Current Cardiology Reports (2021) 23: 180
https://doi.org/10.1007/s11886-021-01615-y

PSYCHOLOGICAL ASPECTS OF CARDIOVASCULAR DISEASES (A STEPTOE AND IM KRONISH, SECTION EDITORS)

Metabolic Syndrome and Cognitive Function

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Accepted: 20 September 2021 / Published online: 19 October 2021

Abstract

Purpose of Review Metabolic syndrome (MetS) is a cluster of cardiovascular disease risk factors that are related to several adverse health outcomes, including poor cognitive function. This review seeks to summarize and critically review select recent findings on the association between MetS and cognition.

Recent Findings MetS was associated with lower domain-specific and global cognitive function in most cross-sectional studies, but findings from longitudinal studies are not consistent. The associations varied depending on age, sex, cognitive test, genetic susceptibility, and the duration of follow-up in prospective studies. MetS was associated with a higher risk of mild cognitive impairment (MCI) and progression from MCI to dementia, particularly vascular dementia. Among MetS components, high blood pressure, high waist circumference, and hyperglycemia were the strongest predictors of cognitive function.

Summary MetS is associated with higher risk of cognitive impairment. Research is needed on how preventing or treating MetS affects cognition.

Keywords Metabolic syndrome · Cognition · Dementia · Cognitive impairment · Cardiovascular risk factor

Introduction

Dementia, the most extreme form of cognitive impairment, is defined as a loss of mental abilities combined with impairments in the ability to perform basic activities of daily living. It is estimated that roughly 11% of Americans aged 65 years and older have Alzheimer's disease (AD) or a related dementia [1]. While non-modifiable risk factors, such as age and genetic susceptibility, are primary drivers of the risk of cognitive impairment and dementia [2], identifying modifiable risk factors for dementia is important because it provides an opportunity for intervention and prevention. In particular, there has been increasing interest on how the aggregation of risk factors affects the risk of cognitive impairment. The metabolic syndrome (MetS) is one of the most commonly used definitions of aggregation of risk factors.

MetS refers to a cluster of cardiometabolic conditions with shared pathophysiology that together have been shown to increase the risk of cardiovascular disease (CVD), stroke, and type 2 diabetes (T2D) [3]. MetS has been operationalized in many ways [4]. The World Health Organization (WHO) first defined MetS in 1998, with insulin resistance being at the center of the WHO definition. Without evidence of insulin resistance, a diagnosis of MetS cannot be made even with the presence of the other criteria which are: waist/hip ratio > 0.90 for men, > 0.85 for women; or BMI > 30 kg/m^2 triglyceride ≥ 150 mg/dl or HDL-C: < 35 mg/dl for men, < 39 mg/dl for women, blood pressure ≥ 140/90 mmHg, microalbuminuria [4]. The most widely used definition of MetS was operationalized by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) and later updated by the American Heart Association (AHA) and the National Heart Lung and Blood Institute (NHLBI) in 2005 [5]. This definition combined previous concepts to provide simple criteria that can be readily measured and easily applied in both clinical and epidemiological settings [4]. In this definition, MetS requires the presence of three or more of the following conditions:

This article is part ofthe Topical Collection on *Psychological Aspects of Cardiovascular Diseases*

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1. Central or abdominal obesity measured by waist circumference (men: > 40 inches, women: > 35 inches)
2. High triglycerides ≥ 150 mg per deciliter (mg/dL) or if taking a medication for high triglycerides.
3. Low HDL cholesterol (men < 40 mg/dL, women < 50 mg/dL) or if taking a medication for low HDL cholesterol.
4. High blood pressure ≥ 130/85 mm of mercury (mm Hg) or if taking a medication for high blood pressure.
5. High fasting glucose ≥ 100 mg/dL, or if taking a medication for high blood glucose.

Epidemiology and Prevalence of MetS

Data from the National Health and Nutrition Examination Survey (NHANES) conducted between 1988 and 2012 estimated the prevalence of the MetS to be nearly 34% among US adults [6]. The prevalence of MetS is often difficult to ascertain due to the secular trends in increasing obesity and incidence of T2D and because of differences in MetS criteria and adiposity thresholds applied across various studies. The prevalence of MetS also differs by age, sex, and race. It has been reported that the prevalence of MetS is higher among older (35–64 years old) compared to younger (20–34 years old) adults and among Mexican Americans compared to non-Hispanic Whites [7]. MetS is also higher in non-Hispanic white men compared to non-Hispanic black men and in non-Hispanic black women compared to non-Hispanic white women [6]. Differences in the prevalence of MetS have also been observed by socioeconomic status and education subgroups [6].

Important Concepts of Cognitive Function

The American Psychological Association (APA) defines cognition as "all forms of knowing and awareness, such as perceiving, conceiving, remembering, reasoning, judging, imagining, and problem solving" [8]. Major cognitive processes (or domains) that are often measured by neuropsychological tests include: memory (encoding, storing, and retrieving information), learning (acquiring and integrating new information), language (understanding and expressing thoughts), visual-spatial skills (processing a visual stimulus and understanding the spatial relationship between objects), and executive function (mental processes that leads to a goal-driven action). Standardized and validated neuropsychological tests are often used to assess performance in a single cognitive domain or across multiple cognitive domains. Impairments in cognition may be present if an individual has difficulty in operating and performing in one or more cognitive domains compared to the expected performance for an individual's age and level of education [9]. Cognitive impairment can range from mild to severe. Mild cognitive impairment (MCI) represents an intermediate phase between normal cognitive functioning and clinical dementia. The primary distinction between MCI and dementia is the loss of independence in functional abilities, such as basic activities of daily living, among individuals with dementia [10]. MCI is often subdivided into amnestic MCI (aMCI) and non-amnestic (naMCI). In aMCI, memory is impaired while in naMCI, memory is preserved and domains other than memory are impaired [10–12]. Both aMCI and naMCI can progress to dementia [10, 12].

Search Strategy

We used PubMed as the main database for our literature search with a focus on observational studies published in the past 5 years through March 9th, 2021. We searched both original and relevant review articles. We used the search term "metabolic syndrome" paired with; cognition, cognitive, dementia in the abstract/title of each article or as a Medical Subject Headings (MeSH) term. An article was selected if it investigates MetS as a construct and any measure of cognitive function as an outcome in Humans. Studies examining only individual components of MetS were not included. A separate search was performed for MetS and biomarkers of Alzheimer's disease and other dementias using the search term "metabolic syndrome" paired with amyloid, tau, cerebrovascular disease and neurodegeneration. Reference lists of included studies and relevant review articles were reviewed to identify additional studies.

MetS and Cognitive Performance

A summary of select recent studies that examined the association of MetS with cognitive performance using individual neuropsychological tests or cognitive domain scores are detailed in Table 1.

Most recent cross-sectional studies reported an inverse association between the presence of MetS and lower global and domain-specific cognitive performance [13–24]. The reported association in most of the studies differed depending on the type of neuropsychological test used with some neuropsychological tests being more sensitive than others [15, 16, 18, 19]. Lower performance across multiple cognitive domains was reported among those with MetS compared with those without MetS, including memory [13, 15, 17, 20], executive function [13–15, 19, 20], attention/speed [13, 16, 18], and global cognition [13, 20].

Age and sex are other important factors to take into consideration that can influence the association between MetS and cognitive function. Studies among both middle-aged

Table 1 Summary of studies published within the last 5 years on the association between metabolic syndrome (MetS) and cognitive performance

Author and year	Study population *N*, age	Study type	MetS definition	Cognitive construct used	Summary of the results
Wang et al. 2021 [23]	100 patients from Xuanwu Hospital, Capital Medical University, China Mean age ≈75 ± 7 years	Case–control, 1-year follow-up	Criteria recommended by the Chinese Medical Association	MMSE	-MetS patients had worse cognitive function and decreased ability to participate in ADLs ($p = 0.001$ and 0.046, respectively) -Risks of worse cognitive function were MetS diagnosis (62.1% vs 36.4%, $p < 0.001$), ApoEε4 carrier e (22.3% vs 10.1%, $p = 0.019$), higher systolic blood pressure and larger waist circumference ($p < 0.05$) -One year follow-up showed a continuous deterioration of cognitive function in MetS patients and those who are APOE-4 carriers ($p < 0.001$ for both)
Bahchevanov et al. 2020 [17]	112 Bulgarian Mean age = 50.04 ± 3.31	Cross-sectional	NCEP ATP III criteria	CERAD neuropsychological battery	-Subjects with MetS had lower CERAD scores, especially in the Word List Recall subtest (7.16 ± 1.52 vs. 7.99 ± 1.52) -Subjects with more MetS components ($\beta = -8.31$; 95% CI: −14.13, −2.50 for fours vs. 0 components) or with high MetS severity score (MSSS) ($\beta = -3.19$; 95% CI = −4.67, −1.71) had lower CERAD scores: MSSS was a better predictor of CERAD scores than MetS components -Hypertension was independently associated with lower CERAD scores ($\beta = -4.00$; 95% CI = −6.81, −1.19)
Buyo et al. 2020 [16]	2150 non-demented Japanese Mean age = 72.22 ± 6	Cross-sectional	Japanese Mets criteria[a]	Battery of NPs measuring:	-Subjects with MetS had lower performance in attention tasks compared to those without MetS ($p = 0.012$)

Table 1 (continued)

Author and year	Study population *N*, age	Study type	MetS definition	Cognitive construct used	Summary of the results
				MMSE Attention, logical memory, verbal, and category fluency	-No differences in MMSE scores or other domains between those with and those without MetS ($p > 0.05$)
Foret et al. 2020 [15]	197 participants Mean age = 46 ± 6 years	Cross-sectional	NCEP ATP III criteria	Battery of NPs measuring global cognition executive function memory	-The count of MetS components was associated with poor executive function (F (4, 191) = 3.94, p = .004) and memory (F (4, 192) = 7.86, $p < 0.001$) -MetS diagnosis was associated with poor memory ($\beta = -.19$, $p = 0.006$) but not executive function ($\beta = -0.05$, $p = 0.506$)
Kazlauskaite et al. 2020 [29•]*	2149 US women traversing menopause from the Study of Women's Health across Nation (SWAN) Mean age = 50.7 ± 2.9 years	Longitudinal 17-year follow-up	NCEP-ATP III criteria with some modifications	Battery of NPs measuring perceptual speed working memory episodic memory	-Women with MetS (vs those without MetS) had a larger 10-year decline in perceptual speed, after adjustment for cognitive testing practice effects, sociodemographic, lifestyle, mood, and menopause factors (95% CI, –0.150 to –0.024; p = 0.007): MetS accelerated the loss of perceptual speed by 24% -MetS had a neutral effect on the change in working memory or episodic memory ($p > 0.5$)
Lai et al. 2020 [14]	108 participants with memory complaints and ≥ cardiovascular risk factors from the Australian Imaging Biomarkers and Lifestyle (AIBL) Mean age ≈73.4 years	Cross-sectional	NCEP-ATP III criteria	Battery of NPs measuring verbal memory, executive function and global cognition	Higher MetS Z scores were associated with lower cognition in executive function ($\beta = 0.23$, $p < 0.05$) and global cognition ($\beta = 0.26$, $p < 0.05$)

Table 1 (continued)

Author and year	Study population *N*, age	Study type	MetS definition	Cognitive construct used	Summary of the results
Mehra et al. 2020 [24]	186 subjects with hypertension Mean age = 47.7 ± 13.9	Cross-sectional	NCEP ATP-III criteria	MoCA	-Participants with MetS had poor MoCA scores compared to those with no MetS ($p < 0.001$) -MCI prevalence was 65.6%, MetS prevalence was 45.7%
Przybycien-Gaweda et al. 2020 [13]	823 non-demented Chinese Asians Mean age = 65.3 ± 7.2 years	Longitudinal 4.5-year follow-up	NCEP ATP III criteria	Battery of NPs measuring attention/working memory, executive function, processing speed memory and learning, global cognition	***Cross-sectionally:*** -MetS was associated with lower cognition in processing speed, memory/learning and executive function ($p = 0.018$ to $p = 0.003$) -The count of MetS components was associated with lower cognition in all cognitive domains ($p = 0.025$ to $p = 0.002$) -Hyperglycemia was associated with lower processing speed ($p = 0.045$), central obesity with lower executive function ($p = 0.046$) and high blood pressure with lower processing speed ($p = 0.024$), attention/working memory ($p = 0.034$) with lower executive function ($p = 0.024$) ***Longitudinally:*** -MetS diagnosis was not associated with cognitive decline: there was a trend but did not reach significance -The count of Mets components was associated with cognitive decline (attention/working memory, memory and learning, global cognition) ($p = 0.032$ for global cognition) -Dyslipidemia was associated with memory and learning decline ($p = 0.022$)

Table 1 (continued)

Author and year	Study population *N*, age	Study type	MetS definition	Cognitive construct used	Summary of the results
					-The effect of the presence of 4 MetS components on cognition was equivalent to the effect of 14 years of additional age
Bangen et al. 2019 [30•]*	2892 participants from the Framingham Offspring	Longitudinal: 41 years for Metabolic risk and 13 years of cognitive testing	NCEP ATP-III criteria with slight modifications	Battery of NPs measuring processing speed/executive function, memory, and general cognition	-MetS is associated with cognitive functioning but not with cognitive trajectories
					-Onset of MetS was associated with lower cognition in non-demented vs demented (β = –0.664, 95% CI = –1.214 to –0.112 for general cognition) and in non-APOE-ε4 carriers vs APOE-ε4 carriers (β = –0.733, 95% CI = –1.370 to –0.096)
					-Participants with rapid cognitive decline were more likely to have MetS vs those with slow cognitive decline ($p < 0.001$)
Wooten et al. 2019 [18]	93 participants from the Cerebrovascular Integrity and Risk for Cognitive decline in Aging (CIRCA) study Mean age = 61.94 ± 9.46 years	Cross-sectional	NCEP ATP III criteria	Battery of NPs measuring executive function vs the gradual-onset continuous performance task (gradCPT) which is a measure of sustained attention	Participants with lower vascular risk factors (Zero vascular risk factors) had better scores in sustained attention using the (gradCPT) (F (2, 87) = 3.60, p = 0.03) but not in tests of attention using the standard NPs (F (2, 87) = 2.11, p = 0.13)
González et al. 2018 [20]	9136 subjects from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) Mean age = 56.5 ± 9.9 years	Cross-sectional	NCEP ATP III criteria	Battery of NPs measuring verbal fluency, episodic learning, memory, processing speed/executive function, global neurocognition	-MetS was associated with lower global neurocognition (β = 20.07 [SE 0.023]), memory (β = 20.07 [SE 0.025]), verbal fluency (β = 20.15 [SE 0.028]), processing speed/executive function (β = 20.15 [SE 0.022])

Table 1 (continued)

Author and year	Study population *N*, age	Study type	MetS definition	Cognitive construct used	Summary of the results
					-Age was a modifier for the association between MetS and learning/memory: MetS had significant effects on learning and memory among middle-aged vs older adults (memory: β main = 0.42 [SE 0.162]; β interaction = 20.01 [SE 0.003], episodic learning (β main = 0.47 [SE 0.158]; β interaction = 20.01 [SE 0.003])
Mangone et al. 2018 [19]	296 overweight urban adolescents predominantly Hispanic	Cross-sectional	Criteria adjusted to adolescent populations	Battery of NPs measures using the CNS Vital Signs (CNS-VS) computerized neurocognitive battery that assesses cognitive domains of memory, processing speed, reaction time, executive function, complex attention, and cognitive flexibility	-MetS group (29.2%) performed lower than the non-group, in 2 cognitive domains: executive function ($p = 0.020$, $r = 0.15$) and cognitive flexibility ($p = 0.020$, $r = 0.15$)
					-Waist circumference was a significant predictor of performance in domains of executive function ($\beta = -0.13$, 95%CI = − 6.98 to − 1.08) and cognitive flexibility ($\beta = -0.11$, 95%CI = − 6.67 to − 0.41)
Overman et al. 2017 [28]	1965 males from the European Male Aging Study (EMAS) Mean age≈58.5 ± 10.7 years	Longitudinal 4.4-year follow-up	NCEP ATP-III criteria	Battery of NPs measuring visual-constructional abilities, memory recall, visual recognition memory, processing speed	-The presence of baseline MetS was not associated with cognitive decline over time (all $p > 0.05$)
					-Hyperglycemia was related to a decline in tests of visual constructional abilities ($\beta = -0.42$, $p < 0.05$) and processing speed ($\beta = -0.39$, $p < 0.001$)

Table 1 (continued)

Author and year	Study population *N*, age	Study type	MetS definition	Cognitive construct used	Summary of the results
Viscogliosi et al. 2017 [31]	Data of 195 men from 1991 to 2000 of the Italian cohorts of the Finland, Italy, the Netherlands, Elderly (FINE) study baseline age 76.1 ± 3.1 years	Longitudinal 10-year follow-up	NCEP ATP-III criteria	MMSE to assess global cognition Functional disability assessed by measures of mobility and ADLs IADLs	-Baseline MetS was prospectively associated with greater 10-year cognitive decline ($\beta = -1.68$, 95%CI = −2.20 to −1.16, $p < 0.001$) and functional decline in ADLs (OR = 1.35, 95%CI = 1.12 to 1.62, $p < 0.001$) and IADLs (OR = 1.09, 95% CI = 1.01 to1.20, $p = 0.048$) -The associations observed were not attributable to individual altered components of MetS nor to their sum
Sweat et al. 2017 [36]	162 adolescents Mean age = 19.53 ± 1.53	Cross-sectional	Criteria adjusted for adolescents[b]	Battery of NPs measuring frontal lobe integrity and sustained attention	-No significant contribution of any MetS risk factors, singly or in combination with any of the cognitive domains -Obese adolescents (vs normal weight peers) had lower scores in all processing speed tests (all $p < 0.04$) but not in executive function
Chen et al. 2016 [38]	3988 participants Mean age = 66.4 ± 8.8	Cross-sectional	Chinese Medical Association Diabetes Association criteria	MoCA	-No differences in MoCA scores between participants with (21.0 ± 5.4) and without MetS (21.3 ± 5.3) -Participants with diabetes had a higher risk of MCI (OR = 1.24, 95% CI = 1.03–1.50). Participants with dyslipidemia had a lower risk of MCI (OR = 0.81, 95% CI = 0.68–0.97)
Del Brutto et al. 2016 [37]	212 stroke-free participants from rural Ecuador Mean age = 69.2 ± 7.2 years	Cross-sectional	IDF criteria	MoCA	-No differences in MoCA scores between participants with (18.2 ± 4.6) and without MetS (19 ± 4.7), $p > 0.1$

Table 1 (continued)

Author and year	Study population *N*, age	Study type	MetS definition	Cognitive construct used	Summary of the results
					-Among MetS components, only hypertriglyceridemia was independently associated with the MoCA score ($p=0.009$)
Rubens et al. 2016 [22]	1170 participants from NHANES-III Age: 12–16 years	Cross-sectional	NCEP ATP-III criteria adjusted for adolescents	Battery of NPs measuring mathematics, reading tests, spatial visualization, motor skills, working memory and attention	-Adolescents with MetS had lower scores in reading ($\beta=1.25$, 95% CI = −2.14 to −0.36) and working memory/attention ($\beta=0.89$, 95% CI = −1.65 to −0.13) compared to those without MetS
					-Among components of MetS, high waist circumference and high systolic blood pressure were associated with impaired working memory/attention ($\beta=0.72$, 95% CI = −1.41 to −0.03, $\beta=1.11$, 95% CI = −1.79 to −0.43 respectively)
					-Hyperglycemia and high waist circumference were associated with lower reading test scores ($\beta=2.91$, 95% CI = −5.45 to −0.38, $\beta=0.79$, 95% CI = −1.43 to −0.15 respectively)
Tsai et al. 2016 [21]	2252 participants from the National Health and Nutrition Examination Survey (NHANES) database mean age≈70.8 ± 7	Cross-sectional	NCEP ATP-III criteria	1 test: Digit symbol substitution test (DSST) for speed and attention	-Participants who had more MetS components had lower DSST scores ($p<0.001$)
					-Among MetS components, the strongest association with the DSST scores were with hyperglycemia ($\beta=-3.26$, 95%CI = −4.85 to −1.66) and high blood pressure ($\beta=-2.81$, 95%CI = −4.37 to −1.24)

Table 1 (continued)

Author and year	Study population *N*, age	Study type	MetS definition	Cognitive construct used	Summary of the results
Viscogliosi et al. 2016 [27]	104 hypertensive stroke free non-demented subjects Mean age≈80.2 ± 5.45 years	Longitudinal 1-year follow-up	NCEP ATP-III criteria	1 test: The Clock Drawing Test (CDT) (a measure of executive function)	-Participants with MetS had lower scores in the CDT vs those without MetS (–1.78 ± 1.47 versus − 0.74 ± 1.44, $p < 0.001$) -The prediction of CDT score by MetS was independent of Mets components, age, baseline cognition, levels and duration, neuroimaging blood pressure levels, and duration of hypertension ($\beta = -0.32$, $p = 0.003$) -Among MetS, only systolic blood pressure predicted cognitive decline ($\beta = -0.43$, $p < 0.001$)

MetS, metabolic syndrome; *NCEP ATP*, the National Cholesterol Education Program Adult Treatment Panel; *IDF*, International Diabetes Federation; *NP*, neuropsychological test; *MCI*, mild cognitive impairment; *MMSE*, Mini-Mental State Exam; *CERAD*, Consortium to Establish a Registry for Alzheimer's Disease; *MoCA*, The Montreal Cognitive Assessment; *ADLs*, activities of daily living; *IADLs*, instrumental activities of daily living; *GradCPT*, Gradual-Onset Continuous Performance Task; *DSST*, Digit symbol substitution test; *CDT*, The Clock Drawing Test; *CI*, confidence interval; *OR*, odds ratio; *SE*, standard error

*Refers to studies "Of importance"

[a]Mets criteria include waist circumference (male ≥ 85 cm, female ≥ 90 cm), hypertriglyceridemia (≥ 150 mg/dL) and/or low HDL cholesterol (< 40 mg/dL), systolic blood pressure (≥ 130 mmHg) and/or diastolic blood pressure (≥ 85 mmHg), FBS (≥ 110 mg/dL). [b]MetS criteria include: central adiposity (waist circumference at the 90th percentile or higher for age and sex), hypertriglyceridemia (triglyceride level ≥ 110 mg/day), low high-density lipoprotein cholesterol (HDL) (≤ 40 mg/dL), (4) elevated blood pressure (for children ≤ 18 years, a systolic or diastolic blood pressure exceeding the 90th percentile adjusted for age, sex, and height or ≥ 130/85 mmHg, whichever is lower; for those older than 18 years, ≥ 130/85 mmHg), and (5) HOMAIR of 3.99 or higher

[15, 17] and older adults [16, 18, 21] reported a lower cognition among individuals who have MetS. Age, however, can be a modifier in this association. González et al. [20] reported that the association of MetS with cognition was stronger among middle-aged as compared to older adults, particularly in tests of verbal memory. The observation of weaker association between MetS and cognition in older adults was also previously described in longitudinal cohorts [25, 26]. Differences in the magnitude and strength of associations between MetS and cognition when comparing studies conducted in mid-life as compared to late-life may be due to several factors including survival bias [25], differential validity of measures of the MetS components across the lifespan, and the fact that some MetS components change with age. For example, triglyceride levels and waist circumference may be lower among older adults as a result of inadequate nutrition and sarcopenia, which has its own adverse health consequences [25, 27].

Longitudinal studies are critical to establishing temporality in the associations between MetS and cognitive function. There have been several recent reports on the longitudinal associations of MetS with cognition, but the results are inconsistent [13, 27, 28, 29•, 30•, 31]. The Women's Health across Nation (SWAN) study reported that the presence of MetS in midlife was associated with a 24% accelerated decline in perceptual speed over 10 years [29•]. In the Singapore Longitudinal Aging Study (SLAS), there was a trend of cognitive decline in memory/learning, executive function, processing speed, attention/working memory, and global cognition related to the presence of MetS among late-middle aged adults over 4.5-year follow-up but the results did not reach statistical significance [13]. In contrast to the SWAN study, the European Male Aging Study (EMAS) reported no significant cognitive decline in those with MetS compared with those without MetS over a mean of 4.4 years [28]. EMAS, however, reported hyperglycemia, a component of the MetS, as the primary predictor of cognitive decline in tests of processing speed and visual-spatial abilities [28]. The discrepant results between these studies may be due to the characteristics of the study population or follow-up time. EMAS included a representative cohort of healthy European men, while the SWAN study included a cohort of US women traversing menopause. It is also possible that these discrepant results reflect sex differences in the association between MetS and cognitive function [32, 33], with the associations being stronger in women compared to men, as reported in some studies [34, 35].

A key large prospective study from the Framingham Offspring Study illustrates additional factors that may influence the association between MetS and cognitive function [30•]. Spanning midlife to late life, the authors reported that baseline MetS was not associated with change in cognitive function in the overall sample. However, results were different after conducting a stratified analysis by APOE-ε4 carrier status and dementia status. Specifically, baseline MetS was associated with lower cognitive function among non-demented vs. demented and APOE-ε4 non-carriers vs. APOE-ε4 carriers. Furthermore, participants with evidence of a more rapid rate of cognitive decline were more likely to have MetS compared to those who had a slower rate of cognitive decline [30•]. Finally, the study reported that both mid-life (at age 50) and late-life (at age 70) MetS were both associated with poor cognitive function; however, mid-life MetS was associated with more affected cognitive domains compared to late-life; memory, global cognition, processing speed/executive function were all affected at mid-life while memory was not affected at late-life [30•]. In addition to midlife and late life, the negative impact of MetS on cognition may extend to adolescents as well. Poor performance of reading, attention, working memory [22], executive function, and cognitive flexibility [19], were all reported in studies among adolescents. It should be noted however that there are only few studies published on Mets and cognition among adolescents and more studies are needed in order to assess these associations.

Severity of MetS, quantified as the overall number of MetS components present, was also related to lower cognition in some studies [13, 17, 21]. In some studies, the number of MetS components present appeared to be more strongly associated with lower cognitive function than the presence/absence of MetS [13]. Among the MetS components, hyperglycemia, high blood pressure, and high waist circumference were the component measures that were mostly strongly associated with cognitive performance [19, 21, 22, 28].

Fewer studies reported no association between the presence vs. absence of MetS and cognitive performance [28, 36–38]. A lack of an association in these studies could be due to common use of less sensitive global cognition screening tools, such as the Montreal Cognitive Assessment (MoCA) or the Mini Mental Status Exam (MMSE), rather than standardized and validated neuropsychological tests. These tests are more commonly used as dementia screening tools and are therefore not able to detect subtle changes in cognition that can be present before cognitive impairment is clinically present [37, 38]. Heterogenous results may also be due to the characteristics of the study population, covariates included in multivariate models, and different criteria used to define MetS.

MetS and Cognitive Impairment Syndromes (MCI, Dementia)

A summary of select recent studies that examined MetS and cognitive impairment syndromes are detailed in Table 2.

Relatively few recent studies have examined the association of MetS with MCI [39, 40•, 41, 42]. The Singapore Longitudinal Ageing Study Cohort (SLAS) reported that MetS was associated with an increased risk of incident MCI [40•]. Similar results were reported in a cross-sectional study by Wang and colleagues [39]. Similarly, fewer studies have examined the association of MetS with MCI subtypes (aMCI vs naMCI). Bae and colleagues [43] reported that MetS was associated naMCI but not with aMCI; however, the study was limited by a small aMCI sample size [43]. Some studies however reported no association between MetS and MCI. As with cognitive function as an outcome, factors such as the study population [42], study design, and definition of MetS used [41] may play a role in the differences across studies. For example, Martinez et al. reported no association between MetS and cognitive impairment among older high socioeconomic status participants, suggesting the importance of socioeconomic factor when it comes to the association between MetS and cognitive impairment [42].

On the other hand, many recent studies reported that MetS is related to an increased risk of progression from MCI to dementia [44, 45]. In the SLAS study, MetS was associated with an increased risk of progression from MCI to dementia [40•]. While the SLAS study did not specify dementia subtypes, Lee, and colleagues reported an increased risk of all dementia types including both Alzheimer's disease (AD) and vascular dementia (VD) [46]. Reports also exist of only VD [44] or only AD dementia [47] when both dementia types are compared to each other. It is more plausible, however, that MetS is more prevalent in VD than it is in AD dementia given that cardiovascular risk factors such high blood pressure, hyperglycemia and dyslipidemia are individual risk factors of VD which is primarily due to micro- and macrovascular disease such as small and large strokes [44, 46].

Among subjects with MetS, there may be differences in dementia progression depending on whether their MetS status improved or worsened. Fan et al. reported that there is a higher risk of dementia in patients with worsened MetS compared to those with improved MetS [48•]. Likewise, improvement in MetS status can result in reduced risk of dementia [46, 48•]. Categories of persistent, worsened and improved were defined by using changes of MetS diagnosis at different screening points. Fan and colleagues used 2 screenings that are 5 years apart where persistent MetS was defined as a diagnosis of Mets at the two screenings points; Worsened Mets as no MetS at the first screening and MetS at the second screening; and Improved MetS as MetS diagnosis at the first screening and no MetS at the second screening [48•]. These findings suggest that interventions that modify the trajectory of MetS may reduce the risk of dementia.

MetS and Biomarkers of Alzheimer's Disease and Other Dementias

Advances in in-vivo brain imaging, cerebral spinal fluid (CSF) and blood biomarkers have led researchers to use in vivo biomarkers to define AD. The current research framework from the National Institute on Aging and Alzheimer's Association (NIA-AA) suggests a biologic definition of AD that focuses on amyloid (Aβ), tau, and neurodegeneration as constructs regardless of cognitive impairment [49]. According to the NIA-AA, evidence of brain Aβ by biomarkers defines AD pathologic change and the AD continuum [49], making Aβ the primary construct of AD. There is a dearth of studies that have examined the association between MetS as a construct and biomarkers of AD and the associations in these studies are inconsistent [50]. Most studies report no association between MetS and AD neuropathology [51, 52]. In the Baltimore Longitudinal Study of Aging (BLSA), Gomez and colleagues [51] reported an association between MetS and accelerated Aβ deposition on amyloid Positron Emission Tomography (PET), only among Aβ positive participants, suggesting that pre-existing amyloid pathology is required in order to have an accelerating effect of MetS on further Aβ deposition. As such, subjects with no significant Aβ deposition at baseline may not be affected by MetS. Therefore, MetS could be an important factor in the progression of AD pathology but not necessarily the initiation of Aβ accumulation [51]. Similar to MetS, conflicting results are reported in regard to components of MetS. Some studies reported no association between Aβ on PET imaging and dyslipidemia [52, 53], high blood pressure [52, 54, 55] and waist circumference/obesity [52, 56]. On post-mortem neuropathology, Crane and colleagues reported no associations between glucose levels and Braak neurofibrillary tangles (representing tau) or neuritic plaque (representing Aβ plaques) [57]. Others however did report positive associations between Aβ on PET imaging, high blood pressure [51], and hyperglycemia [58]. Using CSF biomarkers of Aβ and tau, Nägga et al. reported a positive association between higher levels of triglycerides in midlife and higher CSF $A\beta_{42}$ and $A\beta_{42}$/*p*-tau ratio 20 years later [59]. Inconsistent results between MetS and AD pathology may be due to the few studies with the abilities to examine this association or potentially a result of the heterogeneity between studies in terms of demographics, specifically the age of AD biomarker measurement [50]. More longitudinal studies are needed in order to assess temporality between MetS and AD biomarkers [50].

Several studies have investigated and reported an association between MetS and biomarkers of CVD, an important factor in the clinical manifestation of AD [60, 61]. CVD and MetS are two interlinked conditions [62]. In fact, one of

Table 2 Summary of studies published within the last 5 years on the association between metabolic syndrome (MetS) and cognitive impairment syndromes

Author and year	Study population *N*, age	Study type	MetS definition	Cognitive construct used	Summary of the results
Kim et al. 2021 [47]	84,144 participants from the National Health Insurance Service database of Gangwon province in South Korea Mean age ≈66 ± 5 years	Retrospective cohort study	NCEP ATP-III criteria	AD and VD were defined as per the criteria of ICD-10-CM	-MetS was associated with AD (OR = 11.48, 95% CI = 9.03 to 14.59) but not with VD -All MetS components were associated with AD (high serum triglycerides: OR = 1.87, 95% CI = 1.60 to 2.19; high blood pressure: OR = 1.85, 95% CI = 1.55 to 2.21; high glucose: OR = 1.77, 95% CI = 1.52 to 2.06; abdominal obesity: OR = 1.88, 95% CI = 1.57 to 2.25; low serum high-density lipoprotein cholesterol: OR = 1.91, 95% CI = 1.63 to 2.24) -Only hyperglycemia was associated with VD (OR = 1.26, 95% CI = 1.01 to 1.56) -History of a previous stroke was associated with both AD and VD (AD: OR = 1.827, 95% CI = 1.263 to 2.644; VD: OR = 2.775, 95% CI = 1.747 to 4.406)
Wang et al. 2021 [39]	5854 participants from the Jidong community, China Mean age = 44 ± 13.57 years	Cross-sectional	IDF criteria	MMSE to define cognitive impairment (MMSE < 27)	-Participants with MetS had higher odds of cognitive impairment vs those with no MetS (OR = 2.39, 95% CI = 2.00 to 2.86, $p < 0.05$) -Among MetS components, waist circumference and high blood pressure were associated with cognitive impairment (OR = 1.36, 95% CI = 1.09 to 1.70, $p < 0.001$: OR = 1.32, 95% CI = 1.07 to 1.63, $p < 0.05$ respectively)

Table 2 (continued)

Author and year	Study population *N*, age	Study type	MetS definition	Cognitive construct used	Summary of the results
					-The strongest association was when MetS counts was 3 (OR = 1.86, 95% CI = 1.22 to 2.83, $p < 0.05$)
Lee et al. 2020 [46]*	4,106,590 participants of a biennial National Health Screening Program in 2009–2010 and 2011–2012 in Korea Mean age = 55.8 ± 10.1 years	Retrospective cohort study Mean follow-up = 4.9 years	NCEP ATP-III criteria 4 groups of MetS using changes in MetS for 2 years interval screening: sustained non-MetS (normal), transition to MetS (worsened), transition to non-MetS (improved), and sustained MetS	Newly diagnosed dementia, defined as antidementia drugs prescribed at least twice with codes for AD, VD, or other dementias	-There was an association between MetS status change and the risk of dementia subtypes; improvement of MetS lowered the risk of all dementia types: (HR = 1.18 vs 1.12), AD (HR = 1.13 vs 1.10), and VD (HR = 1.38 versus 1.19) -MetS increased both the risk of AD and VD but was more strongly associated with VD than AD -Among MetS, high blood pressure and hyperglycemia were the most strongly associated with dementia risk (HR = 1.16 vs 1.13, HR = 1.27 vs 1.05 respectively)
Feinkohl et al. 2019 [41]	202 non-demented participants from the BioCog study Mean age = 72.12 ± 4.74 years	Cross-sectional	NCEP ATP-III criteria with slight modifications	The lowest tertile of a cognitive summary score was used to determine cognitive impairment	-Neither MetS diagnosis nor the number of MetS components was associated with cognitive impairment (all $p > 0.05$) -None of the MetS components were associated with cognitive impairment (after adjustments for covariates) -Only low HDL-C was significantly associated with cognitive impairment (OR = 2.70 per 1 mmol/L reduction; 95% CI = 1.25 to 5.56; $p = 0.011$)

Table 2 (continued)

Author and year	Study population *N*, age	Study type	MetS definition	Cognitive construct used	Summary of the results
Lee et al. 2019 [77]	12,296,863 from The National Health Insurance System in Korea with no baseline dementia Mean age≈67 ± 6.6 years	Retrospective cohort study. Median follow-up = 65 months	NCEP ATP-III criteria[a] – 4 subgroups according to MetS and obesity status: Metabolically Healthy Non-Obese (MHNO), Metabolically Unhealthy Non-Obese (MUNO), Metabolically Healthy Obese (MHO) and Metabolically Unhealthy Obese (MUO)	Dementia: overall, AD, VD using ICD-10 codes and anti-dementia drugs	-The MHO group showed the lowest incidence of overall dementia (HR = 0.85; 95% CI = 0.84 to 0.86) and AD (HR = 0.87; 95% CI = 0.86 to 0.88), but not VD, compared with the MHNO group suggesting that being underweight increases the risk of dementia -MetS and MetS components except obesity increased the risk of dementia; and these associations were more pronounced in VD (MetS: overall dementia HR = 1.18, 95%CI = 1.17 to 1.19, VD HR = 1.37, 95%CI = 1.35 to 1.40)
Martinez-Miller et al. 2019 [42]	5200 dementia-free high socioeconomic older adult, Cooper Clinic patients from the Cooper Center Longitudinal Study (CCLS) Mean age = 59.0 years	Cross-sectional	NCEP ATP-III criteria	MoCA to define cognitive impairment. (MoCA < 26)	No association between MetS and cognitive impairment (prevalence ratio = 1.09; 95% CI = 0.97 to 1.23)
Bae et al. 2017 [43]	3312 Japanese from the National Center for Geriatrics and Gerontology Study of Geriatric Syndrome age ≥ 70 years old	Cross-sectional	IDF criteria	Classified to normal cognition, aMCI and naMCI	-MetS was only associated with naMCI subtype (men: OR = 2.45, 95% CI = 1.13to 5.32; women: OR = 1.94, 95% CI = 1.12 to 3.39) -Among MetS components, naMCI was associated with hyperglycemia, low HDL in men (OR = 1.97, 95% CI = 1.25 to 3.12, OR = 1.62, 95% CI: 1.19 to 2.22 respectively) and hyperglycemia high blood pressure in women (OR = 1.32, 95% CI = 1.02 to 1.71, OR = 1.42, 95% CI = 1.03 to 1.94 respectively)

Table 2 (continued)

Author and year	Study population *N*, age	Study type	MetS definition	Cognitive construct used	Summary of the results
Fan et al. 2017 [48•]	3458 participants from the Taiwanese Survey on Prevalence of Hypertension, Hyperglycemia, and Hyperlipidemia in 2002, with follow-up in 2007 Age: 40 to 80 years	Retrospective cohort study	NCEP ATP-III criteria 3 MetS groups: non-Mets, persistent MetS, non-persistent MetS (two subgroups: worsened, improved)	Dementia according to ICD-9-CM diagnosis codes	-Increased dementia risk in patients with worsened MetS during 10-year follow-up period in both age groups < or > than 65 years old (HR = 2.22; 95% CI = 1.32 to 3.72; $p = 0.003$)
Ng et al. 2016 [40•]*	1519 participants from the Singapore Longitudinal Ageing Study Cohort Mean age = 64.9 ± 6.8 years	Prospective longitudinal study	IDF criteria	MCI and dementia defined using criteria from report of the International Working Group on MCI, 2004	MetS was associated with both an increased risk of incident MCI (HR = 1.46; 95% CI = 1.02 to 2.09), and an increased risk of progression from MCI to dementia (HR = 4.25; 95% CI = 1.29 to 14.00) -Other factors that increased the risk of incident MCI were DM (HR = 2.84; 95% CI = 1.92 to 4.19), ≥ 3 cardiovascular risk factors (HR = 1.58; 95% CI = 1.13 to 2.33), central obesity (HR = 1.41; 95% CI = 1.01–1.98), and dyslipidemia (HR = 1.48; 95% CI = 1.01 to 2.15) -Other factors that increased the risk of Progression from MCI to dementia: DM (HR = 2.47; 95% CI = 1.92to 4.19) and ≥ 3 cardiovascular risk factors (HR = 4.92; 95% CI = 1.39 to 17.4)

MetS, metabolic syndrome; *NCEP ATP*, the National Cholesterol Education Program Adult Treatment Panel; *IDF*, International Diabetes Federation; *MCI*, mild cognitive impairment; *aMCI*, amnestic mild cognitive impairment; *naMCI*, non-amnestic mild cognitive impairment; *AD*, Alzheimer's disease; *VD*, vascular dementia; *DM*, diabetes mellitus; *MMSE*, Mini-Mental State Exam; *ICD-10-CM*, International Classification of Disease, Tenth Revision, Clinical Modification codes; *ICD-9-CM*, International Classification of Diseases, ninth Revision, Clinical Modification; *MMSE*, Mini Mental Status Examination; *MoCA*, Montreal Cognitive Assessment; *HDL*, high density lipoprotein; *CI*, confidence interval; *HR*, hazard ratio; *OR*, odds ratio

*Refers to studies "Of importance"

[a]Waist circumference was not used

the feared complications of MetS along with cardiovascular disease is stroke, which is the most common manifestation of CVD [63, 64]. Stroke is a well-known cause of neurologic deficits, cognitive impairment and dementia [65, 66]. MetS is also associated with subclinical manifestations of CVD, including microinfarcts, microbleeds and white matter lesions [63]. These small silent brain insults are usually incidentally found in neuroimaging and a large body of literature do correlate these lesions with cognitive decline and dementia [63, 67, 68]. Among the MetS components, impaired glycemia, high blood pressure, and obesity were most often examined and were associated with cerebrovascular disease measured using magnetic resonance imaging (i.e., higher prevalence of microinfarcts and microbleeds) and worse brain microstructural integrity measured using diffusion tensor imaging (i.e., lower fractional anisotropy suggesting adverse alterations in white matter connectivity) [67].

Conclusion

MetS is an important risk factor for cognitive dysfunction. However, as discussed in the present review, many factors play a role in this association and account for some of the discrepancies observed in the literature. More longitudinal studies are needed to assess causality between MetS and cognitive dysfunction. When examining cognitive function, ideally these studies should use a battery of neuropsychological tests that tap into multiple cognitive domains instead of relying on a single test or on cognitive screening tools. More studies are also needed to assess which MCI subtype is more related to MetS. Similarly, more studies are needed to assess the association between AD biomarkers and MetS. Furthermore, among MetS components: high blood pressure, high waist circumference and hyperglycemia were among the strongest predictors of cognitive function. It should be noted however that our focus in this review was studies that examined MetS as a construct and we discuss MetS components according to findings from these studies.

Finally, there have been several clinical trials that target individual components of MetS such as blood pressure [69, 70], glycemic control [71], or lipid control [72, 73]. An intervention study that targets all MetS components is potentially not feasible due to cost. Most MetS components however are associated with excess weight (blood pressure, glucose, and lipid levels) [74], and therefore may show reductions in response to a weight loss intervention and have downstream impacts on cognitive outcomes [75, 76].

Based on this review, data suggest that MetS is associated with cognitive impairment. Further research is needed on how preventing or treating MetS across the life course will impact downstream cognitive outcomes.

Funding Priya Palta has received grant funding from the National Institutes of Health. José A. Luchsinger reports the following grants: K24AG045334, RF1AG051556, R01AG050440, R01AG058571, R01AG058969, and R01AG055299.

Compliance with Ethical Standards

Conflict of Interest JA Luchsinger receives a stipend from Wolters Kluwer, N.V. as Editor-in-Chief of the journal *Alzheimer's Disease and Associated Disorders*, receives royalties from Springer for the book *Diabetes and the Brain*, and has served as a paid consultant to vTv therapeutics, Inc., Recruitment Partners, and NYU Langone. The other authors have no other conflicts of interests to declare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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