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Impact of Metabolic Syndrome on Cognition and Brain: A Selected Review of the Literature

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Abstract

Metabolic Syndrome (MetS), a clustering of risk factors for type 2 diabetes mellitus and cardiovascular disease, has been associated with cognitive dysfunction and brain abnormalities. This review describes the literature on the impact of MetS on brain and cognition and suggests directions for future research.

A literature search for reports of MetS and cognition and brain imaging was conducted for both non-elderly adults and adolescents. No studies were found describing MetS and brain or cognition among adolescents; therefore we also included studies investigating individual components of MetS in this age group. Most studies found associations between MetS and cognitive dysfunction. Multiple cognitive domains were affected by MetS in adults. In adolescents, the majority of findings were in executive functioning. Brain imaging literature in adults implicated MetS in ischemic stroke, white matter alterations and altered brain metabolism. For adolescents, individual MetS factors were linked to volume losses in the hippocampus and frontal lobes.

MetS negatively impacts cognitive performance and brain structure. Potential explanatory models include impaired vascular reactivity, neuroinflammation, oxidative stress, and abnormal brain lipid metabolism. We posit that insulin resistance-associated impairment in cerebrovascular reactivity is an important mechanism underlying brain deficits seen in MetS.

Keywords

Metabolic Syndrome; Cognitive Performance; Adults; Adolescents; Brain Imaging

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Introduction

The Metabolic Syndrome (MetS) has been called a global epidemic by the WHO[1] and is considered a major public health problem,[2] with 34% of Americans over the age of 20 estimated to be affected.[3–4] Among adolescents, 9.4% are estimated to have MetS and the prevalence rises to 44.2% among those that are obese.[5] Therefore, the MetS is one of the few clinical syndromes that affects a large portion of the general population that is potentially reversible by established interventions.[6]

MetS is known to affect cognition and raise the risk for dementia.[7–8] Interest in understanding the pathophysiologic mechanisms underlying MetS and its impact on brain function, will inform possible interventions. Positive cognitive changes have been seen with some interventions targeting MetS components.[9–10]

MetS, first described as Syndrome X was proposed by Reaven in 1988 [11] in an attempt to provide a unifying pathophysiologic explanation for the tendency of impaired fasting glucose, dyslipidemia, and hypertension to cluster in some individuals, who were at increased risk for CVD and T2DM [12]. Because insulin resistance (IR) is thought to be the key underlying condition in Syndrome X, others then coined the term 'The Insulin Resistance Syndrome'.[13] This focus on the associations between IR and other cardiovascular risk factors led to the creation of clinical MetS definitions by the World Heart Federation (WHO)[14], the International Diabetes Federation (IDF)[15], and the National Cholesterol Education Program Third Adult Treatment Panel (NCEP ATP III)[16], in an attempt to identify patients at increased risk for CVD and T2DM.

The most commonly used definition for MetS in the U.S. is the one described by the NCEP ATP III, which is the presence of three or more of the following criteria: (1) abdominal obesity: waist >102 cm (>40 in) for men or >88 cm (>35 in) for women; (2) triglycerides ≥150 mg/dL; (3) high-density lipoprotein <40 mg/dL for men or <50 mg/dL for women; (4) blood pressure ≥130/≥85 mmHg or current use of anti-hypertensive medications; and (5) fasting glucose level ≥110 mg/dL. The International Diabetes Federation uses a slightly modified definition where one of the three criteria must be abdominal obesity in addition to two of the other four criteria, and the abnormal threshold for fasting glucose is set at ≥ 100 mg/dL) (or previously diagnosed type 2 diabetes).

Goals of the review

Three reviews have been published recently regarding MetS and cognitive decline in older adults with a focus on individuals at high risk for dementia or with dementia.[17–19] This review concentrates on the impact of MetS on cognitive functioning and brain integrity in functionally normal non-elderly adults and adolescents. Although our focus is predominantly in brain associations to MetS proper, our review for young populations also highlights associations of the individual MetS factors with cognition and brain due to the paucity of research for this population. We focus particular attention to insulin resistance, as in our opinion, it is central to the impact of the syndrome on brain. At the end of the review we provide a brief overview of one potential explanatory model for the impact of MetS on brain.

Literature Selection

Cognition

Only articles that examined cognitive functioning as an outcome associated with a diagnosis of MetS were selected for the adult review. Use of multiple neuropsychological tests for at least one cognitive domain was required. Reports that relied on self-report or that utilized

only global/screening measures of functioning such as the Mini-Mental State Examination were excluded. Electronic databases were searched utilizing terms ‘“Metabolic Syndrome” paired “cognition”, “cognitive function”, “cognitive performance”, or “neuropsychological function.”

For the children and adolescent search, inclusion criteria and search terms mirrored that for the adult studies with the exception that papers addressing Prader-Willi Syndrome and/or focusing on children younger than 10 years of age were excluded. An expanded search was conducted including terms such as “obesity”, “overweight”, “body mass index”, “hypertension”, “lipids”, “HDL”, “triglycerides”, “blood pressure”, “insulin resistance”, and “hyperglycemia”. A total of 20 studies were included, 10 for adults and 10 for adolescents.

Brain Imaging

For the brain imaging literature, MEDLINE searches were performed for keywords and terms such as “metabolic syndrome”, “brain”, “cerebral”, “infarct”, “lesion”, “MRI”, “diffusion tensor imaging”, and “spectroscopy”. The literature reporting the brain involvement in MetS in adults was quite limited and we found no publications among children or adolescents describing the associations between MetS and brain. Therefore, among children or adolescents we expanded our search to also include the terms, “insulin resistance”, “pre-diabetes”, and “type 2 diabetes mellitus” (the extreme of the MetS spectrum).

Neuropsychological Assessment of Cognition

Neuropsychological tests assess functioning in cognitive domains such as intelligence, memory and learning, language, executive functioning, processing speed and sensory-perceptual abilities. However, the literature offers little consistency in individual tests used to measure particular cognitive domains.

Impact of MetS on Cognition in Adults

A summary of the studies included in this review can be found in Table 1. Most studies report that MetS and its components have a negative impact on cognition (i.e.,20–26). However, findings may vary by sex, with men being more affected in some reports[23, 27]; women in others[26], and some reporting no sex differences.[24]

Multiple cognitive domains are affected, even after controlling for medical factors such as CVD and T2DM [28], silent brain lesions[22], education and socioeconomic status[22–23], depressive mood, coronary heart disease, and magnetic resonance imaging (MRI) findings.[23] MetS has been linked to deficits in memory, visuospatial abilities, executive functioning, processing speed, and overall intellectual functioning.[22–26, 28–29]

A few studies report no significant associations between MetS and cognition.[30–31] Lack of significant findings could be due to the low sensitivity of the test battery chosen as well as the health status of the “control” group, which often includes subjects with one or two risk factors for MetS. For example, Gatto et al., (2008), showed no group differences; however, regression analysis of their whole population using the actual number of MetS criteria met (0 to 5) showed significant reductions in cognitive performance with each additional MetS criterion met.[32]

Impact of MetS on cognition in Children and Adolescents

There is currently no literature on MetS and cognition in children and adolescents, but there is some on individual MetS components. In 2011, Smith et al[33] published a review exploring

the links between obesity and cognition across the lifespan. In children, the majority of findings on cognition in obesity have been predominantly in executive functioning,[34–37] a cognitive domain known to depend on an intact frontal lobe. Frontal lobes are still developing during adolescence,[38] which may render this brain region more vulnerable to metabolic dysregulation. Impaired executive function may also play a role in the development of obesity, particularly if it leads to impaired response inhibition and overeating.[39] Reductions in attention and global functioning or IQ have also been reported in childhood obesity.[34, 37, 40–41] Impairments in attention can contribute to poor performance in other cognitive domains and may help explain the deficits reported in executive functioning and IQ.

Lande and colleagues (2003)[42] found that 50% of the children with elevated blood pressure were overweight or obese and that those with systolic blood pressure > 90th percentile for age, sex and height scored significantly worse on attention/concentration, visual-spatial, and math tasks.

Impaired fasting glucose (IFG), an important MetS component, is often a precursor for T2DM, which has been strongly linked to cognitive dysfunction in adults.[43] Our lab reported that obese adolescents with T2DM perform consistently worse than well-matched, also obese, peers on global functioning, executive function, memory and attention.[44] Given that it is rare to find a young individual with T2DM, who does not also fulfill criteria for MetS, it is likely that similar findings will be present among obese adolescents with MetS.

There is only one report failing to find statistically significant cognitive impairments associated with obesity and excess weight.[45] However, in this report the heaviest group of children consistently scored lower on all but one of the cognitive measures assessed.

Impact of MetS on Brain in Adults - Imaging

Individual MetS components are known to have independent negative brain consequences,[46–49] but evidence of brain involvement in MetS as a whole remains rather limited. MetS is a known risk factor for ischemic stroke.[50] There have been a handful of reports of subclinical ischemic brain damage in adults with MetS. Increased silent brain infarction has been observed in both elderly[51] and middle-aged individuals with MetS.[22, 52] Others have reported increased prevalence of intracranial arteriosclerosis,[53] periventricular white matter hyperintensivities (PWMH), and subcortical white matter (WM) lesions.[54] Using diffusion tensor imaging (DTI), Segura et al. (2009) characterized reductions of WM micro-structural integrity involving primarily the frontal and temporal lobes.[55] More WM abnormalities have been associated with increasing number of MetS components present[51, 54] and these associations may also be driven by individual vascular risk factors.[51–52, 54]

Haley et al. (2010) demonstrated changes in brain metabolism characterized by increased myoinositol/creatine and glutamate/creatine ratios in occipito-parietal gray matter in cognitively intact middle-aged adults with MetS.[56] Increased myoinositol/creatine ratios, suggestive of increased microglia or neuroinflammation, have been reported in T2DM.[57] Using functional MRI, Hoth et al. (2011) observed blunted brain activation in the absence of cognitive compromise.[58] Taken together, these subclinical alterations in cerebral metabolism and cerebrovascular reactivity may represent early brain compromise associated with peripheral metabolic disturbances.

Impact of MetS on Brain in Children and in Adolescents - Imaging

No data currently exists on the impact of MetS on the pediatric brain. Most individuals with MetS have IR,[59] which is likely the driving force behind the brain complications reported in MetS.[60–61] Bruehl et al. (2011) reported that relative to those without IR, obese adolescents with T2DM had smaller hippocampal volumes and more frontal lobe atrophy.[62] In addition, we have described among adolescents with IR, a blunted cortisol awakening response (CAR), a good indicator of the hypothalamic-pituitary-adrenal (HPA) axis integrity.[63] More importantly, the finding of an inverse relationship between CAR and fasting insulin levels as well as between CAR and hippocampal volumes supports the role of metabolic disturbances in brain structural abnormalities, which lead to the HPA axis dysregulation.[64] Further, we have described specific gray matter volume reductions in the orbitofrontal cortex, associated with disinhibition of feeding behavior among obese adolescents (with and without IR).[37]

Discussion

There is a lack of consensus on the relationships between MetS and its components and cognitive health, which is partly explained by a lack of consistency in the cognitive domains selected for assessment, differences in quality of tests selected, demographics of populations studied (i.e., differences in age, race, sex, and educational level), lack of a standard definition of MetS, cross-sectional versus longitudinal study designs, and difficulty in uncoupling the impact of individual or combinations of MetS factors from that of the syndrome itself. Cognitive and brain abnormalities associated with MetS may result from synergy of the different component risk factors. In addition, few studies utilized a control group free of any MetS risk factor. Furthermore, sex differences have not been extensively addressed and findings to date have been inconsistent. MetS has been associated with poorer executive performance in women, but not in men.[26] Moreover, impairments have been found in varying cognitive domains across the lifespan with memory preserved until the 6th decade when impairments are found[25] indicating that MetS may be an important contributory factor in worsening memory for women. Although some of the studies that we cited exclude individuals with major psychiatric or neurological illness, studies either do not specify other medications or if they do, they do not account for them. Given that we excluded studies with subjects with a mean age over 65 years, it is less likely that the reported studies will have the confounding effects of the poly pharmacy that often occur in the elderly. However, we have no way of identifying whether some cognitive findings reported in the literature are due to pharmacological side effects.

Potential Explanatory Model for Brain Deficits Associated with MetS

A number of potential explanatory models have been proposed for the ill effect of MetS on brain and cognition including neuroinflammation, oxidative stress, abnormal brain lipid metabolism, and impaired vascular reactivity among others. Since a discussion of all of these models would be beyond the scope of this brief review, we will utilize an explanatory model based on IR-associated vascular reactivity problems as an example.

Impaired cerebrovascular reactivity[65], increased carotid stiffness, and intima-media thickness (IMT)[66–67] have been reported in adults with MetS. Given that the carotid artery is the main blood supply to the central nervous system and that carotid atherosclerosis has been linked to cognitive impairment[68] and increased brain atrophy[69], such findings suggest that the WM damage seen in adults with MetS are likely vascular in nature.

Similarly, endothelial dysfunction, carotid stiffness, and intima-media thickness also have been reported in children with MetS,[70–72] obesity,[73–76] hypertension,[77–79] and T2DM.[80–81] Those with uncontrolled T2DM have more severe carotid alterations.[80] Vascular

involvement likely plays a role in cognitive and brain impairment in adults.[82–83] Given the increasing vascular abnormalities with increasing metabolic alterations along the MetS spectrum in children, MetS also likely adversely impacts brain structure and function in adolescents.

We propose the damaging effects of MetS and IR on brain integrity are partly dependent on the vascular reactivity abnormalities associated with those conditions.[84] We suggest a conceptual model that posits that when a region of the brain is activated (as when performing a cognitive task), there is increased synaptic activity in that region, which normally results in regional vasodilatation.[85] Vascular reactivity is key to maintaining energy-dependent processes such as regional brain activation by clearing the metabolic "waste" produced by neuronal activity (CO_2, excess lactate, other metabolites, heat, etc).[85] We know that in T2DM and MetS there are impairments in endothelial-dependent vasodilatation.[86–87] Consequently, individuals with MetS may not be able to maintain an optimal neuronal environment, particularly during periods of high demand. We propose that among individuals with insulin resistance and MetS vascular reactivity (capillary recruitment, #1 in Figure 1), a mechanism that maintains an optimal neuronal environment during brain activation, is dysfunctional. We propose that these reductions in vascular reactivity are due to the direct or indirect deleterious effects of insulin resistance (#2) and/or obesity-associated inflammation (#3) on the micro-vasculature. There is new evidence to support both that insulin resistance leads to inflammation and that inflammation leads to IR (#4). The resultant effect of both insulin resistance and inflammation is to reduce cerebral vascular reactivity. The impaired vascular reactivity may, in turn, lead to an inability to maintain energy-dependent processes and clear metabolic "waste" under conditions of increased demand. We propose that this endothelial dysfunction, when coupled with other potentially damaging influences such as inflammation, HPA axis dysregulation, or increased oxidative stress, may damage the brain, particularly those regions more vulnerable to damage. The model does not address possible problems that may occur after vascular reactivity (#5 in diagram above).

Future studies should also explore other explanatory models including the impact of inflammation as a potential mediator for the damaging effects of MetS on brain structure and function. Assessment of inflammation and oxidative stress directly in brain by using MRI-based spectroscopy could be a logical next direction to understand the associations between MetS and cognitive impairments. Furthermore, future studies should use prospective longitudinal designs, which will allow stronger conclusions about possible mechanisms and better inform follow-up animal models. Intervention studies as well as those that incorporate protective factors, such as a well balanced healthy diet and exercise, will also assist in better elucidating candidate mechanisms and iteratively improve interventions intending to protect the brain.

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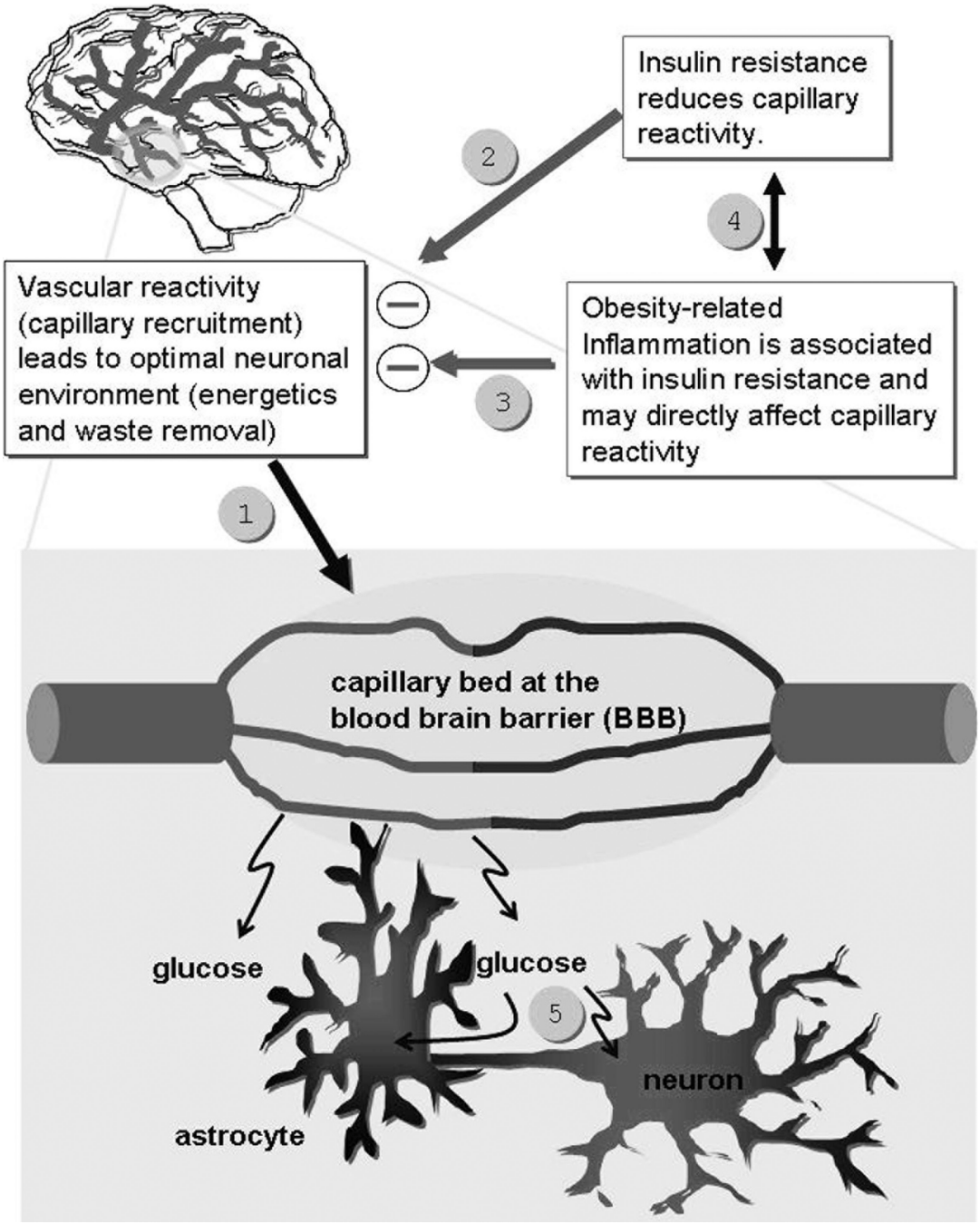

Figure 1.
Model describing hypothesized brain vascular reactivity abnormalities resulting in brain impairments.

Arterioscler Thromb Vasc Biol. Author manuscript; available in PMC 2013 September 01.

Table 1

Ten studies of the association between cognition and Metabolic Syndrome in non-elderly adults (mean age <65 years)

Reference	Clinical population (MetS)	Control Group (No MetS)	Cognitive tests	Covariates/Exclusions	Results
Bokura, et.al. (2010) *	186 Japanese mean age 61.2	1357 mean age 62.2	Koh's Test, FAB, (sig) Okabe's Test (non-sig)	Age, gender, education, smoking, alcohol use, subclinical ischemic brain lesions Exclusions: Neurological & Psychiatric Diseases	MetS is associated with impaired executive function independent of silent brain lesions
Cavalieri, et.al. (2010) *	232 mean age 65.1	587 (W: 149 ± 25.3) mean age 64.8	BLG, WCST, TMT-B, DSB (sig), PPT (not Sig)	Model 1: Age, education, gender, depressive mood, coronary heart disease, physical activity Model 2: Model 1 plus WML volume, presence of lacunes, silent infarcts, brain parenchymal fraction Exclusions: None	MetS is related to memory and executive function in men but not women; further compromise with high hs-CRP and increasing MetS components
Gatto, et.al. (2008) †	112 mean age 61.8	741 (BMI: 26.7 ± 4.7) mean age 60.8	SDMT, TMT-B, JLO, Block Design, Letter-Number Sequencing, Category Fluency, BNT, Shipley, CVLT-II, Logical Memory I and II, Faces I and II. (None significant)	Age, gender, race, education, income, smoking, CVD risk factors, statins, anti-hypertensives, depression Exclusions: CVD; diabetes; uncontrolled lipid abnormalities, hypertension, other endocrine or significant kidney disease; alcohol/substance abuse; hormone therapy	Correlation between hypertension and lower cognition; Significant cognitive impairment with increasing MetS factors
Haley, et.al. (2010) +	13 mean age 47.6	25 (BMI:26.8 ± 4.8) mean age 51.3	MMSE, WASI-IQ, Animal Fluency, CVLT-II, RCF, DSS, COWAT, TMT, GPT, BDI (none were significant)	Age, gender, education, depression Exclusions: Neurological disease, major psychiatric illness, substance abuse, MRI contraindications, age: <40, >60	No significant cognitive differences
Hassenstab, et.al. (2010) *	73 mean age 60.4	70 (BMI: 25.0 ±3.4) mean age 60.1	Shipley, Phonemic & Category Fluency, WMS-R & WAIS-R (selected subtests), CVLT, Stroop, Category Fluency (mixed findings)	Age, gender, education, T2DM Exclusions: Significant psychiatric, neurological or other medical diseases; T2DM; < 12 years education	Significant reductions in recall, lower overall IQ; increasing MetS factors associated with lower performance
Komulainen, et.al. (2007) *	13 Women mean age 63.6	88 (BMI 26.9 ±3.9) mean age 63.8	WRT (sig), Stroop, LDST, MMSE (non sig)	Age, education, depression, hormone replacement therapy, BMI, prevalent cardiovascular disease Exclusions: None	MetS at baseline = greater risk of memory impairment at follow-up; memory declines with increasing MetS factors
Muller, et.al. (2009) *	295 mean age 59	528 (BMI: 26 ± 3) mean age 58	15WLT, RCF, VET, BSAT, Letter Fluency, DART (all sig)	Model 1: Age, sex, education, intellectual functioning, smoking, alcohol use Model 2: Model 1 plus extent of vascular disease, atherosclerosis, inflammation Exclusions: None	MetS is related to memory and visuospatial dysfunction but not executive dysfunction
Schuur, et.al. (2010) *	434 mean age 61.4	1464 mean age 46.2	Stroop (sig), DART, AVLT, TMT, verbal fluency, WAIS-III block design (non sig)	Age, gender, smoking, alcohol use, education, depression, APOE Exclusions: Dementia or inability to perform a neuropsychological tests	MetS and high HOMA-IR associated with executive dysfunction in women but not men
Segura, et.al. (2010) *	19 Spanish mean age 61.26		SDMT associated with FA (sig); Vocabulary (WAIS-III); GPT, CPT-III	Age, education, IQ, gender Exclusions: Hx of psychiatric or neurological disease; <8 years of education, left handed; For controls: any MetS-vascular risk factor	No significant cognitive differences between groups

Reference	Clinical population (MetS)	Control Group (No MetS)	Cognitive tests	Covariates/Exclusions	Results
Tournoy, et.al. (2010)*	1007 European men mean age 61.0	2145 (BMI: 26.3 ± 3.3) mean age 59.3	RCF, CTRM, DSST (sig when applied to individual MetS components)	Age, age leaving education, smoking, alcohol consumption, physical activity, depression, hs-CRP, and center location Exclusions: None	MetS not associated with cognitive impairment; Diabetes linked to poorer memory, executive functions and processing speed

*used NCEP-APT III MetS criteria

+used IDF MetS criteria

†used a modified NCEP-APT III MetS criteria

Arterioscler Thromb Vasc Biol. Author manuscript; available in PMC 2013 September 01.

Table 2

Ten cross-sectional studies of the association between cognition and factors of the Metabolic Syndrome in children and adolescents

Reference	MetS Factor	Clinical Population	Control Group	Cognitive tests	Covariates	Results
Cserjesi, et.al. (2007)	Elevated Waist Circumference	12 obese boys mean age 12.1	12 Age-matched non-obese boys	D2 Attention Endurance Test, WCST (sig), Digit Span Memory Task, Raven Matrices, Semantic Verbal Fluency (non-sig)	None	Obese performed worse on WCST & D2 attention endurance task despite similar memory & intelligence
Gunstad, et.al. (2008)	Elevated Waist Circumference	45 BMI≥ 95th % 6–19 y.o.; mean age of entire sample = 12.45	433 BMI <95th % divided into 3 weight groups	Digit Span Backward, TMT-B, Verbal Recall, Animal Fluency, Finger Tapping (all non-significant)	Age, estimated IQ	No associations between BMI & cognition
Lande et.al., (2003)	Elevated Waist Circumference, Hypertension	5,077 6–16 y.o. (NHANES)	None	WISC-R Block Design & Digit Span, WRAT Arithmetic (sig), WRAT Reading (non-sig)	Race, sex, parent ed., poverty, meds/ antihistamines, general health, lead level, BMI, heart rate	Those with systolic BP >90th % performed worse on block design, digit span and math; 55.6% of these were overweight or obese.
Li, et.al. (2008)	Elevated Waist Circumference	360 BMI ≥ 95th % 8–16 y.o. mean age 12.03	2,159 BMI < 95th % divided into 2 weight groups	WISC-R Block Design & Digit Span, global functioning (sig), WRAT Reading & Arithmetic (non-sig)	Age, gender, ethnicity, education, marital status of family head, family income, dwelling, hours watching TV, exercise, health status, blood pressure, heart rate, iron deficiency, psych & social variables	Those with BMI ≥ 95th % performed significantly worse on digit span, block design & global functioning
Lokken, et.al. (2009)	Elevated Waist Circumference	25 12–19 y.o., mean age 16.2, mean BMI=54	Compared performance across existing normative test data	Digit Span, CPT, Verbal Inference, Switching Attn, Maze Task (sig), Go-No-Go (non-sig)	None	Obesity associated with worse performance, esp. attention and executive functioning
Maayan, et.al. (2011)	Elevated Waist Circumference	54 obese 14–21 y.o. Mean age 17.32	37 lean 14–21 y.o. Mean age 17.50	COWAT, TMT, Stroop, Attn/ Concentration & Memory Indexes from WRAML-2 (all sig)	IQ	Obese performed worse on all cognitive measures
Parisi, et.al. (2010)	Elevated Waist Circumference	71 Overweight and 51 obese 6–13 y.o.	188 6–13 y.o.	WISC-R, SDAG (parents) (varying results)	None	Sig. weight group differences on PIQ; BMI group predicts PIQ; Gender & parental ed. predicts VIQ; Parent ed. predicts TIQ
Pauli-Pott, et.al. (2012)	Elevated Waist Circumference	177 overweight and obese 8–15 y.o.	None	Go-No-Go & Incompatibility Tasks of the Attention Assessment Battery (all significant)	Age, gender, education, SES, general mental ability	Obese showed more inattention; at younger ages, high impulsivity is associated with higher body weight

Reference	MetS Factor	Clinical Population	Control Group	Cognitive tests	Covariates	Results
Verdejo-Garcia, et.al. (2010)	Elevated Waist Circumference	8 overweight & 19 obese 13–16 y.o.	34 Normal weight 13–16 y.o.	5 digit test, TMT, Iowa Gambling (sig), Stroop, Letter Number Seq., Similarities, Zoo Map, Rev. Strategy Application, (non-sig)	Age	Excess weight perform worse on inhibition, flexibility & decision making
Yau, et.al. (2010)	Elevated Waist Circumference, Hyperglycemia	18 obese T2DM, mean age 16.46 y.o.	18 Obese non-T2DM mean age 17.16 y.o.	DSST, IQ, WRAML Verbal (sig), WASI Subtests, WRAT, WRAML Visual & Working Memory, Dig Vig, WCST, ToL, COWAT(non-sig)	Matched on age, sex, grade, SES, BMI, Waist, WHR & Sleep apnea	T2DM performed significantly worse performance on all cognitive domains