCI). Studies were not required to have included brain imaging in their assessment but those which used only single test screening measures as indices of dementia or cognitive function were excluded. If it was unclear whether the paper met the inclusion criteria, the full text was obtained. A total of 19 studies were included in this review. Two papers reported results from the same study, but as they assessed different outcome measures, they were treated as two separate studies for the purpose of this review [18, 19].

The studies included in this review varied greatly in terms of study design and outcome measures. Nine studies used standardized neuropsychological testing to assess cognitive performance as the primary outcome measure. Ten studies used a combination of screening measures, neuropsychological testing, clinical evaluations, and brain imaging to make diagnoses of one or a combination of AD, VaD, or MCI.

ASSESSMENT OF COGNITION

Neuropsychological testing

Authors identify the underlying latent variables (cognitive domains) measured by various tests, or test composites, differently. This makes it difficult if not impossible to determine which specific domains of cognitive functioning are affected by MetS and its components. In order to draw conclusions about which cognitive measures are associated with MetS, one must use a standard definition of tests. In this review, we accomplish this objective by what tests measure using Lezak [20], a much recognized authoritative text and taxonomy of measures.

The majority of studies assessed at least three different cognitive abilities. Some studies used a single test as a measure of a particular cognitive ability, while others used a combination of tests. The two case-control studies [21, 22] conducted the most thorough neuropsychological assessments, each one measuring at least six cognitive abilities. The most commonly tested cognitive abilities in terms of the Lezak taxonomy were memory, psychomotor speed, and attention. Verbal learning and recall tests were the most frequently

used measure of memory. Verbal fluency and language tests were also frequently performed. Processing speed was most commonly assessed using letter, symbol or digit substitution tasks. Perception and construction were assessed less frequently.

Dementia status measures

Ten studies determined the likelihood of dementia (including AD, VaD, and MCI) associated with MetS. All used the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) work group criteria for a diagnosis. Five of the six studies used brain imaging as part of their assessment procedure [23–27].

Assessment of metabolic syndrome

The Third Adult Treatment Panel of the National Cholesterol Education Program (ATP III NCEP) criteria [16] was used in 13 studies. Five studies used this definition but with slight variations. As they still required the presence of any three of the five risk factors, they were included in the review. Modifications made to the ATP III NCEP criteria were higher cut-off values for hypertension to adjust for older populations [28] and the use of body mass index instead of waist circumference as an indicator of abdominal obesity [27, 29]. Three studies used slightly altered glucose criterion [22, 28, 29]. One study used a modified version of the ATP III NCEP criteria (diabetes defined by self-report or medication use) and the European Group for the Study of Insulin Resistance (EGIR) criteria to compare any differences in findings by using two definitions which focus on different risk factors [30]. As three components of MetS were still required for diagnosis, the study was included.

MAJOR FINDINGS

Table 1 summarizes all studies that found significant associations between MetS and impaired cognitive performance or dementia. Studies which did not find an association between MetS and cognitive performance or dementia, or which found negative associations between them, are described in Table 2.

Metabolic syndrome and cognitive performance

Classifying tests by Lezak [20], MetS was associated with significantly poorer cognitive performance in four cross-sectional studies [21, 22, 28, 31]. The two cross-sectional case-control studies found that persons with MetS had statistically lower mean levels of performance in psychomotor speed [21, 22], verbal fluency [21], and arithmetic reasoning [21] than the 'control' referent groups. The remaining two cross-sectional studies reported similar findings, with psychomotor speed, verbal memory, perception, attention, concept formation and global cognition negatively associated with MetS [28, 31].

In the one prospective study [32], MetS was associated with a higher risk of poor memory performance at follow up 12 years later. Studies which included longitudinal analyses found that MetS was associated with declines in verbal fluency over a 14-year period [33], and with declines in global cognition (assessed by a screening measure) over three years [34]. The findings of one longitudinal study [29] were in contrast to the other included studies. Although at 5-year follow-up, there was significant decline in cognitive function (MMSE, processing speed, and verbal memory), the authors reported that those with MetS had 'decelerated decline' over this time period [29]. This study was conducted in elderly persons between the ages of 85 and 90.

Metabolic syndrome and dementia risk

MetS-related risk for AD was increased significantly in two studies [25, 26], for VaD in two studies [18, 24], and for progression from MCI to dementia in one study [19]. Associations found between MetS and any dementia type (MCI, AD, VaD) in another study [27] did not remain statistically significant with statistical adjustment for education, ethnicity, and depressed mood. In contrast, a significantly lower risk for AD in those aged 75 years or older with MetS was found in one study [35], which adjusted for demographic and cardiovascular factors.

Two cross-sectional studies did not find an association between dementia and MetS; one did not include any brain imaging in their neuropsychological assessment [36], and neither adjusted statistically for potential confounding variables [23, 36]. These two studies also had considerably smaller sample sizes than the cross-sectional studies that did find positive associations between MetS and dementia, so may have been insufficiently powered to detect such relationships. One prospective study failed to find an association between the presence of MetS and increased risk for dementia and its main subtypes over four years, in an elderly population [30].

Table 1
Studies finding positive associations between metabolic syndrome and cognitive impairment or dementia

Study	n Gender	Cognitive abilities[a] or dementia type (and associated OR/HR, 95% CI) associated with MetS	Single risk factors associated with impaired cognition/dementia	Adjustments
Cross-sectional				
Dik et al. [28][b]	1183 M/F	Perception & abstract reasoning (Fluid intelligence) Psychomotor speed Verbal memory Global cognition (Screening test)	Hyperglycemia (psychomotor speed, perception & abstract reasoning, verbal memory, screening test) Low HDL cholesterol (psychomotor speed, perception & abstract reasoning)	Age, gender, education, smoking, alcohol; diabetics excluded
Cavalier et al. [31][b]	819 M/F	In men: Verbal memory Attention, concept formation (screening test)	Not examined	Age, gender, education, depressed mood, coronary heart disease
Vanhanen et al. [26][b]	959 M/F	AD (OR 2.71, 95% CI 1.44–5.10)	In women: Low HDL cholesterol, high fasting glucose associated with AD prevalence	Age, education, ApoE4 genotype, total cholesterol, diabetes
Cross-sectional: Case-control				
Segura et al. [21][b]	55 MetS, 35 controls M/F	Psychomotor speed Verbal fluency Arithmetic reasoning (Working memory/executive function)	Not examined	Education, gender,
van den Berg et al. [22][b]	83 MetS, 64 DM2, 100 controls M/F	Attention (Information processing speed[c], Executive function[c]) Psychomotor speed[c] Verbal fluency (Executive function)[c]	None	Age, gender, estimated IQ
Razay et al. [25][b]	50 AD, 75 controls M/F	AD (OR 3.20, 95% CI 1.20–8.40)	Elevated triglycerides, hyperglycemia, low HDL cholesterol (in those with AD compared with controls). Hypertension associated with decreased risk of AD	Age, gender, location (controls: Similar age range, no memory complaints, normal scores on MMSE); diaetic treatment excluded
Prospective				
Komulainen et al. [32][b]	101 F	Verbal memory	Low HDL cholesterol (memory)	Age, education, depression
Reffaitin et al. [24][b]	7087 M/F	VaD (HR 2.44, 95% CI 1.25–4.77)	High triglycerides at baseline associated with increased risk of all-cause dementia & VaD risk Diabetes significantly associated with increased risk of all-cause dementia & VaD	Age, gender, education, city center, ApoE4 genotype

(*continued next page*)

Table 1 (*continued*)

Study	*n* Gender	Cognitive abilities[a] or dementia type (and associated OR/HR, 95% CI) associated with MetS	Single risk factors associated with impaired cognition/dementia	Adjustments
Yaffe et al. [34][b]	4895 F	Cognitive impairment (OR 1.66, 95% CI 1.14–2.41)	Multivariate: No longer significant. 17% increase in risk of impairment per unit increase in number of MetS components. High glucose significantly associated with cognitive impairment	Age, race, depressed, mood, education
Solfrizzi et al. [18]	2097 M/F	VaD (HR 3.71, 95% CI 1.40–9.83)	Risk increased when subjects with baseline under- nutrition excluded; risk increased for inflammation. No individual MetS component associated with dementia risk	Age, gender, education, alcohol, smoking, fibrinogen, non-high density lipoprotein cholesterol, ratio of ApoB to ApoA-I, coronary artery disease, stroke
Solfrizzi et al. [18]	2097 M/F	VaD (HR 3.71, 95% CI 1.40–9.83)	Risk increased when subjects with baseline under- nutrition excluded; risk increased for subjects with MetS & high inflammation. No individual MetS component associated with dementia risk	Age, gender, education, alcohol, smoking, fibrinogen, non-high density lipoprotein cholesterol, ratio of ApoB to ApoA-I, coronary artery disease, stroke
Longitudinal				
Van den Berg et al. [29][b]	562 M/F	Global cognition (screening test)[d] Psychomotor speed[d] attention[d]	Elevated fasting glucose (screening test)[d] BMI (screening test)[d]	Gender, education
Yaffe et al. [34][b]	1624 M/F	Global cognition (screening test)	Elevated fasting glucose (verbal memory)	Age, gender, education, birth place, depression, smoking, alcohol, MI
Knopman et al. [33][b]	1130 M/F	Verbal fluency	Hypertension (verbal fluency) Diabetes (psychomotor speed)	Age, gender, religion, education

Abbreviations: AD = Alzheimer's disease; Apo = apolipoprotein; BMI = body mass index; CI = confidence interval; DM2 = type 2 diabetes mellitus; F = female; HDL = high-density lipoprotein; HR = hazard ratio; M = male; MCI = mild cognitive impairment; MetS = metabolic syndrome; MI = myocardial infarct; MMSE = Mini-Mental State Examination; OR = odds ratio; VaD = vascular dementia.

[a]Abilities as defined by Lezak [20]; Ability in parentheses represents ability as described by author(s) if differs from Lezak. [b]Significant after full adjustment; [c]Tests grouped together as *z*-scores; [d]Associated with decelerated cognitive decline.

Table 2
Studies finding negative or no associations between metabolic syndrome and cognitive impairment or dementia

Study	*n* Gender	Cognitive abilities or dementia type assessed	Associatio with MetS	Single risk factors associated with impaired cognition/dementia	Adjustments
Cross-sectional					
Gatto et al. [38][a]	853 M/F	Executive function, verbal learning, logical memory, visual episodic memory, semantic memory, global cognition	Nil	Hypertension (verbal learning, semantic memory, global cognition/sum of scores).	Age, gender, ethnicity, education, income, study, depression, medications
Isik et al. [23]	267 M/F	AD, VaD, MCI	Nil	Insulin resistance - no significant difference between those with and without cognitive impairment.	Nil; diabetics excluded
Choi et al. [36]	175 M/F	Probable AD, MCI	Nil	No MetS components associated with probable AD or MCI. Depression significantly associated with AD prevalence.	Nil
Prospective					
Muller et al. [30]	2476 M/F	All-cause dementia, AD, DAS	Nil (using NCEP - ATP III or EGIR criteria)	Diabetes & hyperinsulinemia significantly associated with increased risk for incident AD, DAS, and overall dementia.	Age, gender, education, ethnicity, ApoE4 genotype, smoking, cohort
Forti et al. [35]	749 M/F	Dementia, AD, VaD	In those 75 y or older: MetS associated with a lower risk of AD (HR 0.33, 95% CI 0.12–0.94)	Abdominal obesity significantly associated with lower risk of overall dementia.	Age, gender, education, ApoE4 genotype, physical activity, CVD, stroke, inflammation status, hyperhomocysteinemia

Abbreviations: AD = Alzheimer's disease; Apo = apolipoprotein; CI = confidence interval; CVD = cardiovascular disease; DAS = dementia associated with stroke; EGIR = European Group for the Study of Insulin Resistance; F = female; HR = hazard ratio; M = male; MetS = metabolic syndrome; MCI = mild cognitive impairment; NCEP-ATP III = National Cholesterol Education Program Adult Treatment Program III; VaD = vascular dementia; *y* = years.

[a] Five cognitive domains determined by factor analysis of 14 cognitive tests.

The majority of studies adjusted their statistical analyses for the effects of age, gender, and education. Four studies took into account individual vascular risk factors [18, 19, 26, 35] and four adjusted for apolipoprotein E4 genotype [24, 26, 30, 35].

SUMMARY OF MAIN FINDINGS

For cognitive function measured by neuropsychological testing, detriments in psychomotor speed, verbal memory and fluency, and attention were the abilities most frequently associated with MetS using standard definitions of what tests measure by Lezak [20]. However, these abilities were also those most frequently assessed. Using definitions of cognitive abilities as defined by authors, decrements in executive function (as well as information processing speed and verbal memory) were most frequently reported [21, 22, 28, 31–34]. In addition, having MetS was associated with AD [25, 26] cross-sectionally, with increased risk for VaD over 3.5 to 4 years [18, 24], and with increased risk of progression from MCI to dementia over the same time period [19]. In populations over the age of 75, having MetS was associated with a lower risk of AD [35], and with decelerated cognitive decline [29].

METHODOLOGICAL ISSUES

The ability to determine the specific cognitive abilities most influenced by MetS is difficult. Firstly, the broad range of cognitive measures affected by MetS, may reflect its diffuse effects on the brain function and structure. There was evidence for global effects on cognition in those that used global screening measures of cognition [28, 34]. Further, it is well known that clinical tests are not pure measures of what they purport to measure and are influenced by task difficulty [37]. Absence of test purity was evidenced by the wide-ranging nomenclature used to classify neuropsychological tests. In part this is due to the fact that many clinical tests measure more than one aspect of cognition, and correlate highly with each other.

The frequently used Stroop Color-Word Test and Trail Making Tests A and B are examples of tests that are commonly classified as tests of executive function [21, 22, 31, 38]. Executive function is extremely difficult to separate from general fluid intelligence, evidenced by the literature attempting to determine relationships between the two [39–42], and from memory and attention [43]. The terms executive function or fluid intelligence are often used for tests measuring more defined abilities such as verbal fluency, arithmetic reasoning, abstract reasoning, and attention. The use of these terms interchangeably can therefore make it difficult to 1) directly compare findings, and 2) draw conclusions from them. In depth considerations of the executive function construct indicate that it is often used uncritically in the literature [37] and executive function is often used synonymously with frontal lobe function, an inappropriate practice [44]. Adding to the problem of test impurity is the fact that tests that measure different cognitive constructs are often not always of the same difficulty level.

There are two possibilities that may help to solve these problems in the future. The use of factor analysis to form constellations of theoretically relevant cognitive domains [45], and the use of highly precise laboratory information processing tasks on single cognitive constructs [46], have both been recommended but have not been widely accepted at this point in time. Defining cognitive domains can be improved by using multiple individual tests that measure the same latent construct, and using factor analytic techniques to extract theoretically relevant variables from comprehensive neuropsychological test batteries [47]. These recommendations present two options for improving test purity.

The second major challenge in this literature is the difficulty in determining the effect that specific single risk factors and combinations of multiple risk factors are having on cognition. Of the 19 studies in this review, 17 examined associations between the various components of MetS and cognitive performance. Hyperglycemia or diabetes were associated with poorer cognitive performance [28], cognitive decline [27, 33, 34], with prevalent AD [25, 26], or future likelihood of developing dementia [24]. Both diabetes and hyperinsulinemia were related to higher risk for AD and dementia associated with stroke in one study [30].

Other investigators reported no significant difference in insulin resistance between those with and without cognitive impairment [23], or that associations between the syndrome and poor cognition remained with the exclusion of diabetics [26, 38]. The Hoorn study [22], comparing cognitive function in individuals with MetS without type 2 diabetes, individuals with type 2 diabetes, and control subjects (without diabetes and no more than one MetS component) found similar associations with cognition for those with MetS and those with type 2 diabetes. However, analyses of associations between the five individual MetS components with cognitive performance failed

to find any significant relationships. Other components of MetS such as low high-density lipoprotein cholesterol, elevated triglycerides, and hypertension have been associated with poorer cognitive performance [28, 32, 33, 38], dementia [24–26], or progression from MCI to dementia [19], and yet there are studies indicating that lower levels of total cholesterol are detrimental to cognitive performance [48–50]. Further investigation, taking into account the precise levels of variables such as blood pressure and cholesterol, may improve our understanding about whether or not these components of MetS are positive or negative risk factors for cognitive performance.

Nevertheless, there is evidence that MetS as a whole has a detrimental influence on cognition and that the relationship between MetS and cognition are not simply driven by one predominant component of the syndrome. In a study speaking directly to this issue, Gatto and colleague [38] found a relationship between the number of MetS components and cognitive function, with global cognition and semantic memory scores significantly decreasing with each addition of a MetS component. Cavalier et al. [31] found that an increasing number of MetS components was associated with progressively worse cognitive performance in men. These findings are supported by those of Yaffe and colleagues [27] who found a 17% increase in the risk of impairment per unit increase in the number of MetS components. Similarly, Komulainen et al. [32] found no significant interactions between single risk factors (blood pressure, glucose levels, or waist circumference) with memory function, but women with MetS had a four-times higher risk of poor memory than those without, and, most importantly, increasing the number of MetS components served to further increase the risk. Finally, Solfrizzi et al. [18] found the risk of VaD due to MetS was about four and a half times higher than the additive risk of its individual components. The design of these studies is exemplary with regard to how the issue of relations between MetS and cognition should be approached.

It is important for investigators to take the steps necessary to determine if the MetS relationship to cognition is simply driven by one or more major risk factors such as obesity or diabetes, compared to the impact of MetS *per se*. It is clear that any combination of multiple risk factors, regardless of whether they are components of MetS, predict cognition better than a single risk factor [5, 51]. However at this point in MetS research, it is not known whether it is the specific MetS risk factors that are affecting cognitive function adversely, or if multiple risk factors of any kind have this effect. Consequently, one of the challenges in future research will be to differentiate between the cumulative negative impact on cognition of risk factors specific to MetS and the generally adverse effect of multiple risk factors, including non-metabolic factors and any other combination of CVD risk factors. Using statistical methods [52] to measure the weights for components of a composite variable, and therefore which component is driving the results, will be needed. Secondly, in order to make this distinction, it is important to use standardized MetS criteria, requiring measures of abdominal obesity (waist circumference), high-density lipoprotein cholesterol, fasting plasma glucose, triglycerides, and blood pressure with cut-offs as defined by the recent joint statement from the International Diabetes Federation, National Heart, Lung, and Blood Institute, and American Heart Association [12].

Finally, a number of potential biases in this literature must be considered. Survival bias may play a role in any health study conducted in very elderly populations. Van den Berg and colleagues [29] acknowledge that a 'survivor effect' may explain their findings of decelerated cognitive decline in individuals between the ages of 85 and 90 years. As noted by these authors, participants who have reached the age of 85 and are able to take part in cognitive and health research may be less susceptible to health problems [29]. Forti et al. [35] make similar conclusions with regard to their finding of an association between MetS and lowered risk for AD in persons aged over 75 years. Muller and colleagues [30] similarly offer survival bias as a potential explanation for the lack of associations found between dementia and MetS in an elderly cohort (mean age of 76 years). Interestingly, the studies that found no association between MetS and dementia risk were all conducted in samples aged at least 60 years [23, 30, 36]. As the effect of risk factors on cognition may change with increasing age [22] and consequently for survivors, it is essential that age be considered as a potential effect modifier and that changes in risk factors and cognitive function over time be considered concurrently.

There are other more obvious needs for methodological improvement in studies. The majority of studies (63%) reviewed here [18, 19, 24, 27, 28, 30–35, 38] did make statistical adjustments for age, gender, and education. Fewer studies (47%) took into account other cardiovascular factors, socio-economic, or lifestyle variables (e.g., activity level, physical exercise, depressed mood, personality characteristics), that impact upon cognition [18, 19, 26, 28, 30, 31, 34,

35, 38] (see Tables 2 and 3). That effect sizes were reduced in some studies when confounders such as age, low education, low total cholesterol, and ApoE4 phenotype were adjusted statistically for [26] demonstrates the need to control for potential confounders. Adjusting for confounders may also reveal stronger relations between MetS and cognitive outcomes; Solfrizzi and colleagues [18] demonstrated an increased risk for VaD when baseline nutrition and inflammation status were taken into consideration.

POSSIBLE MECHANISMS FOR METS-COGNITION RELATIONS

Typically, exploring the underlying mechanisms for relations between MetS and cognition has involved considering the individual pathophysiological effects on the brain from each individual component of the syndrome. As recognized by Frisardi and colleagues [53], this view may be reductive to explain the apparent global effects on cognitive decline. Consequently, 'metabolic-cognitive syndrome' (MCS; MetS plus cognitive impairment of degenerative or vascular origin) has been proposed as a pathophysiological model to explain the complex relationship between metabolic disorders, cognitive disturbances, and pathological condition [54]. The mechanisms linking MetS with age-related cognitive decline, MCI, dementia, and AD, are discussed in detail in an excellent review by Frisardi et al. [53], integrating the individual components of MetS and their influence on cognitive decline. The identification of a clinical profile of MCS, as developed by these authors, will be important for future identification of persons at higher risk of developing cognitive impairment.

CONCLUSION

Despite the small number of studies, widespread variations in study design and assessment of cognition, the results of this review suggest that the presence of MetS increases the risk of poor performance cognitively, and of cognitive impairment in an absolute sense (MCI or dementia). Using conventional and relatively standardized definitions of various tests, the strongest evidence for MetS related deficits prior to dementia is for information processing speed, verbal memory, and attention.

This review has hopefully raised awareness of several issues of importance in MetS-cognition research. Not enough evidence with multiple test batteries is available to determine whether these results do not merely reflect a diffuse influence of MetS on global cognition [28, 34] rather than on specific abilities. The use of more comprehensive test batteries and factor analysis applied with an emphasis on theory and empirical relations among variables is recommended. It is extremely important to deal with this issue in future studies as it is important to know if, as recent research suggested, specific patters of cognitive deficit predict decline from normal cognition to MCI and from MCI to different forms of dementia [55, 56].

Finally it is important in future research to have studies that accomplish what should be two major goals in MetS research: 1) To determine whether MetS relations to cognition simply reflect the effects of one or two dominant MetS components, e.g., diabetes, hypertension, and obesity, rather than a synergistic effect of multiple MetS components; and 2) to separate the impact of multiple risk factors of any kind on cognition from the impact of multiple risk factors specific to MetS. This is needed to improve our understanding of what is driving the results between poorer cognition and the syndrome, and how brain function is being affected.

ACKNOWLEDGMENTS

This research was supported in part by the Maurice de Rohan International Scholarship (University of South Australia).

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=940).

REFERENCES

[1] United Nations, World Population Ageing 2009, http://www.un.org/esa/population/publications/WPA2009/WPA2009_WorkingPaper.pdf, Accessed August 10, 2010.

[2] Elias MF, Beiser A, Wolf PA, Au R, White RF, D'Agostino RB (2000) The preclinical phase of Alzheimer disease: A 22-year prospective study of the Framingham Cohort. *Arch Neurol* **57**, 808-813.

[3] Tierney MC, Moineddin R, McDowell I (2010) Prediction of all-cause dementia using neuropsychological tests within 10 and 5 years of diagnosis in a community-based sample. *J Alzheimers Dis* **22**, 1231-1240.

[4] Tierney MC, Yao C, Kiss A, McDowell I (2005) Neuropsychological tests accurately predict incident Alzheimer disease after 5 and 10 years. *Neurology* **64**, 1853-1859.

[5] Waldstein SR, Elias MF, eds. (2001) *Neuropsychology of Cardiovascular Disease*, Lawrence Erlbaum Associates, New Jersey.

[6] Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kareholt I, Winblad B, Helkala EL, Tuomilehto J, Soininen H, Nissinen A (2005) Obesity and vascular risk factors at midlife and the risk

of dementia and Alzheimer disease. *Arch Neurol* **62**, 1556-1560.

[7] Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R (2005) Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology* **65**, 545-551.

[8] Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K (2005) Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology* **64**, 277-281.

[9] Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB (2003) Lower cognitive function in the presence of obesity and hypertension: The Framingham heart study. *Int J Obesity* **27**, 260-268.

[10] Arnolov J, Ingelsson E, Sundstrom J, Lind L (2010) Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. *Circulation* **121**, 230-U288.

[11] Ho JS, Cannaday JJ, Barlow CE, Mitchell TL, Cooper KH, FitzGerald SJ (2008) Relation of the number of metabolic syndrome risk factors with all-cause and cardiovascular mortality. *Am J Cardiol* **102**, 689-692.

[12] Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr (2009) Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and international association for the Study of Obesity. *Circulation* **120**, 1640-1645.

[13] Chen HJ, Bai CH, Yeh WT, Chiu HC, Pan WH (2006) Influence of metabolic syndrome and general obesity on the risk of ischemic stroke. *Stroke* **37**, 1060-1064.

[14] Arsenault BJ, Despres JP, Stroes ESG, Wareham NJ, Kastelein JJP, Khaw KT, Boekholdt SM (2010) Lipid assessment, metabolic syndrome and coronary heart disease risk. *Eur J Clin Invest* **40**, 1081-1093.

[15] Alberti KG, Zimmet P, Shaw J (2006) Metabolic syndrome–a new world-wide definition. A consensus statement from the international diabetes federation. *Diabet Med* **23**, 469-480.

[16] 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 (2005) Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Executive summary. *Cardiol Rev* **13**, 322-327.

[17] Hao ZL, Wu B, Wang DR, Liu M (2011) Association between metabolic syndrome and cognitive decline: A systematic review of prospective population-based studies. *Acta Neuropsychiatrica* **23**, 69-74.

[18] Solfrizzi V, Scafato E, Capurso C, D'Introno A, Colacicco AM, Frisardi V, Vendemiale G, Baldereschi M, Crepaldi G, Di Carlo A, Galluzzo L, Gandin C, Inzitari D, Maggi S, Capurso A, Panza F (2009) Metabolic syndrome, mild cognitive impairment, and progression to dementia. The Italian Longitudinal Study on Aging. *Neurobiol Aging*, doi:10.1016/j.neurobiolaging.2009.12.012.

[19] Solfrizzi V, Scafato E, Capurso C, D'Introno A, Colacicco AM, Frisardi V, Vendemiale G, Baldereschi M, Crepaldi G, Di Carlo A, Galluzzo L, Gandin C, Inzitari D, Maggi S, Capurso A, Panza F, Italian Longitudinal Study A (2010) Metabolic syndrome and the risk of vascular dementia: The Italian Longitudinal Study on Ageing. *J Neurol Neurosurg Psychiatry* **81**, 433-440.

[20] Lezak MD, Howieson DB, Loring DW (2004) Neuropsychological Assessment, Oxford University press, New York.

[21] Segura B, Jurado MA, Freixenet N, Albuin C, Muniesa J, Junque C (2009) Mental slowness and executive dysfunctions in patients with metabolic syndrome. *Neurosci Lett* **462**, 49-53.

[22] van den Berg E, Dekker JM, Nijpels G, Kessels RPC, Kappelle LJ, de Haan EHF, Heine RJ, Stehouwer CDA, Biessels GJ (2008) Cognitive functioning in elderly persons with type 2 diabetes and metabolic syndrome: The Hoorn Study. *Dement Geriatr Cogn Disord* **26**, 261-269.

[23] Isik AT, Cankurtaran M, Bozoglu E, Comert B, Doruk H, Mas MR (2007) Is there any relation between insulin resistance and cognitive function in the elderly? *Int Psychogeriatr* **19**, 745-756.

[24] Raffaitin C, Gin H, Empana JP, Helmer C, Berr C, Tzourio C, Portet F, Dartigues JF, Alperovitch A, Barberger-Gateau P (2009) Metabolic syndrome and risk for incident Alzheimer's disease or vascular dementia, the Three-City Study. *Diabetes Care* **32**, 169-174.

[25] Razay G, Vreugdenhil A, Wilcock G (2007) The metabolic syndrome and Alzheimer disease. *Arch Neurol* **64**, 93-96.

[26] Vanhanen M, Koivisto K, Moilanen L, Helkala EL, Hanninen T, Soininen H, Kervinen K, Kesaniemi A, Laakso M, Kuusisto J (2006) Association of metabolic syndrome with Alzheimer disease: A population-based study. *Neurology* **67**, 843-847.

[27] Yaffe K, Weston AL, Blackwell T, Krueger KA (2009) The metabolic syndrome and development of cognitive impairment among older women. *Arch Neurol* **66**, 324-328.

[28] Dik MG, Jonker C, Comijs HC, Deeg DJ, Kok A, Yaffe K, Penninx BW (2007) Contribution of metabolic syndrome components to cognition in older individuals. *Diabetes Care* **30**, 2655-2660.

[29] van den Berg E, Biessels GJ, de Craen AJM, Gussekloo J, Westendorp RGJ (2007) The metabolic syndrome is associated with decelerated cognitive decline in the oldest old. *Neurology* **69**, 979-985.

[30] Muller M, Tang MX, Schupf N, Manly JJ, Mayeux R, Luchsinger JA (2007) Metabolic syndrome and dementia risk in a multiethnic elderly cohort. *Dement Geriatr Cogn Disord* **24**, 185-192.

[31] Cavalier M, Ropele S, Petrovic K, Pluta-Fuerst A, Homayoon N, Enzinger C, Grazer A, Katschnig P, Schwingenschuh P, Berghold A, Schmidt R (2010) Metabolic syndrome, brain magnetic resonance imaging, and cognition. *Diabetes Care* **33**, 2489-2495.

[32] Komulainen P, Lakka TA, Kivipelto M, Hassinen M, Helkala EL, Haapala I, Nissinen A, Rauramaa R (2007) Metabolic syndrome and cognitive function: A population-based follow-up study in elderly women. *Dement Geriatr Cogn Disord* **23**, 29-34.

[33] Knopman DS, Mosley TH, Catellier DJ, Coker LH (2009) Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: The ARIC MRI Study. *Alzheimers Dement* **5**, 207-214.

[34] Yaffe K, Haan M, Blackwell T, Cherkasova E, Whitmer RA, West N (2007) Metabolic syndrome and cognitive decline in elderly Latinos: Findings from the Sacramento Area Latino Study of Aging study. *J Am Geriatr Soc* **55**, 758-762.

[35] Forti P, Pisacane N, Rietti E, Lucicesare A, Olivelli V, Mariani E, Mecocci P, Ravaglia G (2010) Metabolic syndrome and risk of dementia in older adults. *J Am Geriatr Soc* **58**, 487-492.

[36] Choi SJ, Jung SS, You YS, Shin BS, Kim JE, Yoon SW, Jeon DW, Baek JH, Park SW, Lee JG, Kim YH (2008) Prevalence of Alzheimer's dementia and its risk factors in community-dwelling elderly Koreans. *Psychiatry Invest* **5**, 78-85.

[37] Rabbitt PMA ed. (1997) *Methodology of Frontal and Executive Function*, Psychology Press, East Sussex.
[38] Gatto NM, Henderson VW, John JAS, McCleary C, Hodis HN, Mack WJ (2008) Metabolic syndrome and cognitive function in healthy middle-aged and older adults without diabetes. *Aging Neuropsychol Cogn* **15**, 627-641.
[39] Burgess GC, Braver TS, Gray JR (2006) Exactly how are fluid intelligence, working memory, and executive function related? Cognitive neuroscience approaches to investigating the mechanisms of fluid cognition. *Behav Brain Sci* **29**, 128-+.
[40] Garlick D, Sejnowski TJ (2006) There is more to fluid intelligence than working memory capacity and executive function. *Behav Brain Sci* **29**, 134-+.
[41] Heitz RP, Redick TS, Hambrick DZ, Kane MJ, Conway ARA, Engle RW (2006) Working memory, executive function, and general fluid intelligence are not the same. *Behav Brain Sci* **29**, 135-+.
[42] Roca M, Parr A, Thompson R, Woolgar A, Torralva T, Antoun N, Manes F, Duncan J (2010) Executive function and fluid intelligence after frontal lobe lesions. *Brain* **133**, 234-247.
[43] Lyon GR, Krasnegor NA (1996) *Attention, Memory and Executive Function,* H Paul, Brookes, Baltimore.
[44] Roberts AC, Robbins TW, Weiskrantz L eds. (1998) *The Prefrontal Cortex: Executive and cognitive functions*, Oxford University Press, New York.
[45] Elias MF, Elias PK (1993) Hypertension affects neurobehavioral functioning: So what's new? *Psychosom Med* **55**, 51-54.
[46] Blumenthal JA, Madden DJ, Pierce TW, Siegel WC, Appelbaum M (1993) Hypertension affects neurobehavioral functioning. *Psychosom Med* **55**, 44-50.
[47] Loehlin JC (2004) *Latent variable models: An introduction to factor, path, and structural analysis*, *Lawrence Erlbaum Associates*, Mahwah, NJ.
[48] Elias PK, Elias MF, D'Agostino RB, Sullivan LM, Wolf PA (2005) Serum cholesterol and cognitive performance in the Framingham Heart Study. *Psychosom Med* **67**, 24-30.
[49] Muldoon MF, Ryan CM, Sereika SM, Flory JD, Manuck SB (2004) Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. *Am J Med* **117**, 823-829.
[50] Pfrieger FW (2003) Role of cholesterol in synapse formation and function. *Biochim Biophys Acta* **1610**, 271-280.
[51] Elias MF, Sullivan LM, D'Agostino RB, Elias PK, Beiser A, Au R, Seshadri S, DeCarli C, Wolf PA (2004) Framingham stroke risk profile and lowered cognitive performance. *Stroke* **35**, 404-409.
[52] Harris RJ (2001) *A primer of multivariate statistics*, Lawrence Erlbaum Associates, Mahwah, NJ.
[53] Frisardi V, Solfrizzi V, Seripa D, Capurso C, Santamato A, Sancarlo D, Vendemiale G, Pilotto A, Panza F (2010) Metabolic-cognitive syndrome: A cross-talk between metabolic syndrome and Alzheimer's disease. *Ageing Res Rev* **9**, 399-417.
[54] Frisardi V, Solfrizzi V, Capurso C, Imbimbo BP, Vendemiale G, Seripa D, Pilotto A, Panza F (2010) Is insulin resistant brain state a central feature of the metabolic-cognitive syndrome? *J Alzheimers Dis* **21**, 57-63.
[55] Marra C, Ferraccioli M, Vita MG, Quaranta D, Gainotti G (2011) Patterns of cognitive decline and rates of conversion to dementia in patients with degenerative and vascular forms of MCI. *Curr Alzheimer Res* **8**, 24-31.
[56] Mosconi L, Perani D, Sorbi S, Herholz K, Nacmias B, Holthoff V, Salmon E, Baron JC, De Cristofaro MTR, Padovani A, Borroni B, Franceschi M, Bracco L, Pupi A (2004) MCI conversion to dementia and the APOE genotype - A prediction study with FDG-PET. *Neurology* **63**, 2332-2234.