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MicroRNAs and mild cognitive impairment: A systematic review

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ABSTRACT

Background: Mild cognitive impairment (MCI) is usually described as an intermediate phase between normal cognition and dementia. Identifying the subjects at a higher risk of progressing from MCI to AD is essential to manage this condition. The diagnosis of MCI is mainly clinical. Several biomarkers have been proposed, but mostly for research purposes, as they are based on an invasive procedure to obtain the sample, such as cerebrospinal fluid (CSF). As a consequence, rapid and non-invasive biomarkers are needed to improve diagnosis. The objective of this systematic review is to summarize available evidence on the use of miRNAs as biomarkers in subjects with MCI.

Methods: Relevant literature published up to June 2018 was retrieved searching the databases PubMed, ISI Web of Knowledge and the Cochrane Database. Only studies considering microRNAs (miRNAs) and a diagnosis of MCI were included. Data were extracted using a specifically-designed standardized form, and their methodological quality was assessed using QUADAS-2 and QUIPS.

Results: Twenty-one studies of 153 retrieved articles met the predefined inclusion/exclusion criteria. Studies included participants ranging from 6 to 330. More than 40 miRNAs resulted as dysregulated, and miR-206 was the only miRNA that was found as differentially expressed in patients with MCI by more than two studies. However, these results have either not yet been confirmed in other independent cohorts, or data are still inconsistent. Inconsistencies among included studies could be due to several issues including the selection of participants, pre-analytical and analytical procedures, and statistical analyses.

1. Background

Mild cognitive impairment (MCI) is usually described as an intermediate phase between normal cognition and dementia. A subject with MCI is defined as having an objective deficit in cognitive abilities and minimally impaired functional independence (Langa and Levine, 2014; Petersen, 2011). Recently, the cohort Studies of Memory in an International Consortium (COSMIC) estimated a 5.9% prevalence of MCI in people 60 years and older (Sachdev et al., 2015). Approximately 9.6% of cases annually progress from MCI to dementia (Mitchell and Shiri-Feshki, 2009), though up to 18% of cases also revert from MCI to normal cognition (Canevelli et al., 2016). Research on possible biomarkers capable of detecting etiological factors and predicting the progression of the condition is constantly growing. Identifying the subjects at a higher risk of progressing from MCI to AD is, in fact, essential to effectively manage this condition.

Biological markers or biomarkers are defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention" (Naylor, 2003). Biomarkers from blood, urine, and cerebrospinal fluid can be useful for the screening and diagnostic process, and to predict the prognosis of diseases (Mayeux, 2004). Ideally, a biomarker should be able to detect a fundamental pathological feature of the disease; it should be validated in pathological proven cohorts, and should be precise, reliable, non-expensive, and detectable through a non-invasive procedure, simple to perform.

The National Institute of Aging and Alzheimer's Association has developed new diagnostic guidelines for AD (Jack et al., 2011). These guidelines include an updated classification of the phases of AD, specifically the dementia phase, the symptomatic pre-dementia phase

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(MCI), and the asymptomatic, preclinical phase of AD (pre-MCI). The new guidelines also provide recommendations for the diagnosis of pre-MCI, MCI and AD dementia and emphasize the importance of identifying useful biomarkers to assess the MCI and AD preclinical phases. To date, the most frequently used biomarkers are CSF proteins, such as Aβ42, Total-Tau, and Phospho-Tau (Hansson et al., 2006). Hippocampal atrophy assessed through magnetic resonance imaging (Jack et al., 1999), abnormal brain metabolism diagnosed with 18F-FDG PET (Choo et al., 2013), and amyloid deposition detected through PET imaging (Grimmer et al., 2016) are also widely used to support the diagnosis. However, these tests are difficult and invasive, thus these procedures are, in fact, unfeasible in clinical practice. Recently, circulating miRNAs, being inherently stable and easy to manage, have been reported as promising biomarkers for neurodegenerative disorders and for conditions affecting the central nervous system, in particular in older adults (Grasso et al., 2014; Piscopo et al., 2016).

MicroRNAs (miRNAs) are a family of short, single-stranded 21–22 nucleotides non-coding RNAs, accounting for about 1% of all human genes, while being the most abundant class of small RNAs in animals. MiRNAs are a class of gene expression modulators, acting at a post-transcriptional level, and fine-tuning the expression of protein-encoding genes. MiRNAs modulate gene expression binding to 3′-untranslated region (3′UTR) of target mRNAs and leading to translational inhibition or mRNAs degradation (Bartel, 2004).

They are widely present within the nervous system, and some miRNAs are specific for or enriched in particular brain areas. They act as key regulators of different biological functions, including synaptic plasticity and neurogenesis, and they can indirectly influence neurogenesis by regulating the proliferation and self-renewal of neural stem cells (Grasso et al., 2014). Moreover, the importance of miRNAs and their emerging role in neurodegenerative disorders is becoming increasingly evident (Grasso et al., 2014; Piscopo et al., 2016). They are inherently stable, which explains their emerging use as potential biomarkers of human diseases, and as targets for new treatments. MiRNAs have been identified in several body fluids and excretory products, such as plasma, saliva, urine, and feces, and they are actively released by cells in micro-vesicles, exosomes, or are bound to proteins (Chevillet et al., 2014). Secretion of miRNA in the extracellular milieu in non-vesicular form is associated with AGO proteins especially AGO2. Besides, miRNAs are contained in the exosomes, which are secreted by multi-vesicle bodies and released by the fusion of the cell membrane (Ghai and Wang, 2016).

The objective of this systematic review was to gather and discuss all available evidence on the use of miRNAs as either biomarkers for the diagnosis of MCI, or as markers of conversion to dementia.

2. Methods

The review was performed following the methodology described in the Cochrane handbook for systematic reviews (Higgings and Green, 2011), and was reported based on the PRISMA statement for reporting systematic reviews and meta-analyses (Liberati et al., 2009).

All literature published up to June 2018 was retrieved searching the databases PubMed, ISI Web of Knowledge and the Cochrane Database of Systematic Reviews using the following search terms: (mirna* OR “micro rna” OR “micro-rna” OR “mir-”) AND (mci OR “mild cognitive impairment” OR “minor neurocognitive disorder” OR “minor neurocognitive disorders” OR “minor neuro-cognitive disorder” OR “minor neuro-cognitive disorders”). No restrictions were applied for date of publication, study design, or language. References of considered studies were also searched to identify any further relevant data.

Studies were initially selected by six independent reviewers (NV, LP, PP, MFe, MC, ACr) based on their relevance to the topic of the review. Disagreements were resolved by discussion between the reviewers.

The full texts of selected studies were retrieved and assessed for inclusion based on the following predefined inclusion/exclusion criteria. Only diagnostic or observational studies focusing on the assessment of miRNAs as diagnostic or predictive factors in human subjects with a diagnosis of MCI according to any diagnostic criteria were included. In-vitro, laboratory and functional studies were excluded. Studies that did not report usable data were also excluded. Systematic reviews were considered separately to check for consistency of data.

Included studies were qualitatively assessed by 3 independent reviewers (PP, ACr, MC) with the QUADAS-2 tool for diagnostic studies (Whiting et al., 2011), and the QUIPS tool for prognostic studies (Hayden et al., 2013). Other potential biases and/or methodological flaws or considerations were also taken into account. Data were extracted using a specifically-designed standardized form. Disagreements were resolved by discussion between the reviewers or by involving an external reviewer (NV, EL). The qualitative assessment of diagnostic studies was performed and reported using the software Review Manager, version 5.3, provided by the Cochrane Collaboration.

The data extraction form (*see Supplementary materials*) was specifically designed for this review based on a data collection form for intervention reviews made available by Cochrane Effective Practice and Organization of Care (EPOC) (“Cochrane Effective Practice and Organisation of Care Group (EPOC) resources for review authors,” 2017). The form was designed to extract data from randomized trials and non-randomized trials, thus the sections were changed to allow for data extraction from observational, diagnostic and prognostic studies. A specific section was also added to collect data on the specific laboratory procedures and technical details. The data extraction form designed for this study (*see Supplementary materials*) included, along with other relevant information, the following 9 domains: general information on the study, the methods used within the considered study, the population enrolled and the setting in which the study was carried out, the description of study participants, the test/s investigated by the study, the study outcomes, the results reported by the study, and possible issues on the applicability of study results. The main new elements that we included in the form were some fields to gather specific methodological information on the sampling and analysis of miRNAs. Thus, the “study test” domain was modified to include the following items: the methodological approach used for the test and its timing, procedures for sample processing and the isolation of the biomarker, procedures to check the quality of miRNA samples, methodology of miRNA analysis and its technical replication, and the reference chosen for normalization of miRNA data. Including all these information was crucial to allow a more accurate and appropriate assessment of the comparability and heterogeneity of studies. Even in case two studies analyzed the same miRNA or set of miRNAs, a meta-analysis could be inappropriate or biased due to differences in these set of variables that deeply affect the results of the study. Moreover, these could be considered as elements that contribute to the quality of the study, as the appropriateness of each of these procedures can affect the reliability of results. As no quality assessment tools are available for diagnostic or observational studies, including such information, we considered it essential to take into account these elements in the quality assessment of the studies included in this review.

Data were summarized in a narrative form, considering both quantitative and qualitative results, and results from the quality assessment. Reviews were excluded, but still considered separately to browse their bibliographic references, and to check for consistency of results. A meta-analysis was also planned, using the RevMan software provided by the Cochrane Collaboration, if and/or when possible.

3. Results

Bibliographic searches yielded 153 records. A total of 23 studies were selected based on their relevance to the topic of the review. All studies were in English, no pertinent and relevant studies in other languages were identified. Selected studies were assessed for inclusion. A total of 21 studies met the predefined inclusion/exclusion criteria

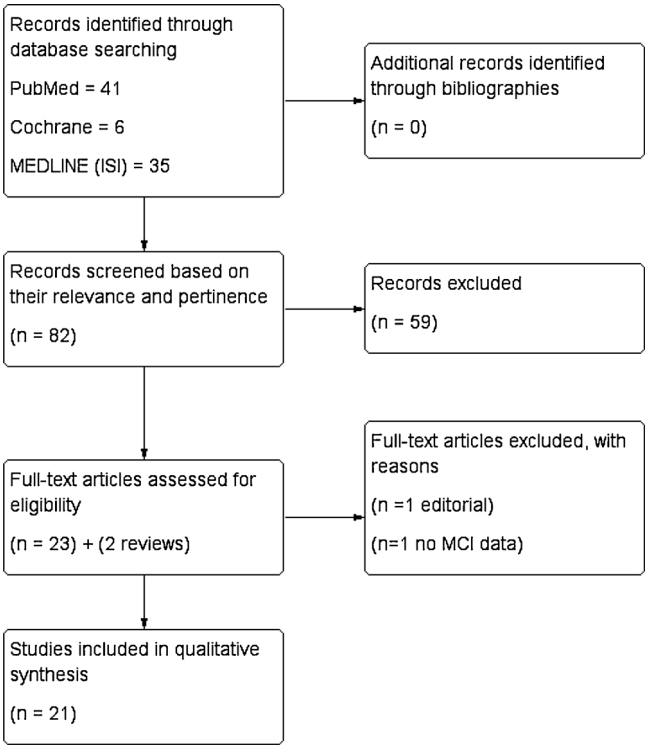

Fig. 1. Flow diagram of included studies.

(Kayano et al., 2016; Sheinerman et al., 2012; Sheinerman et al., 2013; Nagaraj et al., 2017; Xie et al., 2015; Xie et al., 2017; Liu et al., 2014b; Yang et al., 2018; Wang et al., 2015; Liu et al., 2014a; Leidinger et al., 2013; Moon et al., 2016; Dong et al., 2015; Kumar et al., 2017; Liu et al., 2014c; Zhu et al., 2015; Li et al., 2016; Müller et al., 2016; Wang et al., 2008; Weinberg et al., 2015; Keller et al., 2016), while 2 studies were excluded because one was an editorial (Sheinerman and Umansky, 2013) and the other did not include data on MCI (Guedes et al., 2016). The flow diagram of literature is reported in Fig. 1. Data could only be summarized in a narrative way, as the wide heterogeneity in the study design, analytical methods and diagnostic criteria adopted by the included studies, prevented any type of meta-analysis of data.

3.1. Demographic and clinical data

Table 1 reports the demographic and clinical data reported by the included studies.

The ethnic background of the enrolled populations was predominantly Asian, with 10 studies performed in China, 1 in Japan, and 1 in South Korea. The remaining nine studies were carried out in the United States and in some European countries (Table 1).

3.1.1. Sample size

One of the main issues of the included studies was the size of the enrolled samples. A total of 13 studies investigated miRNAs in plasma/serum samples from participants with MCI (included two in plasma/serum exosomes), 2 in blood cells, 1 only in CSF, 1 in olfactory epithelia, and 2 in *post-mortem* brain tissue (Table 1). More than 70% of the 17 studies performed on blood samples enrolled less than 50 participants with MCI. Only five studies included a number of participants ranging from 50 to 330. A total of 39 samples of CSF were used in an exploratory study to investigate miRNAs only in this body fluid, as possible early biomarkers in well-characterized subjects with MCI due to AD, as defined by Albert et al. (Albert et al., 2011), compared to controls and patients with other types of dementia (i.e. frontotemporal dementia, dementia with Lewy bodies) (Müller et al., 2016). *Post-mortem* brain tissue samples were analyzed from a limited number of participants with MCI: two studies investigated the expression profile of miRNAs in *post-mortem* brain tissue, while one study assessed the presence of a candidate miRNA (miR-206) in the olfactory epithelium.

3.1.2. Recruitment and selection of participants

Considering the small sample sizes of the included studies, the methodology adopted to recruit participants with MCI was further assessed. Eight studies did not report how participants were enrolled, while seven studies recruited participants with MCI from hospitals or clinical centers that also provided all the biological samples (Zhu et al., 2015; Dong et al., 2015; Wang et al., 2015; Moon et al., 2016; Müller et al., 2016; Nagaraj et al., 2017; Yang et al., 2018).

One study used a registry (Leidinger et al., 2013), while another one selected patients from the FRONTIERS project ((Kumar et al., 2017). In the only two studies that analyzed brain tissue from autopsies (Wang XB et al 2008; Weinberg RB et al 2015) samples were obtained from biobanks. Two studies, one diagnostic study and one prognostic study, recruited participants from an already existing community-based MCI cohort, seemingly representative of a territorial area (Xie et al., 2015; Xie et al., 2017).

Ethics approval and consent to participate were reported by the majority of studies, but not clearly described in three of the publications (Wang et al., 2008; Keller et al., 2016; Müller et al., 2016).

3.1.3. Mean age and gender distribution of participants

All of the studies, with the exception of the two studies on *post-mortem* brain tissue, reported the mean age of participants that ranged from a mean of 61.6 years to a mean of 81.7 years. Five out of these 19 studies (26.3%) recruited participants who were younger than 60 years old, but apparently none of the participants was younger than 50 years. In general, genders were equally represented in all of the clinical categories included in the studies.

Diagnostic criteria. Considering that the majority of the included studies selectively recruited patients based on their diagnostic status, we analyzed the most commonly used diagnostic criteria. Five of the included studies reported using Petersen's criteria (Petersen, 2011) for the clinical diagnosis of MCI, while 4 studies reported using the revised NINCDS-ADRDA criteria (Alzheimer's Association 2011). Unexpectedly, a relatively recent study (Dong et al., 2015) reported basing the diagnosis on the 1984 NINCDS-ADRDA diagnostic criteria (McKhann et al., 1984). Furthermore, only three studies defined enrolled participants as having "MCI due to AD" adopting the Albert's diagnostic criteria (Albert et al., 2011). In these criteria, the concept of "MCI due to AD" is used to identify those symptomatic but non-demented individuals whose primary underlying pathophysiology is AD. A number of studies used different diagnostic processes, such as predefined cut-offs of cognitive scales, or undefined "consensus diagnostic procedures". Four studies did not describe the diagnostic criteria they used to identify participants with MCI, thus not allowing to determine whether no diagnostic criteria were applied, or the adopted criteria were not reported in the publication. (Table 1).

Overall, for both participants with MCI and controls, the Mini-Mental State Examination (MMSE) was the most commonly used test across all of the included studies. Cognitively healthy cohorts were often poorly described, and were generally only defined as having cognitive scores within the normal ranges. A total of 60% of the included studies did not report a definition of the control subjects. One study reported using the 1984 NINCDS-ADRDA diagnostic criteria to define "nondementia controls" (Dong et al., 2015). One study used the Montreal Cognitive Assessment (MoCA) to identify subjects with normal cognition to be enrolled as controls (Xie et al., 2015), while another study used the CDR scale to the same purpose (Moon et al., 2016). None of the remaining studies reported any specific criteria for the definition of the control group.

Table 1
Main features of 21 studies included in the review.

Studies	Country	Specimen	Patients (Diagnostic criteria)	Sample Size		Age (mean ± SD)		Gender (female)		MMSE ± SD at baseline	
				Cases	Controls	Cases	Controls	Cases	Controls	Case	Controls
Leidinger et al. (2013)	Germany	Blood	MCI (Clinical / NPS criteria[§])	18	21	73.9 ± 6.2	67.1 ± 7.5	9	11	25.3 ± 1.4	29.3 ± 1.2
			AD *(NINCDS-ADRDA)*	94	21	72.7 ± 10.4	67.1 ± 7.5	53	11	18.9 ± 3.4	29.3 ± 1.2
Keller et al. (2016)	Germany	Blood	MCI (NR)	20	55	NR	67.3 ± 7.8	NR	29	NR	29.5 ± 0.86
			AD (NR)	49	55	70.7 ± 8.2	67.3 ± 7.8	22	29	21.6 ± 3.8	29.5 ± 0.86
Sheinerman et al. (2012)	U.S.	Plasma	*MCI (Petersen et al. 2001)*	*Pilot* 10	10	81.7	77.4	5	5	28.1 ± 1.4	28.9 ± 1.1
			AD (NINCDS-ADRDA)	*Valid* 20	20	79.9	80.2	5	8	25.8 ± 3.5	29.2 ± 1.3
				Longitud. st.	NA	77.0	NA	9	NA	28.8 ± 1.3	NA
				HC-MCI 19	20	76.9	80.2	7	8	20.8 ± 8.7	29.2 ± 1.3
				Main st. 20							
Sheinerman et al. (2013)	U.S.	Plasma	MCI ("*diagnosis was based on several tests evaluating cognition*")	50	50	68.2	65.1	29	24	26.0 ± 1.4	29.6 ± 0.6
Wang et al. (2015)	China	Plasma	MCI (Petersen et al. 2001)	116	81	68.6 ± 5.3	71.7 ± 5.4	70	45	23.9 ± 3.8	26.5 ± 3.5
			AD *(NINCDS-ADRDA)*	97	81	70.1 ± 4.6	71.7 ± 5.4	63	45	13.8 ± 5.4	26.5 ± 3.5
Kayano et al. (2016)	Japan	Plasma	MCI (Petersen et al. 2001)	23	30	72.8	70.4	12	18	24.3	28.6
Nagaraj et al. (2017)	Poland	Plasma	MCI (Albert et al., 2011)	Pilot 7	6	64.3 ± 6	66 ± 5	3	4	26.14 ± 2	NR
			AD *(NINCDS-ADRDA 2011)*	Valid 8	9	65.8 ± 7	66 ± 3	5	4	25.62 ± 3	NR
				Pilot 7	6	73.7 ± 5	66 ± 5	3	4	19.85 ± 4	NR
				Valid 13	9	67.5 ± 8	66 ± 3	7	4	20.92 ± 4	NR
Liu et al. (2014a)	China	Serum (exosomes)	MCI (NR)	43	NR	63.8 ± 6.1	NR	23	NR	NR	NR
			AD (NR)	51	NR	64.2 ± 6.5	NR	28	NR	NR	NR
Liu et al. (2014b)	China	Serum, Plasma	MCI (NR)	32	50	63.2 ± 6.1	63.9 ± 5.7	13	28	NR	NR
			AD (NR)	45	50	64.2 ± 5.8	63.9 ± 5.7	18	28	NR	NR
Liu et al. (2014c)	China	Serum	MCI (NR)	31	30	72.8 ± 6.1	75.2 ± 6.5	17	18	NR	NR
			AD (NR)	38	30	76.2 ± 6.	75.2 ± 6.5	23	18	NR	NR
Xie et al. (2015)	China	Serum	MCI (Petersen et al. 2001)	66	76	72.9 ± 7.6	73.2 ± 6.2	42	43	NR	NR
Dong et al. (2015)	China	Serum	MCI *(NINDS-AA 1984)*	30	123	81.1 ± 6.8	79.5 ± 6.8	9	58	25.6 ± 2.3	27.2 ± 1.3
			AD *(NINDS-AA 1984)*	127	123	79.3 ± 8.9	79.5 ± 6.8	55	58	11.5 ± 7.7	27.2 ± 1.3
Kumar et al. (2017)	U.S.	Serum	MCI (NR)	20	18	74.1 ± 7.5	74.6 ± 8.8	10	12	25 ± 2.8	27.2 ± 2.9
			AD (NR)	11	18	76.2 ± 10.1	74.6 ± 8.8	5	12	22.8 ± 4.6	27.2 ± 2.9
Xie et al. (2017)	China	Serum	MCI-MCI[!] (Petersen et al. 2001)	330	NA	69.9 ± 4.0	NA	177	NA	24.4 ± 2.2	NA
			MCI-AD[!!]	128	NA	76.0 ± 4.8	NA	76	NA	23.9 ± 2.1	NA
Yang et al. (2018)	China	Serum (exosomes)	MCI *(NINCDS-ADRDA 2011)*	101	228	61.6 ± 7.3	NR	59	NR	NR	NR
			AD *(NINCDS-ADRDA 2011)*	107	228	74.2 ± 7.9	NR	66	NR	NR	NR
Zhu et al. (2015)	China	Serum, CSF	MCI *(NINCDS-ADRDA 2011)*	30	42	71.6	71.9	12	19	NR	NR
			AD *(NINCDS-ADRDA 2011)*	26	42	72.3	71.9	14	19	NR	NR
Li et al. (2016)	China	Serum	MCI *(NINCDS-ADRDA 2011)*	32	40	64.8 ± 7.2	63.2 ± 6.3	22	22	NR	NR
		CSF	AD *(NINCDS-ADRDA 2011)*	48	40	65.5 ± 6.8	63.2 ± 6.3	26	22	NR	NR
Muller et al. (2016)	Europe	CSF	MCI (Albert et al., 2011)	39	40	73.1 ± 4.9	61.4 ± 11.1	22	19	24.8 ± 1.9	20.0 ± 4.7
			AD *(NINCDS-ADRDA 2011)*	60	40	72.9 ± 7.6	61.4 ± 11.1	31	19	27.2 ± 2.2	27.2 ± 2.2
Moon et al. (2016)	South Korea	Olfactory epithelia	MCI (CDR 0.5)	13	9	68	63	9	5	26.8 ± 0.4	28.3 ± 0.7
			AD	11	9	69	63	5	5	23.8 ± 0.6	28.3 ± 0.7
Wang et al. (2008)	U.S.	Brain tissue	MCI (*Consensus Conference with University of Kentucky)*	6	11°	91.5	91.6 / 84.2	NR	NR	NR	NR
			AD (*Consensus Conference with University of Kentucky*	6	11°	85.5	91.6 / 84.2	NR	NR	NR	NR
Weinberg et al. (2015)	U.S.	Brain tissue	MCI (Albert et al., 2011)	10	12	82.9 ± 4.9	83.0 ± 5.9	5	4	28.0 ± 1.3	28.3 ± 1.7
			AD *(NINCDS-ADRDA)*	10	12	88.6 ± 7.0	83.0 ± 5.9	6	4	17.5 ± 8.1	28.3 ± 1.7

MCI = mild cognitive impairment; AD = Alzheimer disease; NR = not reported; NA = not applicable.
[!]non conversion group [!!] conversion group.
[§] MMSE > 22 and < 28, not demented, memory complaint, preserved general cognitive function, intact activities of daily living, abnormal memory function documented by scoring below the education adjusted cut-off on the Logical Memory II subscale, from the Wechsler Memory Scale-Revised (maximum score = 25) with (a) < 8 for 16 years or more of education, (b) < 4 for 8–15 years of education, (c) < 2 for 0–7 years of education.

3.2. Qualitative assessment

The qualitative assessment was performed using the QUADAS-2 tool for diagnostic studies and the QUIPS tool for prognostic studies. A total of 20 studies were diagnostic studies (Kayano et al., 2016; Sheinerman et al., 2012; Sheinerman et al., 2013; Nagaraj et al., 2017; Xie et al., 2015; Liu et al., 2014b; Yang et al., 2018; Wang et al., 2015; Liu et al., 2014a; Leidinger et al., 2013; Moon et al., 2016; Dong et al., 2015; Kumar et al., 2017; Liu et al., 2014c; Zhu et al., 2015; Li et al., 2016; Müller et al., 2016; Wang et al., 2008; Weinberg et al., 2015; Keller et al., 2016), while 1 study was a prognostic study (Xie et al., 2017).

The QUADAS-2 list of questions was used to review the quality of included diagnostic studies. The tool includes 4 domains analyzing the quality of the methodology adopted for patient selection, the choice and management of the index test and the reference standard, and the accuracy of the flow and timing with which the tests were administered. The tool also includes an assessment of concerns about applicability for 3 of the considered domains (i.e. patient selection, index test, reference standard). The tool does not provide a global scoring, but an overall rating of high, unclear or low risk of bias for each domain, and an overall rating of high, unclear or low concern for applicability for the 3 considered domains. We provided an overview of the quality assessment of included diagnostic studies in Appendix B (Supplementary material).

The overall quality of included studies resulted as lower than expected, as most of the included studies had as their primary objective the assessment of miRNAs in subjects with AD, thus enrolling participants with MCI as a secondary analysis or as “non-dementia” controls.

All of the included studies resulted at a high risk of bias for patient selection. The main reason for this result was that all included studies adopted a case-control design. Moreover, none of the included studies enrolled consecutive subjects, and some of them did not report the source from which participants were enrolled, nor provided any specific details describing the enrolled sample. As for the item referring to the applicability of results, 17 studies resulted as raising unclear concerns about applicability, 2 as raising high concerns about applicability, and 1 as raising low concerns. The main reason for these results is that none of the studies provided a detailed description of the enrolled population, its characteristics, and how and from which source it was enrolled. Moreover, the studies raising high concerns about applicability enrolled highly selected populations, specifically older adults from rural communities of Texas (Kumar et al., 2017), and older adults from China that the study itself described as having a significantly lower educational level (Wang et al., 2015).

All of the included studies had high risk of bias for the domain referring to the index test. This is mainly due to the study design. All of the included studies were case-control studies, therefore the results of the index test were inevitably interpreted knowing the results of the reference standard. Moreover, if a threshold/cut-off for the index test was adopted, it was never pre-specified. As for the applicability of results, 7 studies were rated as raising high concerns about applicability, 12 as raising unclear concerns, and 1 as raising low concerns about applicability. The main reasons for the high and unclear concerns about applicability of results were due the studies not reporting sufficient information on test technology and its execution, for its replicability, and for an appropriate assessment of its reliability ad adequacy. To assess this item within this type of studies analyzing such specific biomarkers, we deemed necessary to take into consideration the items that we specifically included in the dedicated section of the data extraction form that we designed for this review. To assess the appropriateness and replicability of these tests, in fact, it is essential to know at least the following pre-analytical and analytical procedure information: sample processing, miRNA isolation, cellular contamination and hemolysis, control of the inhibition of Reverse Transcription quantitative PCR (RT-qPCR), as reported in Table 2. The most relevant element raising concerns about applicability was a lack of information on cellular contamination and hemolysis, and on RT-qPCR. Only 2 studies described how samples were checked to avoid possible bias originated by samples contaminated with blood. Only 1 study reported having performed a quality control to guarantee the absence of inhibitors of the reverse transcriptase and polymerase enzymes in the analyzed samples by using synthetic RNA spike-ins. Moreover, only 7 studies reported information on technical replication, while 11 did not report any information on this aspect, and in 1 case the item was not applicable. As for the other items, while most studies reported a mostly appropriate amount of information, high heterogeneity in techniques and methods was observed. The highest heterogeneity was observed among the reference used for normalization of miRNA data. A total of 9 studies used one or more endogenous reference miRNA, 4 used one exogenous spike-in artificial synthetic oligonucleotide, 2 used the mean global expression of all the analyzed miRNAs, 1 used absolute quantification based on standard curves generated from synthetic microRNAs, 1 used the five most stable of all analyzed miRNAs, and 2 works described an approach based on normalization for miRNA pairs, where ratios of levels of all possible miRNA pairs from the same sample were calculated and the most promising pairs (self-normalizing biomarkers) were selected. A high methodological heterogeneity was also observed in procedures for RNA isolation from tissue samples. A total of 15 of the included studies described column methods, such as miRNeasy Serum/Plasma kit (Qiagen) or miRCURY RNA Isolation Kit - Biofluids (Exiqon), while 5 works used Trizol or Qiazol.

The highest qualitative heterogeneity was observed in the domain referring to the flow and timing of tests. A total of 11 studies were rated as having a high risk of bias, 7 as having a low risk of bias, and 2 as having an unclear risk of bias (Li et al., 2016; Müller et al., 2016). The main factor increasing the risk of bias was that most of the studies did not apply the same reference standard to all included participants. Moreover, the studies that did not apply any criteria to define control subjects as having normal cognition or “no MCI”, resulted, as a consequence, as not having applied a reference standard to all the enrolled participants. As for the 2 included studies that enrolled participants from a brain bank, the time from the last assessment to death might have been long enough to allow for a progression of the disease, and thus a change in the clinical (and pathological) diagnosis.

A high qualitative heterogeneity was also observed in the domain referring to the reference standard. A total of 10 studies were rated as having a high risk of bias, 5 as having a low risk of bias, and 5 as having an unclear risk of bias. The main reasons increasing the risk of bias were the absence of clinical criteria to define both MCI for cases, and normal cognition or “no MCI” for controls, and the use, in some of the studies, of inappropriate criteria (e.g. NINDS criteria). As stated before, this may also be because most of the studies were designed to assess AD versus MCI, normal cognition or other dementias, thus the criteria were adequate for AD, but inadequate for the other conditions. As for the applicability of results, studies resulted as having the same scores assigned for the risk of bias analysis of this item. As our review aimed at including studies analyzing the possible use of miRNAs as markers of MCI, the studies that did not use any criteria for the definition of MCI and/or normal cognition were rated as both qualitatively at a high risk of bias, and also at a high risk of concerns for applicability.

The only prognostic study was qualitatively assessed using the QUIPS tool. The tool includes 6 domains analyzing the quality of the study participation and attrition, the measurement of the considered prognostic factor/s and outcome, the management of potential confounding factors, and the adequacy of statistical analyses and reporting. The tool does not provide a global scoring, but an overall rating of high, moderate or low bias for each of the included domains. The study resulted as having a low bias in the domains of study participation, outcome measurement, study confounding and statistical analysis and reporting, while it had a moderate bias in the domains of study attrition and prognostic factor measurement. The reasons for the moderate bias were mainly due to a lack of information on the participants lost to

Table 2
Summary of the pre-analytical and analytical procedures adopted in the included studies.

Study	Tissue	Anticoagulant	Sample Processing	Storage	RNA isolation	Hemolysis control*	Control of miRNA isolation*	Enzymatic reaction control*	Method of miRNA analysis	Reference	Technical replication
PROFILING STUDIES											
Leidinger et al. (2013)	Blood	PAXgene tubes	NA	NR	column	NA	NR	NR	qRT-PCR	RNU48	NR
Sheinerman et al. (2012)	Plasma	EDTA	1380 g, 5 min, 4 °C	−80 °C	column	NR	Yes	NR	qRT-PCR	Normalization on miRNA pairs	triplicate
Kayano et al. (2016)	Plasma	NR	3000 g, 5 min, 4 °C	NR	column	NR	NR	NR	qRT-PCR	miRNAs mean	NR
Nagaraj et al. (2017)	Plasma	EDTA	NR	−80 °C	column	Yes	Yes	Yes	qRT-PCR	5 most stable miRNAs	triplicate
Kumar et al. (2017)	Serum	NA	NR	NR	Qiazol	NR	NR	NR	microarray	U6	triplicate
Wang et al. (2008)	Brain tissue	NA	NA	−80 °C	Trizol	NA	NR	NR	microarray	miRNAs mean	NR
Weinberg et al. (2015)	Brain tissue	NA	N/A	−80 °C	column	NA	NR	NR	microarray	RNU48	NR
MIRNA CANDIDATE STUDIES											
Keller et al. (2016)	Blood	PAXgene tubes	NA	NR	column	NA	NR	NR	qRT-PCR	NA	NA
Sheinerman et al. (2013)	Plasma	NR	NR	−80 °C	Trizol and silica binding	NR	Yes	NR	qRT-PCR	Normalization based on miRNA pairs	triplicate
Wang et al. (2015)	Plasma	EDTA	3000 rpm, 20 min, 4 °C	−80 °C	Trizol	NR	NR	NR	qRT-PCR	miR-423-5p	NR
Liu et al. (2014a)	Serum (exosomes)	NA	NR	−80 °C	column	NR	NR	NR	qRT-PCR	U6	NR
Liu et al. (2014b)	Serum	NA	1200 g, 7 min	Liquid nitrogen	column	NR	NR	NR	qRT-PCR	miR-39	NR
Liu et al. (2014c)	Serum Plasma	NA NR	NR NR	−80 °C −80 °C	column	NR	NR	NR	qRT-PCR	U6	NR
Xie et al. (2015)	Serum	NA	3000 g, 10 min, r.t. then 16,000 rpm 10 min, 4∘C	−80 °C	column	NR	NR	NR	qRT-PCR	miR-39	duplicate
Dong et al. (2015)	Serum	NA	NR	NR	Trizol	NR	NR	NR	qRT-PCR	Calibration curve	triplicate
Xie et al. (2017)	Serum	NA	3000 g, 10 min, r.t. then 16,000 rpm 10 min, 4∘C	−80 °C	column	NR	NR	NR	qRT-PCR	miR-39	duplicate
Yang et al. (2018)	Serum (exosomes)	NA	3000 g 10 min r.t. 12,000 g 5 min 4 °C	−80 °C	column	NR	NR	NR	qRT-PCR	U6	NR
Zhu et al. (2015)	Serum CSF	NA NA	Serum: 12,000 g, 5 min, 4 °C CSF: 1200 g, 5 min, 4 °C	Serum: −80 °C CSF: −20 °C	Trizol	NR	NR	NR	qRT-PCR	U6	NR
Li et al. (2016)	Serum CSF	NA NA	Serum and CSF: 12,000 g, 5 min, 4 °C	Serum: −80 °C CSF: −20 °C	column	NR	NR	NR	qRT-PCR	U6	NR
Muller et al. (2016)	CSF	NA	3000 g, 10 min, then 4000 g 10 min	−80 °C	column	Yes	NR	NR	qRT-PCR	U6, miR-16 and miR-24	NR
Moon et al. (2016)	Olfactory epithelia	NA	N/A	NR	Trizol/column	NA	NR	NR	qRT-PCR	U6	triplicate

NR = not reported; NA = not applicable; r.t. = room temperature; CSF = cerebrospinal fluid.
* pre-analytic procedures to check the quality of miRNA samples.

Table 3
Summary of dysregulated miRNA from studies including MCI patients.

Study	Specimen	miRNA	MCI vs control	MCI vs AD	Sensitivity	Specificity	AUC
PROFILING STUDIES							
Leidinger et al. (2013)	Blood	12 miRNAs	NR	NA	88% 75% (vs AD)	81% 77% (vs AD)	NR
Sheinerman et al. (2012)	Plasma	"miR-132 family"°	↑ $p < 0.001$	NA	79%-89%	83%-100%	0.93-0.95
		"miR-134 family"°°	↑ $p < 0.001$		80%-95%	79%-84%	0.91-0.94
Kayano et al. (2016)	Plasma	20 pairs of miRNA*	NR	NA	NR	NR	0.72-0.88
		miR-191/miR-101 pair[a]	NR		NR	NR	0.96
Nagaraj et al. (2017)	Plasma	miR-483-5p	↑	NA	100%	83%-87%	0.93-0.95
		miR-486-5p	↑	NA	89%-100%	86%-87%	0.87-0.90
		miR-30b-5p	↓	NA	83%-89%	87%-100%	0.82-0.95
		miR-200a-3p	↑	NA	89%-100%	75%-100%	0.83-1
		502-3p	↑	NA	83%-89%	86%-87%	0.86-0.90
		142-3p	↓	NA	78%-100%	87%-100%	0.80-1
Kumar et al. (2017)	Serum	miR-455-3p	↑$p = 0.007$[§]	↓ $p = 0.007$[§]	NR	NR	NR
		miR-4668-5p	↑ $p = 0.016$	NS	NR	NR	NR
Wang et al. (2008)	Brain tissue	miRNA-107	↓ $p = 0.008$	NA	NR	NR	NR
Weinberg et al. (2015)	Brain tissue	miR-212/132	↓ $p < 0.01$	NA	NR	NR	NR
		miR-23a/23b	↓ $p < 0.01$	NA	NR	NR	NR
MIRNA CANDIDATE STUDIES							
Keller et al. (2016)	Blood	148 miRNAs	NR	NA	NR	NR	NR
Sheinerman et al. (2013)	Plasma	"miR-132 family"°	↑	NA	84%-94%	96%-98%	0.97
		"miR-134 family"°°	↑	NA	74%-88%	80%-92%	0.91
		combined			96%	87%	NR
Wang et al. (2015)	Plasma	miRNA-107	↑ $p < 0.001$	NA	98.3%	82.7%	NR
Liu et al. (2014a)	Serum (exosomes)	miRNA-193b	↓ < 0.05	NA	NR	NR	Positive rates 58.1% (25/43)
Liu et al. (2014b)	Pl[a]sm[a], serum	miR-384	↓ $p < 0.05$	↑ $p < 0.05$	NR	NR	Positive rates 53.1% (17/32)
Liu et al. (2014c)	Serum	miR-200b	↓ $p < 0.05$	↑ $p < 0.05$	NR	NR	NR
Xie et al. (2015)	Serum	miR-206	↑ $p < 0.001$	NA	86.4%	76.3%	0.88
		miR-132	↑ $p < 0.001$	NA	69.7%	100%	0.91
		Combined			85.5%	98.5%	0.98
Dong et al. (2015)	Serum	miR-93	↑ $p < 0.01$	NA	NR	NR	NR
		miR-143	↓ $p < 0.01$	NA	NR	NR	NR
		miR-146a	↑ $p < 0.01$	NA	NR	NR	NR
Xie et al. (2017)	Serum	miRNA-206	↑[b] $p = 0.035$	NA	95.3%	77.8%	0.95
		Baseline 5 years FU	↑[b] $p < 0.001$	NA	NR	NR	NR
Yang et al. (2018)	Serum (exosomes)	miR-135a	↑ $p < 0.05$	NS	90%	95%	0.98
		miR-193b	↓ $p < 0.05$	↑ $p < 0.05$	78%	77%	0.80
		miR-384	↑ $p < 0.05$	↓ $p < 0.05$	85%	90%	0.87
		combined			99%	95%	0.995
Zhu et al. (2015)	Serum	miR-210	Serum ↓ $p < 0.05$	Serum ↑ $p < 0.01$	NR	NR	NR
	CSF		CSF ↓ $p < 0.01$	CSF ↑ $p < 0.01$	NR	NR	NR
Li et al. (2016)	Serum	miRNA-613 serum	Serum ↑ $p < 0.01$	NA	NR	NR	NR
	CSF	CSF	CSF ↑ $p < 0.01$	NA	NR	NR	NR
Muller et al. (2016)	CSF	No miRNA dysregulated	NS	NA	NR	NR	NR
Moon et al. (2016)	Olfactory epithelia	miRNA-206	↑ $p = 0.004$	↓ $p < 0.001$	87.5%	94.1%	0.942

NR = not reported; NA = not applicable; NS = not significant; r.t. = room temperature; CSF = cerebrospinal fluid; ↑ = upregulated; ↓ = downregulated.
° "miRNA-132 family": miR-128/miR-491-5p, miR-132/miR-491-5p, mir-874/miR-491-5p °° "miRNA-134 family": miR- 134/miR-370, miR-323-3p/miR-370, miR-382/miR-370.
* hsa-miR-191 hsa-miR-590-5p/ hsa-miR-125b hsa-miR-18a / hsa-miR-140-3p hsa-miR-191/ hsa-miR-103 hsa-miR-19b/hsa-miR-192 hsa-miR-197/hsa-miR-191 hsa-miR-19b/ hsa-miR-152 hsa-miR-191/ hsa-miR-103 hsa-miR-590-5p/ hsa-miR-191 hsa-miR-320a/hsa-miR-125b hsa-miR-20a/ hsa-miR-106a hsa-miR-125b/hsa-miR-101 hsa-miR-103/hsa-miR-125b hsa-miR-24/ hsa-miR-101 hsa-miR-191/15 hsa-miR-103 hsa-miR-222/hsa-miR-197 hsa-miR-378/hsa-miR-103 hsa-miR-223/hsa-miR-125b hsa-miR-223/hsa-let-7b hsa-miR-125b/hsa-miR-125b hsa-miR-484.
[a] miRNA pair with highest AUC value.
[§] results only from an ANOVA analysis.
[b] converted to AD vs non converted to AD (MCI-AD vs MCI-no AD).

follow up and a lack on specific information on the methodology used to perform the analyses of miRNAs.

3.3. Qualitative summary

A total of 7 of the 21 included studies were profiling studies, and 14 were candidate miRNA studies (Table 3). We defined as profiling studies, the studies that used a methodology of global miRNA profiling, with a further step based on the validation of potential biomarkers through quantitative Real Time PCR. We define as candidate miRNA studies, the studies that were based on a chosen set of miRNAs hypothesized as having a functional role in the disease.

Based on the results from data extraction and qualitative assessment, we further categorized included studies according to the tissue they sampled for the analyses of miRNAs. This allowed us to discuss results taking into account the methodological quality of the study, and the adequacy and reliability of the laboratory procedures, along with their overall aim of either identifying possible miRNA through a wide profiling, or to further analyze a specific set of miRNAs.

Eighteen of the 21 studies investigated miRNAs in circulating body fluids, while the others examined olfactory epithelia and brain tissue (Table 3).

3.3.1. Profiling studies

3.3.1.1. Body fluids. Plasma/Serum. Only 1 of the profiling studies on plasma/serum samples resulted as having an overall low risk of bias, while the remaining 3 studies resulted as having an unclear to high risk of bias in all the assessed domains (Appendix B). The profiling study with the highest methodological quality had also the smallest sample size in this category. This study identified 6 miRNA (483-5p, 486-5p, 30b-5p, 200a-3p, 502-3p, 142-3p) that were able to discriminate healthy controls (HC) from subjects with MCI diagnosed defined as probable early AD by CSF biomarker assays. The identified miRNAs resulted as being able to discriminate early AD from controls with the highest fold changes (range 1.32 to 14.72), consistent significance, and with a specificity ranging from 0.78 to 1 and a sensitivity ranging from 0.75 to 1 (Nagaraj et al., 2017).

One of the profiling studies of this section with the lower methodological quality enrolled a total of 23 participants with MCI and 30 controls, all of Japanese origins. The study selected as biomarkers 20 pairs of plasma miRNAs that were able to distinguish subjects with MCI from non-MCI controls (Kayano et al., 2016) with a difference of correlation coefficients of $|r1 - r2| > 0.8$. The mean AUC value for each of the 20 miRNA pairs was 0.800 ± 0.051, ranging from 0.718 to 0.880. Two miRNA pairs (hsa-miR-191/hsa-miR-101, and hsa-miR-103/hsa-miR-222) resulted as having the highest AUC value of 0.962 for MCI detection, along with other two-miRNA pairs that included hsa-miR-191/hsa-miR-125b that also reached AUC values ≥0.95. However, though the observed AUC values for these miRNAs were good, the study did not apply any criteria to define normal cognition in controls.

A second small study identified 2 sets of biomarker pairs, "miR-132 family" (miR-128/miR-491-5p, miR-132/miR-491-5p and mir-874/miR-491-5p) and the "miR-134 family" (miR- 134/miR-370, miR-323-3p/miR-370 and miR-382/miR-370) that resulted as capable to discriminate MCI from HC with a 79% sensitivity and a 100% specificity (miR-132 family), and a 79% sensitivity and a 95% specificity (miR-134 family) respectively (Sheinerman et al., 2012).

One last study performed a miRNA profiling on serum by microarray analysis. The most significantly dysregulated miRNAs were then selected for a secondary screening and validation. Results showed an upregulation of miR-455-3p in participants with MCI when compared to controls, and a downregulation of the same miRNA in participants with MCI when compared to those with AD (MCI: 0.034 ± 0.024, CT: 0.019 ± 0.020, AD: 0.071 ± 0.078 p = 0.007) (Kumar et al., 2017). However, this study resulted as having a high risk of bias in all of the considered domains, mainly due to the fact that it did not provide any information on the diagnostic criteria used to define both MCI and normal cognition, and it enrolled only participants from rural communities of Texas.

3.3.2. Candidate miRNA studies

3.3.2.1. Body fluids. Plasma/Serum. Only 2 of the studies on in plasma/serum samples, resulted as having an overall low risk of bias, while 7 resulted as having an unclear to high risk of bias in all the assessed domains (Fig 2 in Appendix B). The 2 studies with the highest methodological quality were focused on serum samples. One of these studies showed a significantly upregulated expression of miR-206 ($p < 0.001$) and miR-132 ($p < 0.001$) in 66 participants with MCI when compared to the control group (n = 76) (Xie et al., 2015). In particular, miR-132 had an AUC of 0.912 (95% CIs: 0.853-0.953) (optimal cut-off point: −2.05, sensitivity: 69.7%, specificity: 100.0%, PPV: 100.0%, NPV: 79.2%), while miR-206 had an AUC of 0.880 (95% CIs: 0.815–0.928) (optimal cut-off point: −1.15, sensitivity: 86.4%, specificity: 76.3%, PPV: 76.0%, NPV: 86.6%). Moreover, the predicted Receiver Operating Characteristic (ROC) curve, based on the combination of miR-206 and miR-132, was 0.981 (95% CI: 0.942–0.996), with an optimal cut-off of 1.52, and had an 85.5% sensitivity, a 98.5% specificity, a 85.5% PPV, and a 98.5% NPV. The same authors, in 2017, extended the miR-206 study to investigate if this miRNA was able to predict the conversion from amnestic MCI (aMCI) to Alzheimer's disease in a large (458 participants with aMCI) 5-year follow-up study. The study showed higher levels of miR-206 in participants with aMCI that converted to AD (converter), when compared to participants with stable aMCI (non-converter). Moreover, a correlation was observed between serum levels of miR-206 and the rate of progression from aMCI to AD, with higher levels of miR-206 associated to a faster progression (Xie et al., 2017).

Two of the remaining 7 studies on candidate miRNAs that had a lower methodological quality investigated miR-384 levels in participants with MCI. The first study showed a lower expression of miR-384 in both serum and plasma samples ($P < 0.05$) from participants with MCI when compared to the control group, and a higher expression of the same miRNA when compared to participants with AD. Setting the cut-off values at 0.771, according to the ROC curve analysis, the positive rate of serum miR-384 was 53.1% (17/32) for participants with MCI. A strong correlation was observed among the levels of miR-384 obtained from plasma or serum samples ($r = 0.957$, $P < 0.05$) (Liu et al., 2014b). The second study reported opposite results, showing lower levels of miR-384 in participants with MCI when compared to controls, and higher levels of the same miRNA in participants with MCI when compared to those with AD. However, the study analyzed the miRNA in serum exosomes. This study also reported a dysregulation of 2 more miRNAs in subjects with MCI, showing higher levels of miR-135a and lower levels of miR-193b in subjects with MCI compared to controls. All 3 miRs were also combined to analyze the comprehensive predictive value for MCI, that resulted in an AUC of 0.997 (Yang et al., 2018). However, neither of the 2 studies used any criteria for the definition of normal cognition. Moreover, Liu and colleagues did not provide any information about the diagnostic criteria used to define MCI, nor reported sufficient details on test methodology and its execution to allow for its replicability. The same methodological issues were observed in the remaining 2 studies on serum samples. One study documented both plasma and serum miRNAs, and reported lower serum miR-200b levels in the MCI group when compared to the control group ($P < 0.05$), and higher levels of the same miRNA in the MCI group when compared to participants with AD ($P < 0.05$). A strong correlation was observed between serum levels and plasma levels within the same subject ($r > 0.950$, $P < 0.01$) (Liu et al., 2014c). The second study investigated exosomal miRNAs in serum samples, showing lower serum levels of exosomal miR193b in participants with MCI compared to controls, and higher levels of the same miRNA in participants with MCI compared to the AD group. Setting the cut-off value at the mean concentration ± 2 SD of the controls, the positive rate of exosomal miR193b was 58.14% (25/43) in the serum of participants with MCI (Liu et al., 2014a).

The miR-132 and miR-134 families were further investigated in another study from the same research group, and validated in a larger population of MCI (n = 50). The study found that the miR-132 family and the miR-134 family were able to discriminate MCI from HC with a 84%-94% sensitivity and a 96%-98% specificity (miR-132 family), and a 74%-88% sensitivity and 80-92% specificity (miR-134 family) respectively. When miRNAs of the same family were combined, the miR-132 and miR-134 family biomarkers resulted as having a 96% and 87% overall accuracy respectively (Sheinerman et al., 2013).

A further study on candidate miRNAs reported a significantly higher concentration of miR-93 and miR-146a, and a significantly lower concentration of miR-143 in participants with MCI when compared to controls. However, the study used the NINDS-ADRDA criteria to diagnose MCI, as its main objective was the analysis of these miRNAs in participants with AD, while analyses on participants with MCI were a secondary objective (Dong et al., 2015).

One last study reported data on miR-107 as a candidate miRNA. The study reported significantly different plasma levels of this miRNA in participants with MCI compared to healthy controls (1.02 ± 0.51 vs 3.98 ± 1.88 $p < 0.001$), with a 98.3% sensitivity and an 82.7%

specificity (Wang et al., 2015). However, this study resulted as having a high-risk bias due to a lack of information about diagnostic criteria used for the definition of control group and high concerns about applicability because they enrolled older adults from China as having a significantly lower educational level.

Whole blood. Only 2 studies analyzed miRNAs in whole blood samples. Both of these studies resulted as having an overall unclear or high risk of bias in all the assessed domains. One study selected 12 miRNAs, including strongly dysregulated miRNAs that showed a potential to discriminate AD from controls (brain-miR-112, brain-miR-161, hsa-let-7d-3p, hsa-miR-5010-3p, hsa-miR-26a-5p, hsamiR-1285-5p, hsa-miR-151a-3p, hsamiR-103a-3p, hsa-miR-107, hsa-miR-532-5p, hsa-miR-26b-5p, and hsa-let-7f-5p). These miRNAs were also analyzed in participants with MCI, who showed a strong overall upregulation of these miRNAs. The 12-miRNA signature's potential to distinguish AD from MCI was calculated, and resulted in a 75.6% overall accuracy, and an 84.2% accuracy in discriminating between MCI and controls. However, the study did not report any description of the criteria used to define controls, nor of the clinical criteria adopted for the diagnosis of MCI (Leidinger et al., 2013). In 2016, the same authors published a replication study in a German cohort using Next Generation Sequencing (NGS) to compare miRNA levels in participants with AD and MCI. Results showed that 148 miRNAs were differentially expressed in the two cohorts. The study, however, did not report any information on the criteria used to define normal cognition, nor on the clinical criteria used to diagnose MCI (Keller et al., 2016).

CSF and serum. A total of 2 studies assessed miRNAs in CSF and serum samples. Both of the studies resulted as having an overall unclear to high risk of bias in all the assessed domains. The first study (Zhu et al., 2015) observed that levels of miRNA210 in the CSF and serum were significantly lower in the MCI group compared with the control group (for CSF, $P < 0.01$; for serum, $P < 0.05$). However, the study also reported a significantly higher expression levels of miRNA210 in the MCI group compared to the AD group (both $P < 0.01$). In the second study (Li et al., 2016) on CSF and serum, miR-613 expression levels were significantly higher in participants with MCI compared to healthy individuals. The same results was also observed for the AD group ($p < 0.01$).

CSF. Only one study reported data on levels of miR-27a, miR-125b, and miR-146a in CSF samples from participants with MCI due to AD. The study had an overall mostly unclear risk of bias, mainly due to its not reporting details on the criteria used to define controls. The study did not found any difference in the level of expression of each miRNA between cases and controls (Müller et al., 2016).

3.3.2.2. Solid tissues. Olfactory epithelia. One study reported data on the levels of miR-206 in olfactory epithelia. The study had an overall high to unclear risk of bias, and did not report detailed information on the criteria and tests used to define MCI. The study showed higher levels of miR-206 in participants with MCI compared to the control group (7.8 fold-change). The ROC analyses for the diagnosis of MCI showed an AUC value of 0.942, and when the relative expression of miR-206 exceeded $7.06 \times 10 - 4$, the sensitivity was 87.5% (95% CI, 69.0–95.7) and the specificity was 94.1% (95% CI, 73.0–99.0) (Moon et al., 2016).

Brain tissue. Two study reported data on miRNAs in *post-mortem* brain tissue from participants with MCI. The first study analyzed miRNA patterns of cerebral cortex in participants defined as having "MCI with moderate AD", as they had clinical MCI with a moderate amyloid pathology.. Approximately 200 different miRNAs were expressed at levels above background on this array, but only about 70 miRNAs reached levels high enough to be included in comparative studies. Results showed that participants with MCI had lower levels only of miR-107 compared to non-demented patients without any amyloid pathology ($P = 0.008$). However, this study is characterized by an overall high to unclear risk of bias, mainly due to the fact that they used tissues from a brain bank, thus they did not report detailed information on the diagnostic criteria adopted for MCI, nor on the characteristics of the enrolled population (Wang et al., 2008). The second study also had a high to unclear risk of bias, due to the same reasons as the previous study, except that they used Petersen criteria for the diagnosis of MCI. This last study showed a down-regulation of the miRNA clusters miR-212/132 and miR-23a/23b in the frontal cortex of participants with amnestic MCI compared to controls (Weinberg et al., 2015).

4. Discussion

In this review, we assessed currently available evidence on the use of miRNAs as either biomarkers for the diagnosis of MCI, or as predicting factors for the conversion from MCI to dementia. Twenty-one studies were selected for our systematic review and included participants with MCI ranging from 6 to 330 participants.

The results from the present systematic review showed an ability of several miRNAs to discriminate between MCI and HC with a modest to high sensitivity and specificity. However, in general, these results have not yet been confirmed in other independent cohorts or, when available, data are inconsistent. Based on the qualitative assessment performed with the QUADAS-2 tool and the intrinsic quality of the analytical methods used within the study, the study carried out by Nagaraj et al. resulted as being the study with the highest level of quality, even if carried out on a small sample. To minimize methodological variability, they performed the standardization of blood and CSF assays following the recommendations by the international Joint Programming for Neurodegenerative Diseases (JPND) BIOMARKAPD consortium (Reijs et al., 2015). The study observed that a 6-miRNA profile (miR-483-5p, miR-486-5p, miR-30b-5p, miR-200a-3p, 502-3p, 142-3p) in plasma samples is able to discriminate control subjects from MCI patients diagnosed with probable early AD with the support of CSF biomarker assays. Unfortunately, no studies were carried out to replicate these results and thus confirm these data.

miR-206 was the only miRNA differentially expressed in patients with MCI in more than 2 studies in both serum sample (Xie et al., 2015, 2017) and olfactory epithelia (Moon et al., 2016), among the candidate miRNAs reported in the included studies, even if probably two of them may have used overlapping samples The studies on serum samples investigating miR-206 reached the highest level of quality as assessed with the QUADAS-2 tool. They report higher levels of miR-206 in plasma samples from participants with MCI when comparted to HC (Xie et al., 2015). Moreover, significantly higher serum levels of miR-206 were observed in participants with MCI that converted to AD after a 5-year follow-up compared to non-converters. Another interesting result was a correlation between higher serum levels of miR-206 and a faster progression rate from aMCI to AD (Xie et al., 2017). Bioinformatics and functional studies were also performed to further investigate this miRNA. Results from a bioinformatics analysis (Xie et al., 2015) showed a potential involvement of miR-206 in several biological pathways related to AD, such as learning or memory, nerve development, and the regulation of neuron differentiation. Moreover, higher levels of miR-206 were observed in brain tissue of patients with AD and animal models. This miRNA might contribute to cognitive decline by suppressing BDNF expression in the brains, thus, the inhibition of miR-206, in the study, prevented the detrimental effects of Aβ42 on the impairment of both BDNF and the dendritic spine in Tg2576 neurons (Lee et al., 2012).

A relatively recent systematic review also assessed, as a secondary objective, studies on miRNAs in subjects with MCI, while being focused, as a main objective, on reviewing evidence on miRNAs in subjects with AD (Wu et al., 2015). The review analyzed eight studies enrolling participants with MCI, focusing on the diagnostic accuracy of circulating miRNAs. Our review widened the analysis to 21 studies, as we also included studies on brain tissue. We extended the qualitatively assessment to both laboratory procedures and technical details, as we

created a dedicated section within the data extraction form (see *Supplementary data*). We decided to gather this information as it would allow us to assess the comparability of result, and would provide us all the details needed to appropriately assess the quality and applicability of the test(s) investigated in the included studies. Adding this dedicated section within the data extraction form, therefore, allowed us to gather detailed information on the analytical procedures, and use it to assess the quality of included studies in an integrated way, that is, including both the methodological quality and the intrinsic quality of the analytical methods used within the study (Table 2 and 3). The assessment of laboratory procedure also allowed us to understand the heterogeneity of the methodologies used for the quantification of miRNAs. This heterogeneity could partly explain the inconsistencies among studies that we observed in the review. The main issues, affecting the pre-analytical and analytical procedures, included sample collection, miRNA isolation, cellular contamination and hemolysis, quantification methods, reference genes, and quality control of samples. Both the standardization of sample collection and the pre-analytical methods are two of the most critical steps within the whole analytical process, as they aim at preserving the chemical, biological and morphological characteristics of the original tissue. For example, time and temperature among the blood draw, centrifugation/exosome isolation and freezing sample or numbers of freezing/thawing are information useful to understand how the samples have been preserved. In included studies, only three of them reported these technical details (Sheinerman et al., 2012; Nagaraj et al., 2017; Wang et al., 2015). Another important issue is the method of analysis for miRNA profiling. Sequencing and microarray methodologies are less sensitive and could produce more variable results than qRT-PCR. In miRNA profiling studies, three of them used microarray and the others RT-qPCR (Table 2). Data variability could be also due to the choice of reference. In fact, no studies are available that specifically investigated circulating miRNAs with the objective of identifying ideal molecules for RT-qPCR normalization in the field of neurodegenerative diseases. Moreover, the lack of a recognized and reliable reference gene, when analyzing miRNA in subjects with MCI, seriously interferes with the analyses, and limits the development of study on circulating miRNA. Therefore, all miRNAs currently used as internal references should be screening to find reliable internal references of circulating miRNAs. Another critical point that could explain the heterogeneity of the included studies is the selection of participants. All of the included studies used different criteria for the diagnosis of MCI, such as Petersen's criteria, the revised NINCDS-ADRDA criteria, and, in 1 study, even the 1984NINCDS-ADRDA diagnostic criteria. Moreover, some studies matched participants with MCI to healthy controls according to both age and ethnicity (Kayano 2016), while other studies only matched participants according to age/gender and sex (Sheinerman et al., 2012, 2013). Sample size was also widely variable across the included studies. These differences in the selection of study participants could be one of the reasons explaining the lack of consistency among studies. Moreover, differences in the accuracy of miRNAs in discriminating between MCI and healthy controls also depend on different statistical aspects, such as differences in the normalization procedures, in the selection of miRNAs, and in the statistical analyses used for both the selection of miRNAs and the evaluation of their performance.

A recent systematic review analyzed the diagnostic value of microRNA for Alzheimer's disease (Hu et al., 2016). The review attempted a meta-analysis of data providing cumulative estimates of sensitivity and specificity of the different tests investigated by the studies included in the review. However, in our review, we deemed as inappropriate to attempt any type of meta-analysis of data due to the high heterogeneity among the included studies in the pre-analytical and analytical methods, the diagnostic criteria adopted, and the statistical analysis procedures. We considered more useful and appropriate to provide a detailed description of results from the included studies taking into due account the methodological quality of evidence, its applicability and generalizability, and its replicability, and analyzing the impact of potential methodological limitations and their consequences on the interpretation and utility of results.

Our results might be affected by publication bias. Specifically, as 20 out of the 21 included studies reported at least 1 dysregulated miRNA, while only 1 reported no dysregulated miRNAs in the enrolled population (Table 3). This might suggest that studies showing no dysregulated miRNAs ("negative studies") may be harder to find when searching on standard databases (e.g. PubMed). This means that we could have missed some "negative studies", thus possibly overestimating the association between some of the investigated miRNAs and MCI. However, this type of studies is not frequently registered in trial registers (e.g. Clinicaltrials.gov), thus retrieving unpublished and/or gray literature on this topic is extremely difficult. The main limitation of prior studies is the wide heterogeneity of the included studies. Differences in the criteria used for the definition of both cases and controls, and in the variability of the technical procedure adopted within the study could be the cause. Another source of heterogeneity was the date of publication. Included studies, in fact, were published between 2008 and 2018. The methodology for the quantification of miRNA has sensibly evolved during this 10-year time span. In 2008, some of the elements we included in the data extraction form were not even known, nor considered, while they were progressively investigated and thus included in a standardized procedure.

5. Conclusion

The present review aimed at gathering all available, published, evidence on the accuracy of miRNAs as diagnostic and/or prognostic biomarkers of MCI. Results, while reporting an ability of several miRNAs, particularly miR-206, to discriminate between MCI and HC with a modest to high sensitivity and specificity, also showed a wide heterogeneity and inconsistency in several methodological aspects across all included studies. The use of both a standardized checklist for the assessment of the internal validity and methodological quality of studies, along with the use of a specific form for the assessment of the adequacy and quality of technical procedures allowed us to assess and discuss the several degrees of heterogeneity and inconsistency of literature on this topic. This methodological approach was deliberately adopted as no tools were available for the assessment of technical procedures in studies included in systematic reviews. The high heterogeneity across included studies prevented a meta-analysis of results, limiting our conclusions to a narrative summary. Further, higher quality, studies are thus needed, using validated and shared criteria to select and enroll participants and standardized procedures for laboratory analysis

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Appendix A. Supplementary data

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