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# Metabolic syndrome, cognitive performance and dementia: A review

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## Review

# Metabolic Syndrome, Cognitive Performance, and Dementia

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**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

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47 pressure, dyslipidemia (elevated triglycerides and lower-  
 48 ed high-density lipoprotein cholesterol), and insulin  
 49 resistance [12]. The clustering of these specific car-  
 50 diovascular disease (CVD) risk factors is associated  
 51 with an increased risk of developing CVD and diabetes  
 52 [12] as compared with the risk associated with each  
 53 individual risk factor acting alone. MetS is associated  
 54 with an increased risk of stroke [13], and in addition,  
 55 abdominal obesity and MetS are strongly associated  
 56 with elevated concentrations of atherogenic lipopro-  
 57 teins, and therefore increase the risk of coronary heart  
 58 disease [14]. While there is no single known cause  
 59 for MetS, a number of non-modifiable factors includ-  
 60 ing age, genetics, ethnicity, and gender, influence its  
 61 prevalence [15]. Importantly, lifestyle factors, such as  
 62 diet, are a primary contributor to both the development  
 63 and subsequent course of MetS [16].

## 64 GOALS OF THE REVIEW

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

## 82 LITERATURE SELECTION

83 A search was undertaken on electronic databases  
 84 for studies that examined cognitive functioning asso-  
 85 ciated with MetS, or estimated prevalence or incidence  
 86 of probable dementia associated with MetS. The search  
 87 was limited to studies that reported on MetS as a global  
 88 indicator of vascular risk, and excluded studies that  
 89 examined only one or more of the individual com-  
 90 ponents of the syndrome. MetS had to be diagnosed  
 91 based on having any three of five risk factors (elevated  
 92 waist circumference, elevated triglycerides, reduced  
 93 high-density lipoprotein cholesterol, elevated blood

94 pressure, elevated fasting glucose) according to Alberti  
 95 et al. [12]. Cognitive function studies had to provide  
 96 measures for at least one aspect of cognition obtained  
 97 from neuropsychological testing. Publications which  
 98 used self-reported cognitive function were excluded.  
 99 Dementia risk studies had to provide an estimate of  
 100 probable dementia, including AD, VaD, or mild cog-  
 101 nitive impairment (MCI). Studies were not required  
 102 to have included brain imaging in their assessment  
 103 but those which used only single test screening mea-  
 104 sures as indices of dementia or cognitive function were  
 105 excluded. If it was unclear whether the paper met  
 106 the inclusion criteria, the full text was obtained. A  
 107 total of 19 studies were included in this review. Two  
 108 papers reported results from the same study, but as they  
 109 assessed different outcome measures, they were treated  
 110 as two separate studies for the purpose of this review  
 111 [18, 19].

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

## 120 ASSESSMENT OF COGNITION

### 121 *Neuropsychological testing*

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

133 The majority of studies assessed at least three differ-  
 134 ent cognitive abilities. Some studies used a single test  
 135 as a measure of a particular cognitive ability, while oth-  
 136 ers used a combination of tests. The two case-control  
 137 studies [21, 22] conducted the most thorough neu-  
 138ropsychological assessments, each one measuring at  
 139 least six cognitive abilities. The most commonly tested  
 140 cognitive abilities in terms of the Lezak taxonomy  
 141 were memory, psychomotor speed, and attention. Ver-  
 142 bal 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 <sup>a</sup> 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] <sup>b</sup>	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] <sup>b</sup>	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] <sup>b</sup>	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] <sup>b</sup>	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] <sup>b</sup>	83 MetS, 64 DM2, 100 controls M/F	Attention (Information processing speed <sup>c</sup> , Executive function <sup>c</sup> ) Psychomotor speed <sup>c</sup> Verbal fluency (Executive function) <sup>c</sup>	None	Age, gender, estimated IQ
Razay et al. [25] <sup>b</sup>	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); diaietic treatment excluded
Prospective Komulainen et al. [32] <sup>b</sup> Reffaitin et al. [24] <sup>b</sup>	101 F 7087 M/F	Verbal memory VaD (HR 2.44, 95% CI 1.25–4.77)	Low HDL cholesterol (memory) 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, education, depression Age, gender, education, city center, ApoE4 genotype

(continued next page)

Table 1 (continued)

Study	n Gender	Cognitive abilities <sup>a</sup> 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] <sup>b</sup>	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] <sup>b</sup>	562 M/F	Global cognition (screening test) <sup>d</sup> Psychomotor speed <sup>d</sup> attention <sup>d</sup>	Elevated fasting glucose (screening test) <sup>d</sup> BMI (screening test) <sup>d</sup>	Gender, education
Yaffe et al. [34] <sup>b</sup>	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] <sup>b</sup>	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.

<sup>a</sup>Abilities as defined by Lezak [20]; Ability in parentheses represents ability as described by author(s) if differs from Lezak. <sup>b</sup>Significant after full adjustment; <sup>c</sup>Tests grouped together as z-scores;

<sup>d</sup>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] <sup>a</sup>	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.

<sup>a</sup>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

336 to find any significant relationships. Other components  
337 of MetS such as low high-density lipoprotein chole-  
338 sterol, elevated triglycerides, and hypertension have  
339 been associated with poorer cognitive performance  
340 [28, 32, 33, 38], dementia [24–26], or progression from  
341 MCI to dementia [19], and yet there are studies indicat-  
342 ing that lower levels of total cholesterol are detrimental  
343 to cognitive performance [48–50]. Further investiga-  
344 tion, taking into account the precise levels of variables  
345 such as blood pressure and cholesterol, may improve  
346 our understanding about whether or not these compo-  
347 nents of MetS are positive or negative risk factors for  
348 cognitive performance.

349 Nevertheless, there is evidence that MetS as a whole  
350 has a detrimental influence on cognition and that the  
351 relationship between MetS and cognition are not sim-  
352 ply driven by one predominant component of the  
353 syndrome. In a study speaking directly to this issue,  
354 Gatto and colleague [38] found a relationship between  
355 the number of MetS components and cognitive func-  
356 tion, with global cognition and semantic memory  
357 scores significantly decreasing with each addition of  
358 a MetS component. Cavalier et al. [31] found that an  
359 increasing number of MetS components was associ-  
360 ated with progressively worse cognitive performance  
361 in men. These findings are supported by those of Yaffe  
362 and colleagues [27] who found a 17% increase in the  
363 risk of impairment per unit increase in the number of  
364 MetS components. Similarly, Komulainen et al. [32]  
365 found no significant interactions between single risk  
366 factors (blood pressure, glucose levels, or waist cir-  
367 cumference) with memory function, but women with  
368 MetS had a four-times higher risk of poor memory than  
369 those without, and, most importantly, increasing the  
370 number of MetS components served to further increase  
371 the risk. Finally, Solfrizzi et al. [18] found the risk  
372 of VaD due to MetS was about four and a half times  
373 higher than the additive risk of its individual compo-  
374 nents. The design of these studies is exemplary with  
375 regard to how the issue of relations between MetS and  
376 cognition should be approached.

377 It is important for investigators to take the steps  
378 necessary to determine if the MetS relationship to cog-  
379 nition is simply driven by one or more major risk  
380 factors such as obesity or diabetes, compared to the  
381 impact of MetS *per se*. It is clear that any combina-  
382 tion of multiple risk factors, regardless of whether they  
383 are components of MetS, predict cognition better than  
384 a single risk factor [5, 51]. However at this point in  
385 MetS research, it is not known whether it is the specific  
386 MetS risk factors that are affecting cognitive func-  
387 tion adversely, or if multiple risk factors of any kind

388 have this effect. Consequently, one of the challenges  
389 in future research will be to differentiate between the  
390 cumulative negative impact on cognition of risk fac-  
391 tors specific to MetS and the generally adverse effect  
392 of multiple risk factors, including non-metabolic fac-  
393 tors and any other combination of CVD risk factors.  
394 Using statistical methods [52] to measure the weights  
395 for components of a composite variable, and there-  
396 fore which component is driving the results, will be  
397 needed. Secondly, in order to make this distinction, it is  
398 important to use standardized MetS criteria, requiring  
399 measures of abdominal obesity (waist circumference),  
400 high-density lipoprotein cholesterol, fasting plasma  
401 glucose, triglycerides, and blood pressure with cut-offs  
402 as defined by the recent joint statement from the Inter-  
403 national Diabetes Federation, National Heart, Lung,  
404 and Blood Institute, and American Heart Association  
405 [12].

406 Finally, a number of potential biases in this litera-  
407 ture must be considered. Survival bias may play a role  
408 in any health study conducted in very elderly popula-  
409 tions. Van den Berg and colleagues [29] acknowledge  
410 that a ‘survivor effect’ may explain their findings of  
411 decelerated cognitive decline in individuals between  
412 the ages of 85 and 90 years. As noted by these authors,  
413 participants who have reached the age of 85 and are  
414 able to take part in cognitive and health research may  
415 be less susceptible to health problems [29]. Forti et al.  
416 [35] make similar conclusions with regard to their find-  
417 ing of an association between MetS and lowered risk  
418 for AD in persons aged over 75 years. Muller and col-  
419 leagues [30] similarly offer survival bias as a potential  
420 explanation for the lack of associations found between  
421 dementia and MetS in an elderly cohort (mean age  
422 of 76 years). Interestingly, the studies that found no  
423 association between MetS and dementia risk were all  
424 conducted in samples aged at least 60 years [23, 30,  
425 36]. As the effect of risk factors on cognition may  
426 change with increasing age [22] and consequently for  
427 survivors, it is essential that age be considered as a  
428 potential effect modifier and that changes in risk fac-  
429 tors and cognitive function over time be considered  
430 concurrently.

431 There are other more obvious needs for methodolog-  
432 ical improvement in studies. The majority of studies  
433 (63%) reviewed here [18, 19, 24, 27, 28, 30–35,  
434 38] did make statistical adjustments for age, gen-  
435 der, and education. Fewer studies (47%) took into  
436 account other cardiovascular factors, socio-economic,  
437 or lifestyle variables (e.g., activity level, physical exer-  
438 cise, depressed mood, personality characteristics), that  
439 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 patterns 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.

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