Neuropsychology of metabolic syndrome: A systematic review and meta-analysis

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Abstract: There is growing evidence of the relationship between Metabolic Syndrome (MetS) and cognitive decline; however, this has not been conclusively established yet. This systematic review and meta-analysis address the most crucial cognitive performance findings, including those on global cognitive function, memory, attention, and executive functions, in adult people with MetS. Two electronic databases were searched (April–May 2020) using the terms “metabolic syndrome” and “cognition,” including publications from 2010 to 2020. Thirty-six studies were found. Among these, 17 reported negative associations in cognition with MetS, mainly in terms of verbal memory and executive functions, particularly in the middle-aged population. A meta-analysis of global cognitive function revealed that the MetS group had a lower score than the control group (25.26 and 25.6, respectively, 95% CI, −0.60 to −0.12, p = 0.004). MetS is related to the enhanced presentation of cognitive impairment and its evolution into a Major Neurocognitive Disorder (MND). Further research involving longitudinal studies, including assessments with similar instruments, correctly separated by age group and education, is required.

Subjects: Cognitive Neuropsychology; Cognitive Neuroscience; Cognitive Neuroscience of Memory; Cognitive Neuroscience of Language; Cognitive Neuroscience of Vision

Keywords: metabolic syndrome; neuropsychology; cognition; memory; executive function; attention

ABOUT THE AUTHOR

The authors conform to a multidisciplinary research group that work in different areas of neuroscience, neuropsychology, behavior, and metabolism. Their research interest is the study of the causes and consequences of metabolic affection in different organism systems, in particular, the central nervous system, with experience in both animal model and human population.

PUBLIC INTEREST STATEMENT

The presence of obesity, diabetes, hypertension and high blood triglycerides, metabolic alterations which in conjunction are called Metabolic Syndrome (MetS), represents an important public health problem nowadays. MetS is related with a worsening of not only physical health but also of mental health since it is a risk factor for the development of dementia, now called Major Neurocognitive Disorder (MND). A better understanding of the negative effects of metabolic disorders on mental functions opens the possibility to establish preventive measures to ensure their conservation throughout aging, and subsequently, to maintain the independence of elderly population, increasing their quality of life. For this reason, our aim is to actualize and strengthen the evidence of the association of MetS and cognitive deficit in mental health through a systematic review and meta-analysis. As conclusion, MetS is related to an enhanced presentation of cognitive impairment and its evolution to MND.
1. Introduction
In previous decades, the incidence of chronic noncommunicable diseases has increased due to lifestyle changes. Such is the case for Metabolic Syndrome (MetS), meaning that, in the future, it may overtake smoking as a leading risk factor for heart disease (National Heart, Lung and Blood Institute, 2019). This situation might worsen due to the increased life expectancy that has caused an increased risk for suffering from this kind of illness (Álvarez-Cisneros et al., 2017). MetS refers to a group of disorders including high blood pressure, abdominal obesity, glucose intolerance, insulin resistance, high serum triglyceride levels, and a low concentration of High-Density Lipoprotein (HDL) cholesterol (Yates et al., 2012). The importance of MetS in public health is that there is an association between this syndrome and an increased risk of developing cardiovascular disease, type 2 diabetes, certain types of cancer, and mortality in general (Zhang et al., 2019). This condition is made up of different pathological components with particular prevalence levels, and there are no precise data on the incidence and prevalence of MetS, since its diagnosis has not yet been fully agreed upon between specialists. Nevertheless, considering that MetS is about three times more common than diabetes, it is possible to estimate that it affects one-quarter of the world’s population or, put another way, over a billion people could have MetS (Saklayen, 2018). In recent years, there has been a growing interest in the association of metabolic ailments with cognitive dysfunction (Hao et al., 2011; Siervo et al., 2014) because cognitive deficit may be one of the consequences of MetS. There is evidence that this syndrome could be a predecessor to the development of mild cognitive impairment, such as Major Neurocognitive Disorder (MND), due to cerebrovascular disease (previously called vascular dementia), or even Alzheimer’s disease (Wang et al., 2019). Frisardi et al. (2010) proposed the use of the term metabolic-cognitive syndrome. They suggested an insulin-resistant brain status as an additional feature of this compound syndrome, and also identified the molecular profiles of patients with an increased risk of developing MND. A recent study showed that participants who suffer from diabetes mellitus present with memory dysfunction and mild cognitive decline (Huang et al., 2019). The mechanisms that link this syndrome with cognitive impairment include insulin resistance (Ma et al., 2015), ischemic brain lesions (Bokura et al., 2011), and inflammation (Yaffe, 2007). There is a significant association between MetS and a higher C reactive protein concentration with cognitive impairment in the elderly population (Ghosh et al., 2015). Moreover, cardiometabolic risk factors can lead to hypersensitivity in the brain white matter, and something fundamental to consider is that the frontal brain cortex is especially vulnerable to cerebrovascular factors and vascular disease (Alcorn et al., 2017; Keage et al., 2015). However, if this is related to cognitive decline, it is uncertain, and some mechanism associated with MetS could be activated in order to compensate for the cognitive decline (Alkan et al., 2019). MetS is related to characteristics associated with motor dysfunction and neuropsychological decline (Li et al., 2016), such as impairment of short-term memory, cognitive slowdown, and executive dysfunction (Chang et al., 2015; Bonilla & Galindo-Aldana, 2017 & Yogi-Morren et al., 2014). Regarding other processes, such as language, minimal negative effects have been found, and this has been associated, in some cases, with education, which has a neuroprotective effect on this cognitive process (Alcorn et al., 2017; Philippou et al., 2018). Perception has not shown significant affection (Alcorn et al., 2019). Specific studies have found that expressive language naming skills do not differ among people with MetS (Cahana-Amity et al., 2015). That is, the differences found in the multiple spheres of cognitive processing reveal have not yet revealed conclusive results. This could be due to the wide variety of methodologies and instruments that different authors have used to measure cognitive decline, as for a given instrument, different approaches may be used and different cognitive aspects measured. This situation makes it complicated to do comparisons.

There are some systematic reviews in the literature about this issue (Alcorn et al., 2019; Assuncao et al., 2018; Hao et al., 2011; Yates et al., 2012); however, it is important to reanalyze the existent evidence for two main reasons. First, some of the previous works incorporated studies in which samples consisted of teenagers or subjects who were already experiencing cognitive decline, had a neurological history, or even had MND. In these cases, it is essential to consider that
the neuropsychological impairment found could have been associated with a previous history of cerebrovascular disease or even a genetic predisposition to accelerated neuronal death. Second, these previous revisions were mostly qualitative. In the last published meta-analysis conducted by Siervo et al. (2014), a tendency for declined cognition was observed in MetS participants, but the findings were not statistically significant. It is noteworthy that new data have been published in recent years that may strengthen the conclusions reached until now. For these reasons, it is necessary to revise the existing evidence through a more in-depth analysis using quantitative methods. This analysis should only include studies in which the sample consisted exclusively of adult participants with no severe cognitive decline so that the effects of MetS in cognitive function can be appreciated in the subclinical stages and preventive measures can be proposed with the purpose of developing a better understanding about what is known nowadays and which studies are necessary to conduct in the future. It is for these reasons that the present systematic review and meta-analysis aimed to evaluate the most critical findings associated with the actual research on global cognitive function in adults with MetS but with no previous clinical history using quantitative methods. The importance of carrying out this analysis is to present the latest findings in this area and strengthen the evidence regarding the relationship between MetS and cognitive impairment.

The Population/Intervention/Comparison/Outcome (PICO) question that will serve as a guide to this review is shown in Table 1.

| Table 1. The PICO description |
|--------------------------------|
| **Population:** Adults with no history of cerebrovascular or cardiovascular events, as well as no psychiatric history |
| **Intervention:** MetS |
| **Comparison:** Adults with no MetS |
| **Outcomes:** Deficits in: |
| • Global cognitive status |
| • Memory |
| • Attention |
| • Verbal fluency |
| • Executive functions |

2. Methods

2.1. Search strategy and study selection

In April and May 2020, database searches were performed in PubMed and EBSCO using the following keywords “metabolic syndrome” AND “cognition.” Broad search terms were used to facilitate maximum coverage of the literature. These two words were the only ones used since the syndrome includes several independent components and diseases; however, the interest of the present review was the complete diagnosis and not only individual components. The cognition term includes a global sphere of the neuropsychological profile, rather than mental processes independently. Three researchers independently identified the studies through manual searches. No limits were added during the database search. By reading the abstract, the search was restricted to human studies reported in English. The method used to merge the articles identified in the two databases consisted of the results from the databases including the full names of the articles, their authors, and links to
access them in a single word processor document. Later, using the match search tool included in the word processor document, duplicates were identified and eliminated from the list.

The bibliographies of relevant articles were reviewed. Only papers that met the following criteria were included: (a) the study referred to MetS as an organismic variable and not only its individual components; (b) neuropsychological assessments were made to define the general cognitive function measured by neuropsychological tests; (c) the study population was adults; and (d) studies published from January 2010 until May 2020 were considered. We took into consideration the fact that the first systematic review on this topic was made in 2011 and included studies up to 2009 (Hao et al., 2011).

Only original studies with abstracts and full-texts available were included. Articles were excluded accordingly if they met the following criteria: studies focused only on one component of MetS; neuropsychological assessments of just a single cognitive process, rather than considering the entire cognitive sphere; participants with a clinical psychiatric history such as previous diagnosis of depressive disorder, anxiety, or other mood disorders, as well as personality disorders such as schizophrenia; participants with a clinical history of MND; participants with a history of cerebrovascular or cardiovascular events; and studies involving individuals younger than 19 years old.

The titles and abstracts were selected, and relevant articles were retrieved and evaluated according to the criteria mentioned above. Discrepancies for the inclusion and selection of the articles between investigators were resolved by discussion.

2.2. Data extraction and quality assessment
The three investigators independently extracted data from the included studies using standardized tables. For each study, we recorded the title, the lead author’s last name, the year of publication, the country of origin, the demographic characteristics of the participants (range of age, mean age, and education mean), and the cognitive domains assessed with their respective neuropsychological tests. Additionally, we recorded the criteria that were used to consider (or not) the definition of MetS (see Table 2). The search and review were conducted with adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Urrutia & Bonfill, 2010).

2.3. Diagnostic criteria for MetS
Several variations exist depending on the organization that proposes the diagnostic criteria. The precise criteria used to define and diagnose MetS vary among organizations; however, in general, it is well accepted that the criteria comprise a set of abnormalities that include insulin resistance, elevated triglyceride levels, dyslipidemia, arterial hypertension, and central obesity (Zhang et al., 2019). The most commonly used definition for MetS is that described by the United States National Cholesterol Education Program (NCEP-ATP III), which considers that the presence of three or more of those criteria is required for diagnosis. However, other criteria, such as those proposed by the World Health Organization (WHO), include glucose intolerance, impaired glucose tolerance or diabetes mellitus, and insulin resistance together with two or more of the following components: impaired glucose regulation, insulin resistance, raised arterial pressure, raised plasma triglycerides, central obesity, and microalbuminuria. The WHO states that other components of MetS have been described, e.g., hyperuricemia and coagulation disorders, but they are not necessary for the diagnosis (World Health Organization, 1999). The International Diabetes Federation considers central obesity to be a necessary prerequisite (for men, this is considered a waist circumference greater than 90 cm and in women greater than 80 cm) as well as at least two of the following aspects: having a fasting glycemic score greater than 100 mg/dL or being in treatment for it, triglyceride values greater than 150 mg/dL or receiving drug treatment for this condition, high blood pressure (>130/85) or receiving drug treatment for it, and an HDL cholesterol level lower than 40 mg/dL for men or 50 mg/dL for
## Table 2. General characteristics of the revised articles

| Leader author and year | Country and sample size (n) | Design | Demographics | Definition of MetS | Cognitive domain | Neuropsychological test |
|------------------------|----------------------------|--------|--------------|-------------------|-----------------|------------------------|
| (1) M. M. Y. Lai et al. (2020) | Australia (108) | Cross-Sectional Study | Age: 60+, mean age: 73.4 Female: 13% Mean education years: 13.6 | NCEP-ATP III | Verbal fluency, delayed recall, visual scanning, processing speed, and mental flexibility | MMSE, ADAS-cog, CERAD & TMT |
| (1) Bangen et al., 2019) | USA (5,124) | Prospective cohort study | Age range: 35—54, mean age at baseline 35.9, mean age at first neuropsychological assessment 63.5, Female: 50.4% Education: < High school degree (4.6%), High school degree (28.4%), some college (26.2%), ≥ college degree (40.8%). | NCEP-ATP III | Global cognitive function, processing speed/executive function & memory | WMS, TMT, WAIS, FAS, Category fluency, Boston naming test |
| (1) Alkan et al., 2019) | Brazil (61) | Step-wise regression models | Age range: 50—85, mean age 60.75, Female: 63.9%, education years mean: 6.15 | NCEP-ATP III | Memory | CERAD |
| (1) Gross et al. (2018) | Brazil (200) | Cross-Sectional Study | Age range: 66—78, mean age 72, sex: Female 68.5%, Formal education years: 5 | IDF | Global cognitive function | ACE-R protocol, MMSE |
| (1) González et al. (2018) | USA (16,415) | Cross-Sectional Study | Age range: 45—74, mean age: 57.8, Female: 56.3%, Education less than high school: 43.4%, high school or equivalent: 20.7% and more than high school: 35.9%. | IDF | Global cognitive function, attention, memory, language | SIS, B-SEVLT, WF, the test of Multilingual Aphasia Examination, DSS. |
| (1) Philippou et al. (2018) | Greece (640) | Cross-Sectional results from a greater longitudinal study | Age range: 55–92 Mean age: 72.3 Female: 59.1% Years of education 8.65 ± 4.43 | None | Global cognitive function, language, executive function, and verbal episodic memory | MMSE, Peabody, Boston naming test, TMT, digit symbol, verbal fluency, Wechsler memory scale, Hopkins |

(Continued)
| Leader author and year | Country and sample size (n) | Design | Demographics | Definition of MetS | Cognitive domain | Neuropsychological test |
|------------------------|-----------------------------|--------|--------------|-------------------|-----------------|------------------------|
| (1) Bae et al., 2017   | Japan (5,278)               | Cross-Sectional Study | Age range: 70–79, female: 55.8%, Age mean: men 76.0, women 75.8, Education years: men ≤9 20.1%, 10–12 41.6%, ≥13 38.2%. Women ≤9 30.9%, 10–12 47.0%, ≥13 22.1%. | IDF | Memory, attention, executive function, and processing speed | MMSE, National Center for Geriatrics and Gerontology–Functional Assessment Tool, TMT |
| (1) Overman et al., 2017 | Multiple European countries (1,965) | Longitudinal study | Age range: 40–49, 0% female (100% men), mean age 60.0, age left education in years 21.9. | NCEP-ATP III | Visuo-constructional abilities and memory recall, visual recognition memory, psychomotor speed, and visual scanning. | ROCF, CTRM, DSST |
| (1) Foong et al., 2017 | Malaysia (2,322) | Cross-Sectional Study | Age range: 60–92, mean age 69.1, Female 52%, mean years of education 5.1. | Self-defined | Processing speed, executive function, incidental memory, perceptual organization, visuomotor coordination, and selective attention | DSST |
| (1) Alfaro et al., 2016 | USA, Taiwan, Korea (32) | Cross-sectional post hoc analysis | Age range: 50–85, Mean age: 64.8, Female 56.2%, mean education MetS group 15 (SD 3.1), mean education control group 16 (SD 3). | IDF | Executive Function, verbal learning, and memory function | TMT, VF, HVLT, ROCF, DS & MMSE |
| (1) Chen et al., 2016 | China (3,988) | Cross-Sectional Study | Age range: 50–81, age mean: 66.4, Female 53.1%, years of education: <6 17.3%, 6–12, 17.2%, >12 15.7%. | Criteria by Chinese Medical Association Diabetes Association | Global cognitive function | MoCA |
| Leader author and year | Country and sample size (n) | Design | Demographics | Definition of MetS | Cognitive domain | Neuropsychological test |
|------------------------|----------------------------|--------|--------------|-------------------|-----------------|------------------------|
| (1) Yao et al. (2016)  | China (379)                | A Case-Control Study | Age range: 70–82, age mean 76.1, female 73.6%, education: without formal education 78%, primary school 15%, middle school or higher 5%. | NCEP-ATP III | Global cognition function | C-MMSE |
| (1) Lamar et al. (2015)| USA, UK (119)              | Cross-Sectional Study | Age range: 47–73, age mean: Low risk 62, high risk 60.6, education years: low risk 15.3, high risk 14.1, female 54.6%; low risk 48%, high risk 56% | NCEP-ATP III | Global cognitive function, verbal intelligence, learning, recognition memory, attention/information processing, executive functioning. | MMSE, SCID, HDRS, Wechsler Test of Adult Reading, CVLT-II, WMS-III, Stroop Color and Word, TMT, WAIS-III, Digit-symbol, Delis-Kaplan Executive Function system batter |
| (1) Del Brutto et al., 2015 | Ecuador (212)           | Cross-Sectional Study | Age range: 60–76, mean age: 69.2, female 64%, only elementary school 81%. | IDF | Global cognitive function | MoCA |
| (1) Harrison et al. (2015) | United Kingdom (845) | Longitudinal, population-based cohort study. | Age: 85+, female 67.8%, education years 0–9 66.2%, 10–11 23.8%, ≥12 21% | NCEP-ATP III | Global cognitive function, attention, and episodic memory | MMSE and Cognitive Drug Research battery |
| (1) M. Liu et al. (2015) | China (2,102)            | Cross-Sectional Study | Age range: 60–95, mean age 71.2, female 59.6%, education ≥6 years: male 82.6%, female 64.5% | Harmonizing definition | Global cognitive function | MMSE |
| (1) Levin et al. (2014) | USA (1,290)              | Longitudinal | Age range: 55–73, age mean 64, Female 60.8%, Education <8th grade 40.6%, not HS graduate 13.6%, HS graduate, 15.5%, some college 14.1%, college graduate 14.1% and college 12.0% | Self-defined criteria | Language, executive function, psychomotor and memory | WRAT, WAT, Grooved Pegboard, Color Trails, Odd-Man-Out Color Trails 2, 15-Item Boston Naming, Peabody Picture Vocabulary Test |
| Leader author and year | Country and sample size (n) | Design | Demographics | Definition of MetS | Cognitive domain | Neuropsychological test |
|------------------------|-----------------------------|--------|--------------|-------------------|------------------|------------------------|
| (1) Goh and Hart (2014) | Australia (472)             | Cross-Sectional Study | Age range: 29–72, female 0% (100% men) | NCEP-ATP III | Perceptual capacity and short-term memory | Symbol digit and digit spam subtests from SPES |
| (1) Lai et al. (2014)  | Taiwan (209)                | Cross-Sectional Study | Age range: 56–81, mean age: 68.07, Female 53%, education years mean: 10.58 | NCEP-ATP III | Attention, mental manipulation, orientation, short-term memory, long-term memory, language ability, constructional praxis, category fluencia and abstraction and judgment. | CASI, MMSE |
| (1) Collinson et al. (2014) | Singapur (97) | Cross-Sectional Study | Age range: 58–73, mean age: 65.6, Female 45.3%, Education years mean: 10.42 | IDF | Global cognitive function, memory, executive functions, visuospatial memory and associative learning, visual discrimination, attentional flexibility, spatial planning, spatial working memory. | MMSE, PAL, IED, SOC, SWM, CANTAB |
| (1) C. L. Liu et al. (2013) | Taiwan (276) | Prospective cohort study | Age range: 78–87, mean age: 82.4, Female 0%, (100% men) | NCEP-ATP III & IDF | Global cognitive function | MMSE |
| (1) Shigoeff et al. (2013) | Brazil (49)                 | Cross-Sectional Study | Age range: 68–80, mean age: 73.9, Female 100%, mean years of schooling: 3.0 | American Heart Association and the National Heart, Lung, and Blood Institute | Global cognitive function, alternating attention, executive function and memory. | MMSE, TMT, WAIS-III, RAVLT, WCST, BNT, FAS, CDT, |
| (1) C. L. Liu et al. (2013) | USA (2,975)                | Cross-Sectional Study | Age range: 60–80, mean age: men 70.4, woman 71.1. Female 51.6% | NCEP-ATP III | Global cognitive function and attention. | DSS, WAIS III |
| Leader author and year | Country and sample size (n) | Design | Demographics | Definition of MetS | Cognitive domain | Neuropsychological test |
|------------------------|-----------------------------|--------|--------------|-------------------|------------------|------------------------|
| Luo et al. (2013)      | China (870)                 | Cross-Sectional Study | Age range: 90–108, mean age 93.6, female 67.3%, educational levels: illiteracy 73%, primary school 24%, middle school 2% and high school 1%. | IDF | Global cognitive function | MMSE |
| Viscoaglisi et al. (2012) | Italia (159)               | Cross-Sectional Study | Age range: 65–75, mean age 69.8, females 63.5% | NCEP-ATP III | Global cognitive function | MMSE |
| McEvoy et al. (2012)   | USA (993)                   | Longitudinal        | Age range: 42–89, mean age: 66.9, female 58.8%, education: Some college: Men 73.7%, woman 48.1% | NCEP-ATP III | Global cognitive function, executive function, semantic fluency, long term recall. | MMSE, TMT-B, verbal category fluency, Buschke–Fuld Selective Reminding Test |
| Katsumata, (2011)      | Japan (196)                 | Prospective pilot cohort study | Age range: 80–89, mean age: 85.0, Female 74.3%, Years of education mean: 7.4 | NCEP-ATP III | Global cognitive function, executive function and memory. | JMMSE, VFL, SPMT |
| Vieira et al. (2011)   | USA (3,150)                 | Cross-Sectional Study | Age range: 58–80, mean age 69.0, female 63%, education: high school graduate 46%. | NCEP-ATP III | Global cognitive function | MMSE |
| Raffatini et al. (2011) | Francia (9,294)            | Longitudinal        | Age range: 68–79, age mean 73.4, Female 61%, educational level 23.6. | NCEP-ATP III | Global cognitive function, verbal fluency, and visual working memory | MMSE, IST and BVRT. |
| Akbaraly et al. (2010) | United Kingdom (4,150)     | Longitudinal        | Age range: 35–55, mean age: 61.1, Female 26%, educational level: 8% had no academic qualification and 7% had occupational positions, lowest position. | NCEP-ATP III | Short-term verbal memory, verbal and mathematical reasoning, vocabulary, verbal fluency and global cognitive function | 20-word free recall test, The Alice Heim 4–1 (AH4–1), Mill Hill Vocabulary test, verbal fluency test (phonemic “S”, and semantic with animal category) and MMSE. |
| Leader author and year | Country and sample size (n) | Design | Demographics | Definition of MetS | Cognitive domain | Neuropsychological test |
|------------------------|----------------------------|--------|--------------|-------------------|-----------------|------------------------|
| (1) Cavalieri et al. (2010) | Austria (819) | Prospective study | Age range: 57–73, mean age: 64.9, female 56%, years of education mean: 10 | NCEP-ATP III | Memory and learning abilities, psychomotor skills and executive functions, global cognitive function | Baumler's Lern und Gedachtnistest, Purdue's Pegboard Test, Wisconsin Card Sorting Test, part B of the Trail Making Test, Digit Span Backwards and MMSE |
| (1) Lai et al. (2010) | Taiwan (145) | Cross-Sectional Study | Age range: 56–81, mean age 67.7, female: 53%, years of education mean: 11.38 | modified versions of NCEP-ATP III | Attention, concentration, orientation, short-term memory, long-term memory, language abilities, visual construction, list-generating fluency, abstraction, and judgment | Cognitive Abilities Screening Instrument (CASI) |
| (1) Hassenstab et al. (2010) | USA (143) | Cross-Sectional Study | Age range: 51–69, mean age 60.2, female: 57%, educational level: 1 = less than 12 years, 2 = 12 years, 3 = 12-15 years, 4 = 16 years, 5 = more than 16 years, educational mean level: 3.9 SD 1. | NCEP-ATP III | Attention/working memory, executive functioning, psychomotor speed and declarative memory. | Shipley Institute of Living Scale, subtests from Wechsler Memory Scale-Revised, subtests from the Wechsler Adult Intelligence Scale-Revised, Stroop interference test, phonemic fluency and category fluency tests and the California Verbal Learning Test. |
| (1) Schuur et al. (2010) | Netherlands (1,898) | family-based cohort study | Age range: 18–86, mean age: 48.4, female: 57%, educational levels: Low: 31%, low intermediate: 40%, high-intermediate: 23% and high 6% | NCEP-ATP III | General cognitive ability, memory function, executive function and visuo-spatial ability | Dutch Adult Reading Test (DART), auditory verbal learning test, Trail Making Test parts A and B (TMT), the Stroop Color and Word Test cards I, II and III, and verbal fluency tests, and WAIS-III block-design subtest. |

(Continued)
| Leader author and year | Country and sample size (n) | Design | Demographics | Definition of MetS | Cognitive domain | Neuropsychological test |
|------------------------|----------------------------|--------|--------------|-------------------|-----------------|------------------------|
| (1) Lee et al. (2010)  | South Korea (2,944)        | Longitudinal | Age range: 60–80, mean age: 72.1, female: 70%, educational mean: 4.8 SD 4.5. | Modified NCEP-ATP III standard | Global cognitive function | K-MMSE |
| (1) Tournay et al. (2010) | Multiple European countries (3,152) | Cross-sectional | Age range: 40–79, mean age: 59.3, female: 0% (100% men), educational mean: 20.7 | NCEP-ATP III | Visuo-constructual ability, visual memory, executive function, attention and processing speed | Rey-Osterrieth Complex Figure, Camden Topographical Recognition Memory (CTRM) and Digit Symbol Substitution Test (DSST) |
Figure 1. Flow chart of the articles search.

- Total studies identified through database searching (n=637)
- Studies after duplicates removed (n=39)
- Studies screened (n=598)
  - 384 not consider all components of MetS
  - 14 had animal models
  - 45 did not make neuropsychological evaluations
  - 57 participants already had dementia, other psychiatric or neurological history
  - 4 were in a minor population
  - 5 interventions were made (pharmacological, herbal, or other)
  - 28 for being bibliographic or systematic reviews and meta-analyzes
  - 7 were not available for access
  - 18 were published before 2010
- Full-text articles assessed for eligibility (n=598)
- Studies included that pass the inclusion criteria (n=36)
- Studies included in the meta-analysis (n=12)
  - For global state cognition (n=12)
women. Other criteria less frequently found in publications are those from the American Heart Association and the Harmonizing the Metabolic syndrome project (Pacheco-Armenta MC, 2017).

2.4. Neuropsychological assessment
The studies focused on measuring cognitive domains such as memory, attention, executive functions, language, and general cognitive function in a broad and general way. This last factor was measured through brief instruments that identified whether participants had a significant cognitive impairment and the degree of severity; however, a wide variety of instruments were used to measure the state of these mental processes. For this reason, in this review, we chose those used with the highest frequency to make comparisons. Tables considering these instruments corresponding to their quantitative descriptions were made and were prepared so that they could be analyzed in a more in-depth way.

2.5. Meta-analysis
The information extraction strategy was based on reviews by three independent researchers who extracted the quantitative data. The meta-analysis was conducted using Review Manager 5.4 software from the Cochrane Collaboration (Higgins et al., 2020). This software was used to analyze the data according to the random effect model, and for the generation of the forest plot, we opted to compare crude means and standardized them according to each case. Data are presented as mean scores and standard deviations for cognitive scores and 95% confidence intervals (95% CI). Studies that did not report means and standard deviations or compare participants with MetS against participants without MetS were not included in the meta-analysis. Forest plots were generated to provide graphical presentations of the individual and pooled effect size estimates. Statistical heterogeneity across studies was assessed using the Tau², Chi², and I². Finally, to evaluate the risk of publication bias, a Funnel Plot was generated using the same software.

3. Results
In the initial search, we identified 637 relevant articles. From these, we removed 39 duplicated documents, and 598 studies were screened. Finally, 562 were excluded (Figure 1). Of the total that were eliminated, some did not consider all of the components of MetS (n = 384), some used animal models (n = 14), some did not do neuropsychological evaluations (n = 45), and some included participants who already had a psychiatric or neurological history or who had been diagnosed with MND (n = 57). Additionally, some had samples that included children or teenagers (n = 4), some included interventions (pharmacological or herbalist) (n = 5), and some articles were bibliographic or systematic reviews and meta-analyses (n = 28). Additionally, we could not access some documents (n = 7). Ultimately, 36 studies comprising 73,071 participants were included in the present systematic review and meta-analysis.

3.1. Characteristics of the included studies
The 36 studies were published from different continents (Table 2), especially America and Asia; some were from Europe and a couple from Oceania. The number of participants ranged from 32 to 16,415. Different methods were used to define the MetS criteria. The Mini-Mental State Examination (MMSE) was the most commonly used scale to assess general cognitive decline (n = 22), but other tests were used with a lower frequency, like the Montreal Cognitive Assessment (MoCa) (n = 2), for the same purpose. Verbal fluency tests were also used to examine executive functions through language skills (n = 12). The Trail Making Test part B (TMT-B) was used to evaluate executive function and information processing speed (n = 9), and digit symbol subtests (n = 7) were used to evaluate visual attention.
Table 3. Principal results of the twenty-four studies that used MMSE or MoCA for assessment of global cognition

| Leader Author (Year) | Outcome | Conclusion |
|----------------------|---------|------------|
| Akbaraly et al. (2010) | Not reported MMSE mean, instead reported mean differences T scores | No significant differences in cognitive function were observed between participants with nonpersistent metabolic syndrome (one of the three screenings) and those who never had metabolic syndrome during the follow-up. |
| Alfaro et al. (2016) | MMSE mean score in MetS group = 28.8, DS (±1.3) MMSE mean score in control group = 28.8, DS (±1.6) | There was no significant difference in the participants’ performance with or without the metabolic syndrome and what would label them as “cognitive intact.” |
| Bae et al. (2017) | Participants with nonamnestic mild cognitive impairment showed higher odds ratios (OR) of MetS (men: 2.45, 95% confidence intervals (CI): 1.13–5.32; women: OR: 1.94, 95% CI: 1.12–3.39) compared with participants with normal cognition. Not reported MMSE mean | MetS were associated only with no amnestic mild cognitive impairment regardless of sex, suggesting etiologic differences in mild cognitive impairment subtypes. Also found sex differences in the relationship between no amnestic mild cognitive impairment risk and MetS and its components. |
| Cavalieri et al. (2010) | MMSE mean in MetS group = 27.4, DS (±1.5) MMSE mean in control group = 27.5, DS (±1.5) | The statistical analysis showed no significant difference between the groups means. |
| Chen et al. (2016) | MoCA mean in MetS group = 21.0, DS (5.4±) MoCA mean in control group = 21.3, DS (5.3±) | MetS were not associated with cognitive performance. However, suggest that dyslipidemia might be reversely associated with cognitive function. |
| Collinson et al. (2014) | MMSE mean in MetS group = 27.43, DS (±2.24) MMSE mean in control group = 27.74, DS (±1.85) | Executive and memory impairment is present in Asian patients with midlife MetS who may be particularly vulnerable to the detrimental impact of MetS in midlife. |
| Del Bruto | MoCA mean in MetS group = 18.2, DS (4.6±) MoCA mean in control group = 19.0, DS (6.7±) | MetS was not associated with MoCA scores, but hypertriglyceridemia was independently associated with the MoCA score. |
| Gross et al. (2018) | MMSE mean in MetS group = 23.0, DS (±4.0) Without control group | The conducted study revealed that the dependence between MetS and Cognitive Variables (CI and its direct determinants) exists and depends on both Body Mass Index (BMI) and age. |
| Harrison et al. (2015) | MMSE Mean score of participants with MetS in baseline = 28.0 DS (±4.0) MMSE Mean score of participants with NO-MetS in baseline = 28.0 DS (±4.0) | The association between MetS and cognitive decline, which has been described in younger populations (<75), was not apparent in this population of individuals aged 85 and older at baseline. |
| Katsumata (2011) | Total MMSE Score = 23.9 DS (± 3.8) MMSE mean score in MetS group = 24.1 DS (±3.6) MMSE mean score in Non MetS group = 23.8 (±3.2) | The participants generally showed fewer errors in JMMSE at the second follow-up. However, the interaction of the time (first and second follow-up) and metabolic syndrome or each component of metabolic syndrome was all insignificant, suggesting that there was no difference in changes in the number of errors of JMMSE between the two groups. |

(Continued)
### Table 3. (Continued)

| Leader Author (Year) | Outcome                                                                 | Conclusion                                                                                       |
|----------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Lai et al. (2014)    | MMSE mean score of participants by the presence of the metabolic syndrome | There were no differences in cognitive performance, ApoE epsilon4 (ε4) carrier status, or CYP46 genotypes between participants and those without metabolic syndrome. |
|                      | MMSE mean score in MetS group = 25.97 DS(±2.47)                           |                                                                                                  |
|                      | MMSE mean score in Non MetS group = 26.26 DS(±2.37)                        |                                                                                                  |
| M. M. Y. Lai et al. (2020) | In their, MetS Model reported the β for clinical criterion was 0.09, with a SE 0.10, z-score of risk burden β N = 0.07 and SE 0.11, β for the number of MetS factors 0.13 and SE 0.10. Not reported MMSE mean. | In the multivariate analyses MetS clinical status was not significantly associated with performance on cognitive tests. |
| Lamar et al. (2015)  | MMSE Mean score of participants with MetS components = 28.8 DS(±1.3)      | MetS compromised mood, cognition, and hippocampal structure with incremental risk applying to some but not all of these outcomes. |
| Liu and Lippa (2013) | Not reported MMSE mean, just declare that decreased the score of Mini-Mental Status examination ≥ 3. | MetS are associated with worse cognitive function among younger elderly. Managing MetS and its components may contribute to control cognitive decline and reduce related disease and social burden. |
| M. Liu et al. (2015) | The β (95% CI) of MetS was −0.68 (−0.99, 0.37). For the prevalence of mild cognitive impairment, as the dichotomy dependent variable, the odds ratio (OR) of MetS is 1.52 compared to the control group (or baseline) with a 95% confidence interval (CI) of 1.16 to 1.95. Not reported MMSE mean. | Age and central obesity were significant risk factors of cognitive decline, but late-life MetS were defined and had a protective effect on cognitive function. |
| Luo et al. (2013)    | The general MMSE scores reported: Cognitive impairment = 11.6, DS (±2.4)   | MetS may be associated with better cognitive function among the oldest. Among male nonagenarians and centenarians, high triglyceride levels and systolic blood pressure, which are parts of MetS, are also associated with better cognitive function. |
|                      | Noncognitive impairment = 21.1, DS (±2.6)                                |                                                                                                |
|                      | And separated by sex men = Cognitive impairment = 12.0, DS (±2.4)        |                                                                                                |
|                      | Noncognitive impairment = 21.8, DS (±2.7)                                |                                                                                                |
|                      | women = Cognitive impairment = 11.5, DS (±2.4)                           |                                                                                                |
|                      | Noncognitive impairment = 20.4, DS (±2.3)                                |                                                                                                |
| McEvoy et al. (2012) | MMSE mean score participants no MetS = 27.5 (0.1)                        | There was no significant difference in the scores between men participants with and with metabolic syndrome (p = .51) and either on woman participants with and wit metabolic syndrome (p = .43) |
|                      | MMSE mean score participants MetS = 27.5 (0.2)                          |                                                                                                |
| Philippou et al. (2018) | MMSE mean score 26.81, SD(±2.10).                                       | It was referred that an MMSE cutoff of 22 was chosen to exclude participants with cognitive impairment, lower than 26, which is the cutoff limit for that test. It was not reported more conclusions other than that. |
### Leader Author (Year) | Outcome | Conclusion
--- | --- | ---
Raffaitin et al. (2011) | MMSE mean score in MetS group = 27.1, DS(±2.0) MMSE mean in Non MetS group = 27.5, DS (±1.8) | MetS as a whole and several of its components had a negative impact on global cognitive decline and specific cognitive functions in older persons.
Shigaeff et al. (2013) | They have not reported MMSE mean. | There was no statistical difference in general between groups (MetS vs. control), but it was not reported in the MMSE test to check out the p values.
Soo Lee et al., 2010 | K-MMSE mean score in MetS group = 21.6, DS(±4.6) K-MMSE mean in Non MetS group = 22.4, DS (±4.7) | MetS was not associated with cognitive impairment (K-MMSE score <18) after adjusting for age, sex, and educational level.
Vieira et al. (2011) | MMSE mean score in MetS group = 27 (24–29) MMSE mean in Non MetS group = 27 (25–29) | MetS were associated with lower cognition in a multi-ethnic population. Further studies of the effect of MetS on cognition are warranted and should account for demographic differences.
Viscogliosi et al. (2012) | Total MMSE Score = 26.8 DS(± 1.5) MMSE mean score in MetS group = 26.1 DS (± 1.1) MMSE mean score in Non MetS group = 27.4 DS(± 1.5) | We found that subjects with metabolic syndrome have lower MMSE scores than those without symptomatic cognitive impairment and that the number of metabolic abnormalities is independently associated with lower MMSE scores.
Yao et al. (2016) | C-MMSE mean score in Mild cognitive impairment with MetS = 17 (16-19) C-MMSE Control group = 23(20-25) | MetS and its components, particularly abdominal obesity and hypertension, were found to be significantly associated with the risk of mild cognitive impairment.

#### 3.2. Characteristics of the results regarding MetS and cognition

Of the 36 studies selected, 17 found a clear association with adverse changes in cognition and the presence of the syndrome (M. Liu et al., 2015; Liu & Lippa, 2013; Raffaitin et al., 2011; Vieira et al., 2011). The combined risk of multiple factors in MetS was related to a lower overall performance on cognitive screeners and executive function (M. M. Y. Lai et al., 2020). On the other hand, adverse neurocognitive conditions were mainly identified in the middle-aged population (Akbaraly et al., 2010; González et al., 2018). According to the findings of Alfaro et al. (2016), one of the most evident losses in patients with MetS was in the verbal memory cognitive domain, in addition to verbal fluency.

Likewise, Lamar et al. (2015) found an association with a previously described relationship of the condition with the hippocampal structure. Some more specific findings were also reported regarding the syndrome components; Yao et al. (2016) reported that particularly abdominal obesity and arterial hypertension were more significantly associated with the risk of mild cognitive impairment. Viscogliosi et al. (2012) discovered that cognitive impairment was even assessable through the use of brief instruments, such as the MMSE, and that performance in these tests was lower in those even without symptomatic cognitive impairment. Coincidentally, Levin et al. (2014) noted that blood pressure was significantly correlated with all cognitive domains, except memory. In addition to identifying this deterioration in patients with MetS, some authors were also able to identify neuroprotective factors, such as education (Collinson et al., 2014).
Some of these studies yielded inconclusive results; for example, Bangen et al. (2019), despite finding a lower overall performance in cognitive screening tests in individuals of both middle and late age, did not find a significant change in the “cognitive trajectories.” Bae et al. (2017) found that MetS was associated with mild cognitive impairment but only the nonamnestic type. There were also particular findings around the MetS indicators. Overman et al. (2017) found that high blood glucose was significantly associated with visuo-constructional skills and processing speed, while Chen et al. (2016) found that dyslipidemia was inversely associated with cognitive function. Del Brutto et al. (2015) reported that only hypertriglyceridemia was associated with worse cognitive performance. Some findings suggest that the negative effect on cognition is secondary. According to Foong et al. (2017) MetS increases an individual’s chance of suffering from other chronic conditions that can reduce cognition.

Other studies even considered the genotypes involved in cognitive impairment. Lai et al. (2014) stated that MetS might play a role in subtle cognitive dysfunction in ε4 polymorphism carriers. Moreover, better performance in episodic memory tasks but not executive functions was found. Liu and Lippa (2013) noted that central obesity is the most significant risk factor for cognitive decline. In contrast to the previously mentioned study, McEvoy et al. (2012) stated that MetS is associated with better executive functions. With a decrease in long-term memory, and mainly when diabetes was present, MetS was associated with an accelerated decrease in executive functioning, but only in women. Katsumata et al. (2012) noted that having a high level of glycosylated hemoglobin was associated with decreased memory function. It is possible to see that there is considerable variation in the general findings since some authors identified unfavorable changes, while others found them only under specific conditions. Finally, some studies did not report changes and even showed cognitive advantages in those with the syndrome (Lai et al., 2010; Tournoy et al., 2010).

3.3. Global cognitive function

As previously mentioned, the most widely used global cognitive assessment instrument (by 22 studies) was MMSE. Some of the authors reported the statistical means (except 6). Most authors used a 0–30 scale to rate the components of the instrument, and the corresponding standard deviations were given. It is noteworthy that, despite having some population adaptations, such as for the Chinese and Japanese versions of the MMSE, all of them used the same maximum value of 30. In 10 of the studies, conclusions suggested a more significant cognitive impairment associated with MetS, while the other nine studies had insignificant or suggestive findings, suggesting an unclear relationship between both variables. However, MMSE is not the only instrument available to assess general cognitive status. The MoCA test is also available. Like the MMSE, it assesses the main cognitive spheres of the global mental state. In the same way, it is scored on a scale of 0–30. Two studies (Chen et al., 2016; Gross et al., 2018) that assessed their participants with this instrument were included (see details below in Table 3).

3.4. Principal results of the twenty-four studies that used MMSE or MoCA for the assessment of general cognition

Of the twenty-four studies reviewed that used MMSE or MoCA to measure general cognitive status, 12 reached similar conclusions. There were discrete differences in performance between participants with MetS and controls. Given the nature of these tests, which assesses the general cognitive function, some reported generic changes in cognition (C. L. Liu et al., 2013; Lamar et al., 2015; Liu & Lippa, 2013; Raffaitin et al., 2011; Vieira et al., 2011; Viscogliosi et al., 2012).

On the other hand, other authors suggested that MetS is associated with cognitive impairment but only that of the nonamnestic type (Bae et al., 2017) or with general impairment in memory and executive functioning (Collinson et al., 2014). Similar findings related to mood, cognition, and hippocampal structure were described by Lamar et al. (2015). Particularly, in younger older adults (C. L. Liu
Table 4. Principal results of the 12 studies that used verbal fluency for assessment

| Leader Author (Year) | Outcome | Conclusion |
|----------------------|---------|------------|
| Akbaraly et al. (2010) | Not reported verbal fluency mean, instead reported mean differences T scores | Participants with persistent metabolic syndrome had lower scores for semantic fluency compared with participants who never had metabolic syndrome. |
| Alfaro et al. (2016) | The mean phonological verbal fluency in the MetS group was 46.3 ± 10.4; the mean semantic verbal fluency (animals) was 31.6 ± 12.3; The mean phonological verbal fluency on the non-MetS group was 52.3 ± 7.9; The mean semantic verbal fluency (animals) was 48.3 ± 11.3 P value <0.0001 | Hyperglycemia was the only MetS component associated with worse cognitive performance in domains of verbal fluency. |
| González et al. (2018) | MetS group 17.6 ± 8.6 Control group 18.3 ± 16.9 | MetS status was associated with lower performance on the verbal fluency test (b = 20.15 [SE 0.028]). |
| Hassenstab et al. (2010) | Not reported the verbal fluency means, instead reported F (3.14) and p (0.06) for category fluency, and F (4.57) and p (0.03) for phonemic fluency in the multivariate analysis of covariance and univariate contrasts | MetS was associated with lower performance on phonemic fluency (p = 0.034) and category fluency tests (p = 0.079). |
| M. M. Y. Lai et al. (2020) | Not reported verbal fluency means. MetS Model reported the β for clinical criteria was 0.02, with a SE 0.10, z-score of risk burden β 0.08 and SE 0.11, β for the number of MetS factors 0.02 and SE 0.10. | There was not found a significant difference on the verbal fluency tests. |
| Levin et al. (2014) | The second assessment found the verbal fluency means 28 ± 12.5 | None of the cardiometabolic factors were predictors of the executive function factor outcomes, which includes verbal fluency. |
| Philippou et al. (2018) | A modified version of the Controlled Oral Word Association Test COWAT was used to assess verbal fluency. In the semantic category (animals), the mean value was 10.45 ± 3.37. The phonological verbal fluency (F) mean was 7.87 ± 3.35 | The MetS factors variable's standardized coefficients on the cognitive factors were negative, as anticipated, but small in magnitude; the effects were significant for executive functions and language βs = −0.27 and −0.19. |
| Katsumata (2011) | MetS group 5.7 ± 2.1 Control group 6.7 ± 2.6 P = 0.035 | The metabolic syndrome and its components were not associated with baseline and changes in the verbal fluency tests (VFL letters), the latter indicated by nonsignificant interaction terms with first and second follow up. |
| McEvoy et al. (2012) | Women MetS 17.3 ± 0.6 No MetS 18.2 ± 0.2 Men MetS 20.2 ± 0.6 No MetS 19.8 ± 0.2 | There was no significant difference in the scores obtained between men participants with and without metabolic syndrome (p = .54) and either on woman participants with and without the syndrome (p = .24). |
| Schuur et al. (2010) | Women MetS 60.0 ± 17.1 No MetS 63.7 ± 18.0 Men MetS 53.5 ± 18.7 No MetS 63.0 ± 17.9 | An increasing number of MetS components was associated to lower verbal fluency and z-executive scores (P = 0.04 and 0.02) in women. |

(Continued)
et al., 2013; Liu & Lippa, 2013), central obesity was identified as a significant risk factor for cognitive decline, but it was also shown to have a neuroprotective effect in late old age. Finally, some authors found no differences in the performance of those with the syndrome compared with controls (Alfaro et al., 2016; Harrison et al., 2015; Katsumata et al., 2012; Lai et al., 2014; M. M. Y. Lai et al., 2020; McEvoy et al., 2012; Shigaeff et al., 2013) or even stated that MetS could be associated with better cognitive function performance, especially in the elderly (Luo et al., 2013).

### 3.5. Cognitive domain: executive function

With respect to TMT, the current analysis is made from those who specifically mentioned having used part B, since this one measures executive functioning while part A is limited to processing speed tasks. Researchers who evaluated executive function and/or information processing speed through the TMT-B test had mixed results; of the eight studies reviewed, two did not find significant results regarding MetS having a negative influence on these mental functions (McEvoy et al., 2012 & Shigaeff et al., 2013). On the other hand, three studies reported a statistically significant lower performance in those with the syndrome (Bangen et al., 2019; Cavalieri et al., 2010; Philippou et al., 2018). Moreover, two more studies had inconclusive findings because they did not find a difference and also participants were not separated into those with and without the syndrome but rather by their levels of physical activity (Coll-Padrós et al., 2019; M. M. Y. Lai et al., 2020).

Other studies evaluated executive function through the verbal fluency task. It was found that in seven of the 11 studies (Table 4), the MetS groups showed a negative association between cardiometabolic risk factors and neuropsychological performance in this cognitive domain; however, a significant difference was not found (Katsumata et al., 2012; Levin et al., 2014; M. M. Y. Lai et al., 2020; McEvoy et al., 2012; Schuur et al., 2010; Shigaeff et al., 2013). Hassenstab et al. (2010) found that MetS was associated with a lower level of performance, specifically for the executive function phonetic fluency. Alfaro et al. (2016) found that hyperglycemia was the only component of MetS that was associated with lower cognitive performance in the domain of verbal fluency (Table 4), and González et al. pointed out that having MetS led to lower performance in verbal fluency (González et al., 2018).

### 3.6. Cognitive domain: attention

Visual attention skills were assessed through the digit symbol test (the details of the obtained scores and the general results are described in (Table 5), in which data from seven studies were reported, five of which referred to the possible negative effects of MetS on this essential ability (Coll-Padrós et al., 2019; Foong et al., 2017; González et al., 2018; Philippou et al., 2018), especially
in relation to elevated glucose levels (Overman et al., 2017). However, others concluded that causal interpretations could not be applied to the relationship of MetS with attentional impairment (C. L. Liu et al., 2013; Tournay et al., 2010).

### 3.7. Cognitive domain: memory

Of the articles reviewed, multiple studies measured this mental process, including Akbaraly et al. (2010); Alfaro et al. (2016); Alkan et al. (2019); Bae et al. (2017); Bangen et al. (2019); Cavalieri et al. (2010); Collinson et al. (2014); Foong et al. (2017); Goh and Hart (2014); González et al. (2018); Harrison et al. (2015); Hassenstab et al. (2010); Lai et al. (2010); Lai et al. (2014); Lamar et al.
Levin et al. (2014); Overman et al. (2017); Philippou et al. (2018); Schuur et al. (2010); Shigaeff et al. (2013); and Tournoy et al. (2010). However, despite this recurrence in the assessment of that process, the studies differed in terms of the instruments used. Some used extensive scales with multiple subtests, and others used a single word list. Therefore, it was impossible to analyze all studies using the same quantitative comparison parameters. The expected averages differed markedly, as did the tests used. On the other hand, some studies reported significant differences; for example, González-Castañeda et al. (2018) found that having a higher number of MetS components was consistently associated with more pronounced impairment in memory. Alfaro et al. (2016) found that patients with the syndrome had lower memory performance, as did Lamar et al. (2015) who found learning and memory alterations related to compromise in the hippocampal structures of the brain, and Collinson et al. (2014) described this condition in middle-aged individuals and found that memory performance was worse in MetS participants. McEvoy et al. (2012) reported that long-term memory was significantly affected in women with MetS. Raffaïtin et al. (2011) found an association of the syndrome with an increased risk of cognitive impairment, including a decline in memory. Other studies had inconclusive results about the association between the MetS and memory function. Bangen et al. (2019) found that abdominal obesity was associated with lower cognitive performance in terms of memory but not the syndrome’s fundamental components. Philippou et al. (2018) reported a significant negative coefficient for the body mass index for memory, but this is just one component of the syndrome. Katsumata et al. (2012) described an association between memory impairment and glycated hemoglobin but not with all MetS components. Moreover, the study by Alkan et al. (2019), in general, did not support the idea that MetS is reliably associated with memory deficits. Bae et al. (2017) found no significant difference in memory performance between those with and without the syndrome. Overman et al. (2017) found no evidence of a relationship between MetS and memory impairment. Harrison et al. (2015) did not find a significant relationship between MetS and memory, these findings being consistent with those of Goh and Hart (2014), Lai et al. (2014), and Levin et al. (2014). Despite finding a relationship between high blood pressure and other cognitive domains, particularly concerning memory, they did not find significant data. Furthermore, Lai et al. (2014) did not report a significant relationship between memory and MetS, and Shigaeff et al. (2013) found no differences in memory associated with MetS.

4. Meta-analysis
Due to the presentations of data, not all studies were candidates to be included in the meta-analysis of global cognitive function only in 12 were presented mean and standard deviations and comparisons between an MetS group and a control group shown.

The pooled results of the 12 studies that evaluated global cognitive function revealed that the MetS group had a significantly lower score for this variable in comparison with the control group (25.26 and 25.6, respectively, 95% CI [-0.60 to -0.12] (p = 0.004). However, the level of heterogeneity was high
Figure 3. Forest Plot from studies that measured global cognition by applying of the MMSE and MoCA in participants with a mean age inferior to 70 years old.

Figure 4. Forest Plot from studies that measured global cognition by applying of the MMSE and MoCA in participants with a mean age superior to 70 years old.

(I² = 89%; p < 0.00001) (see Figure 2). The studies were divided into groups based on the participants’ mean age (mean age inferior to 70 years old and superior to 70 years old) to reduce heterogeneity.

Studies involving participants younger than 70 years old (see Figure 3) were found to be significantly responsible for heterogeneity observed (I² = 84%; p < 0.00001). Still, significant differences between MetS and control groups were found in this age group (25.28 and 25.67, respectively, 95% CI [−0.73 to −0.04] (p = 0.03).

When only studies involving participants with a mean age superior to 70 years old were included in the analysis (see Figure 4), the level of heterogeneity decreased (I² = 63%; p < 0.04). The MetS group had a significantly lower score for this variable in comparison with the control group (25.2 and 25.4, respectively, 95% CI [−0.54 to −0.31] (p = 0.00001).

Additionally, to evaluate the risk of publication bias, a Funnel Plot was constructed using the Standardized Mean Difference (SMD) and 1/SE values obtained from studies that assessed global cognition (see Figure 5). It is noteworthy that a mild degree of asymmetry in the global cognitive domain was identified.

5. Discussion

5.1. Summary of the main results
One of the difficulties of doing this kind of analysis is that some studies report their data in a way that is not comparable, even when the same instruments are used to measure cognitive domains. One example of this is memory and this was the most commonly evaluated cognitive process. However, the wide variety of modalities involved in memory makes its assessment widely varied and hard to compare. In addition to this, some studies used instruments that were not common or were used with adaptations. It should be noted that each study had an individualized selection of instruments, which was chosen based on different aspects, such as the convenience in accessing the tests to be acquired, the materials already available in the corresponding institutions, and the feasibility and duration of application of the instruments, among other unknown factors. That raises questions about whether the variability in the results among studies is associated with the
The varied nature of instruments used to assess memory. Each type of study could measure different types of memory based on the instrument selected.

Some assessed short-term verbal memory, while others, by asking for information in a delayed way, measured a different phase of the memory process, for example, delayed recall involving the same type of verbal memory. The studies on the neuropsychology of the MetS carried out until now have shown ambivalent and inconclusive results regarding the specific cognitive processes affected as a result of metabolic conditions and those seem to resist the negative metabolic effects better. Regarding general cognitive function, which is evaluated by the MMSE or MoCA, it briefly and superficially seems to be affected by the syndrome even though there have been some inconclusive results with a tendency to indicate a negative impact of MetS on the general cognitive status. It is pertinent to emphasize that these tests assess cognitive status in a broad and shallow way since assessments with these instruments last for no more than 10 minutes. These screening tests are usually used to identify whether or not a participant is a candidate for a complete and in-depth assessment, so their use has several limitations, such as low sensitivity to mild cognitive impairment because only severe impairment would prevent the patient from answering most of the items in a correct way (Spencer et al., 2013). For this reason, when every study was evaluated individually, general cognitive impairment did not seem to be significantly affected; however, the joint analysis of means through a meta-analysis showed a significant effect of MetS on general cognitive function. However, it is noteworthy that there was a high level of heterogeneity in the meta-analysis. The explanation for this could be the variation in the different populations included in the studies with regard to educational level, socio-economic and cultural conditions, as well as genetic polymorphisms that affect brain neuroplasticity, which benefit from multiple factors throughout life, such as age, among others (Miskolczi et al., 2019; Phillips, 2017; Stewart & Cramer, 2017). Regarding this last topic, when a meta-analysis that involved subdividing by age mean groups was done, it was observed that the same low level of cognitive performance was present in both groups. This could imply that brain plasticity to adapt to the negative metabolic and vascular changes associated with MetS is lower, even from an earlier stage of life. After concentrating the data from multiple individual studies into a single meta-
analytical study, it became apparent that the youngest and the oldest individuals were close in terms of the level of deterioration in cognitive performance, and the potential neuroprotective factor of age was less clear.

Evaluations of superior frontal brain function, made through assessing the executive function of verbal fluency, showed inconclusive results among the different studies, with some showing a statistically significant decrease (Alfaro et al., 2016; González et al., 2018 & Hassenstab et al., 2010) and others finding no difference (Katsumata et al., 2012; Levin et al., 2014; M. M. Y. Lai et al., 2020; McEvoy et al., 2012; Schuur et al., 2010; Shigaeff et al., 2013). A possible cause of the inconclusive results is that this superior function was assessed with tests of various modalities; some studies measured phonological verbal fluency and others measured semantic verbal fluency. Despite some researchers measuring phonological verbal fluency in the same way, the instructions could have involved different letters, but this was not specified in some of the studies. For this reason, it was difficult to determine the general findings regarding the maintenance or deterioration of this function. The performance in visual attentional skills and memory, unlike other cognitive processes, seems to have a more definite negative effect and more consistency in the findings. Since most of the studies reported a coincident deficit in participants with MetS, it is noteworthy that attention and memory are mainly regulated by cerebral prefrontal mechanisms. Some of the most basic processes involved in these cognitive functions (like visual analysis) are carried out in the posterior cerebral cortex structures, and these processes could be more susceptible to metabolic deterioration, especially under hyperlipidemic conditions (Friedman et al., 2014). Lastly, in terms of visual attention skills, findings on whether MetS may or may not negatively impact these cognitive functions have differed with regard to more basic sensory processes, such as sight.

5.2. Clinical Implications
There are multiple current implications of the present findings for clinical neuropsychological practice and mental health care in general, given that current therapeutic options are usually focused on when the patient already has the first neurological indicators of deterioration, such as decreased memory. However, it is crucial to keep in mind that preventive, therapeutic options focus on reducing the future presentation of such damage. However, these therapeutic options aim to modify lifestyle habits before the presentation of neurological damage and psychoeducational processes to inform the community about the importance of making these changes.

It is important to emphasize that the current relationship of MetS with health is not limited to the future presentation of higher cardiovascular risk but goes beyond the possible presence of an MND due to cerebrovascular disease or Alzheimer’s disease. As patients get older, therapeutic options become increasingly limited, as compensatory brain processes, such as brain neuroplasticity, decrease, and the cognitive reserve decreases. The cognitive reserve that individuals with MetS possess at various stages of life should be considered during neuropsychological exploration of general cognitive functioning and in terms of neural compensation and the brain reserve, as some cognitive functions can change both due to the passage of time as well as due to being fundamentally affected by the presence of the syndrome (Strong et al., 2020). Brain compensation can be compromised by nutritional aspects as well as by gradual deficits that force general neurological restructuring and, with it, a highly variable cognitive expression. A significant challenge for therapists is assessing the options of improvement for a patient and directing the treatment regarding the compensatory options for the family.

5.3. Practical Implications
MetS is significantly related to lifestyle aspects, such as low-quality diet, sedentarism, and smoking habits. That is why it is relatively feasible to treat MetS by making life habit changes that prevent its consequences. Due to this, studying how metabolic-related diseases are associated with the risk of
developing cognitive impairment has significant relevance. Public health policies that are focused on mental illness may consider preventing and controlling metabolic-related diseases to hinder the subsequent development of cognitive ailments. Until now, no studies have evaluated how diet and nutritional status, as well as aspects of eating behavior and lifestyle, influence the effects of MetS on cognitive impairment; only one protocol proposed the evaluation of diet through a food frequency questionnaire, has been proposed (Mummee et al., 2019).

Another relevant piece of practical implication is that the assessment of an individual's functionality in instrumental activities of daily life should be included since it is considered that minor defects from youth can gradually diminish a patient’s cognitive condition, leading to potentially less appropriate decisions about their health care in later adult years. Therefore, future studies should evaluate the effects of diet, level of independence, and lifestyle in patients with MetS and their associations with cognitive function.

5.4. Agreements and disagreements with previous results
Previous systematic reviews on this issue have some similarities and several differences with the present one. One of the first systematic reviews was conducted by Hao et al. (2011). They found a relationship between MetS and cognitive impairment in studies that evaluated MND due to cerebrovascular disease, but the association was not found in participants with Alzheimer's Disease. On the other hand, in their review, Yates et al. (2012) included samples of children, teenagers, and adults, and they also evaluated structural damage to the brain. With respect to Alcorn et. al. (2017), one of the main conclusions was that participants with MetS only performed poorly in executive functioning tasks that were not adaptations of the verbal fluency task because in these verbal fluency adaptations, the results were less consistent. A central difference to the present review is that different instruments were considered to measure the diverse executive functions, as the TMT-B test assesses, in addition to the speed of information processing, cognitive flexibility to alternate focus attention, as well as working memory. On the other hand, Alcorn et al. (2017) used the verbal fluency instead and found that this process seems to be maintained more than the other executive functions that are less dependent on language. It is important to note that this process usually has associated neuroprotective factors, such as a high level of education (Goñi Sarriés et al., 2015).

More recently, Assuncao et al. (2018) carried out a systematic review to evaluate cognitive impairment in MetS; one of the differences with the present work is that they only included studies that assessed the elderly population with MND; it is probably for this reason that they concluded that the role of MetS in cognitive decline and the onset of MND showed heterogeneous results. Finally, Siervo et al. (2014) carried out a meta-analysis that found that MetS is associated with a cognitive decline in an age-dependent manner. One of the most important differences to the present study, which is a major weakness, is that they mixed the different cognitive domains evaluated in the publications, including general cognitive assessment with MMSE, executive functions, and memory, in one analysis. They also only analyzed MMSE data, and unlike our review, they found a nonsignificant association of MetS with cognitive decline; the new evidence that has been published in recent years allowed the addition of new data into the present systematic review and meta-analysis, strengthening the evidence of the association of MetS with global cognition.

6. Limitations
Some of the limitations of the present study were the wide variability between the types of instruments used for neuropsychological assessments and the fact that there was no clear standardization between the expected parameters for that range of instruments. There is no clear differentiation between totally regular performances or differences between mild and severe impairment. On the other hand, studies have shown a difficulty with having heterogeneous populations, as this was the root problem of the syndrome itself. It is methodologically necessary
to seek a new paradigm, where longitudinal studies are the key and cross-sectional comparison studies, where more heterogeneity is seen in a single moment, are avoided. In other words, if follow-up studies of patients where it is possible to find these discrete differences between one moment and another are carried out at a global level, it is possible that the slowed change process may lead to compensation factors intervening and having plenty of time for adaptation (Alkan et al., 2019). In a longitudinal study, the compensatory effects of the nervous system of subjects in metabolic crisis that is chronic and graduated over time could be seen. At the current moment, in terms of understanding the neuropsychological profile of MetS, it seems that differences are small and may be due to the cross-sectional measurements being conducted at different stages of illness for each participant, leaving doubt as to whether there is deterioration or not (Bonilla & Galindo-Aldana, 2017). A methodological implication lies in the fact that the aforementioned studies referred to the means of individuals of different educational levels; however, when they provided the results of neuropsychological tests, they usually did not explicitly report the means for those with a low educational level with and without the syndrome or for those with a high educational level with and without the syndrome. We emphasize that educational level functions as a significant neuroprotective factor, and some studies included samples with this more excellent neuroprotective factor. Although the meta-analysis allowed us to compare the group effect sizes, when they were combined, a methodological bias could have been generated when increasing the size of the global effect without correct division by educational level. Moreover, we found slight evidence of a publication bias through the Funnel Plot analysis. In the absence of a publication bias, such a plot is expected to have a shape resembling an inverted funnel. However, asymmetry is observed when studies are absent on one side of the axis, meaning that, for several reasons, they were not considered in the analysis, for example, studies that were not published or presented incomplete data. The risk with this kind of bias is that studies with positive results are more likely to be published and the conclusions reached are influenced by the nature and direction of the results because data from nonpublished studies are not available. The significance of this risk could not be analyzed in depth through statistics such as the Egger test, given the small number of studies that reported complete data on general cognitive function through means and standard deviations. Therefore, studies that report all types of information necessary to generate more complete meta-analyses are required. More research in this field is needed to increase the quality of data available to obtain more reliable results.

7. Conclusion
It is possible to conclude that there are key cognitive processes affected by MetS, such as attention, memory, executive functions, and the global mental state. Through a meta-analysis, it was found that global cognitive state is statistically significantly affected both in the early and later stages of aging. The present findings indicate that the syndrome has an anatomical–functional correlation, in which the metabolic state of the central nervous system has a significant influence on the brain’s ability to function, leading to specific mental abilities.

Neuropsychology teams working in the clinical field and in the research area must apply validated, standardized instruments for which there are normative data on the clinical population. Then, they must make adjustments based on language and culture. It is essential to avoid disparities in instrumentation that lead to the results obtained not being comparable. This process of standardizing neuropsychological work requires that the results are reported uniformly since there are publications in which the results obtained are transformed into z-values, which complicates their potential subsequent comparison. Future systematic reviews and meta-analyses should be conducted to deepen our understanding of the mental health effects of these highly prevalent diseases in our community. The importance of continuing to evaluate the neuropsychological profile of MetS is considered fundamental to elucidate the implications
that lead the central nervous system to have neurological disorders secondary to metabolic diseases in the medium and long term.

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Conflicts of interest
The authors have declared that they do not have a conflict of interest.

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