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*

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Metabolic Syndrome, Cognitive Performance, and Dementia

Georgina E. Crichton, Merrill F. Elias, Jonathan Buckley, Karen J. Murphy and Janet Bryan

and Vincenza Frisardi

Nutritional Physiology Research Centre, University of South Australia, Adelaide, Australia

Department of Psychology and Graduate School of Biomedical Sciences, University of Maine, Orono, Maine, USA

School of Psychology, University of South Australia, Adelaide, Australia

Department of Geriatrics, Center for Aging Brain, Memory Unit, University of Bari, Bari, Italy

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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
pressure, dyslipidemia (elevated triglycerides and low-
ere high-density lipoprotein cholesterol), and insulin
resistance [12]. The clustering of these specific car-
diovascular 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 lipopro-
teins, 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 includ-
ing 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 impair-
ment 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 asso-
ciated 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 com-
ponents 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 cog-
nitive impairment (MCI). Studies were not required
to have included brain imaging in their assessment
but those which used only single test screening mea-
sures 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 out-
come measure. Ten studies used a combination of
screening measures, neuropsychological testing, clin-
eval 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 differ-
cent cognitive abilities. Some studies used a single test
as a measure of a particular cognitive ability, while oth-
ers used a combination of tests. The two case-control
studies [21, 22] conducted the most thorough neu-
ropsychological 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. Ver-
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

<table>
<thead>
<tr>
<th>Study</th>
<th>n Gender</th>
<th>Cognitive abilities^a or dementia type (and associated OR/HR, 95% CI) associated with MetS</th>
<th>Single risk factors associated with impaired cognition/dementia</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dik et al. [28]^b</td>
<td>1183 M/F</td>
<td>Perception &amp; abstract reasoning (Fluid intelligence)</td>
<td>Hyperglycemia (psychomotor speed, perception &amp; abstract reasoning, verbal memory, screening test); Low HDL, cholesterol (psychomotor speed, perception &amp; abstract reasoning)</td>
<td>Age, gender, education, smoking, alcohol, diabetics excluded</td>
</tr>
<tr>
<td>Cavalier et al. [31]^b</td>
<td>819 M/F</td>
<td>In men: Verbal memory (Attention, concept formation (screening test))</td>
<td>Not examined</td>
<td>Age, gender education, depressed mood, coronary heart disease</td>
</tr>
<tr>
<td>Vanhanen et al. [26]^b</td>
<td>950 M/F</td>
<td>AD (OR 2.71, 95% CI 1.44–5.10) In women: Low HDL cholesterol, high fasting glucose associated with AD prevalence</td>
<td></td>
<td>Age, education, ApoE4 genotype, total cholesterol, diabetes</td>
</tr>
<tr>
<td>Cross-sectional: Case-control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van den Berg et al. [22]^b</td>
<td>83 MetS, 64 DM2, 100 controls M/F</td>
<td>Attention (Information processing speed, Executive function)</td>
<td>None</td>
<td>Age, gender, estimated IQ</td>
</tr>
<tr>
<td>Razey et al. [25]^b</td>
<td>50 AD, 75 controls M/F</td>
<td>AD (OR 3.20, 95% CI 1.20–8.40)</td>
<td>Elevated triglycerides, hyperglycemia, low HDL cholesterol (in those with AD compared with controls); Hypertension associated with decreased risk of AD</td>
<td>Age, gender, location (controls: Similar age range, no memory complaints, normal scores on MMSE), diabetic treatment excluded</td>
</tr>
<tr>
<td>Prospective:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Komulainen et al. [32]^b</td>
<td>101 F</td>
<td>Verbal memory (VaD (HR 2.44, 95% CI 1.25–4.77))</td>
<td>Low HDL cholesterol (memory)</td>
<td>Age, education, depression</td>
</tr>
<tr>
<td>Reffaitin et al. [24]^b</td>
<td>7087 M/F</td>
<td>Verbal memory (VaD (HR 2.44, 95% CI 1.25–4.77))</td>
<td>High triglycerides at baseline associated with increased risk of all-cause dementia &amp; VaD risk; Diabetics significantly associated with increased risk of all-cause dementia &amp; VaD</td>
<td>Age, gender, education, city center, ApoE4 genotype</td>
</tr>
</tbody>
</table>

^a: Fluid intelligence or Memory (Global cognition) (Screening test)
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Gender</th>
<th>Cognitive abilities $^a$ or dementia type (and associated OR/HR, 95% CI) associated with MetS</th>
<th>Single risk factors associated with impaired cognition/dementia</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yaffe et al. [34]$^b$</td>
<td>4895</td>
<td>F</td>
<td>Cognitive impairment (OR 1.66, 95% CI 1.14–2.41)</td>
<td>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</td>
<td>Age, race, depressed, mood, education</td>
</tr>
<tr>
<td>Solfrizzi et al. [18]</td>
<td>2097</td>
<td>M/F</td>
<td>VaD (HR 3.71, 95% CI 1.40–9.83)</td>
<td>Risk increased when subjects with baseline under-nutrition excluded; risk increased for inflammation. No individual MetS component associated with dementia risk</td>
<td>Age, gender, education, alcohol, smoking, fibrinogen, non-high density lipoprotein cholesterol, ratio of ApoA-I to ApoA-I, coronary artery disease, stroke</td>
</tr>
<tr>
<td>Solfrizzi et al. [18]</td>
<td>2097</td>
<td>M/F</td>
<td>VaD (HR 3.71, 95% CI 1.40–9.83)</td>
<td>Risk increased when subjects with baseline under-nutrition excluded; risk increased for subjects with MetS &amp; high inflammation. No individual MetS component associated with dementia risk</td>
<td>Age, gender, education, alcohol, smoking, fibrinogen, non-high density lipoprotein cholesterol, ratio of ApoA-I to ApoA-I, coronary artery disease, stroke</td>
</tr>
<tr>
<td>Longitudinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van den Berg et al. [29]$^b$</td>
<td>562</td>
<td>M/F</td>
<td>Global cognition (screening test)$^d$ Psychomotor speed$^d$ attention$^d$</td>
<td>Elevated fasting glucose (screening test)$^d$ BMI (screening test)$^d$</td>
<td>Gender, education</td>
</tr>
<tr>
<td>Yaffe et al. [34]$^b$</td>
<td>1624</td>
<td>M/F</td>
<td>Global cognition (screening test)</td>
<td>Elevated fasting glucose (verbal memory)</td>
<td>Age, gender, education, birthplace, depression, smoking, alcohol, MI</td>
</tr>
<tr>
<td>Knopman et al. [33]$^b$</td>
<td>1130</td>
<td>M/F</td>
<td>Verbal fluency</td>
<td>Hypertension (verbal fluency)</td>
<td>Age, gender, religion, education</td>
</tr>
</tbody>
</table>

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

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.

*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, detrimental 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 true 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 constructions of theoretically relevant cognitive domains [35], 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 within 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, Gaito and colleagues [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. Cavalieri 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, Sollfrizzi 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 may 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].
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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**REFERENCES**


